ADPD 2024 Posters

*Only those abstracts who register for onsite participation will receive a poster shift and board number in February 2024.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0001 / #192

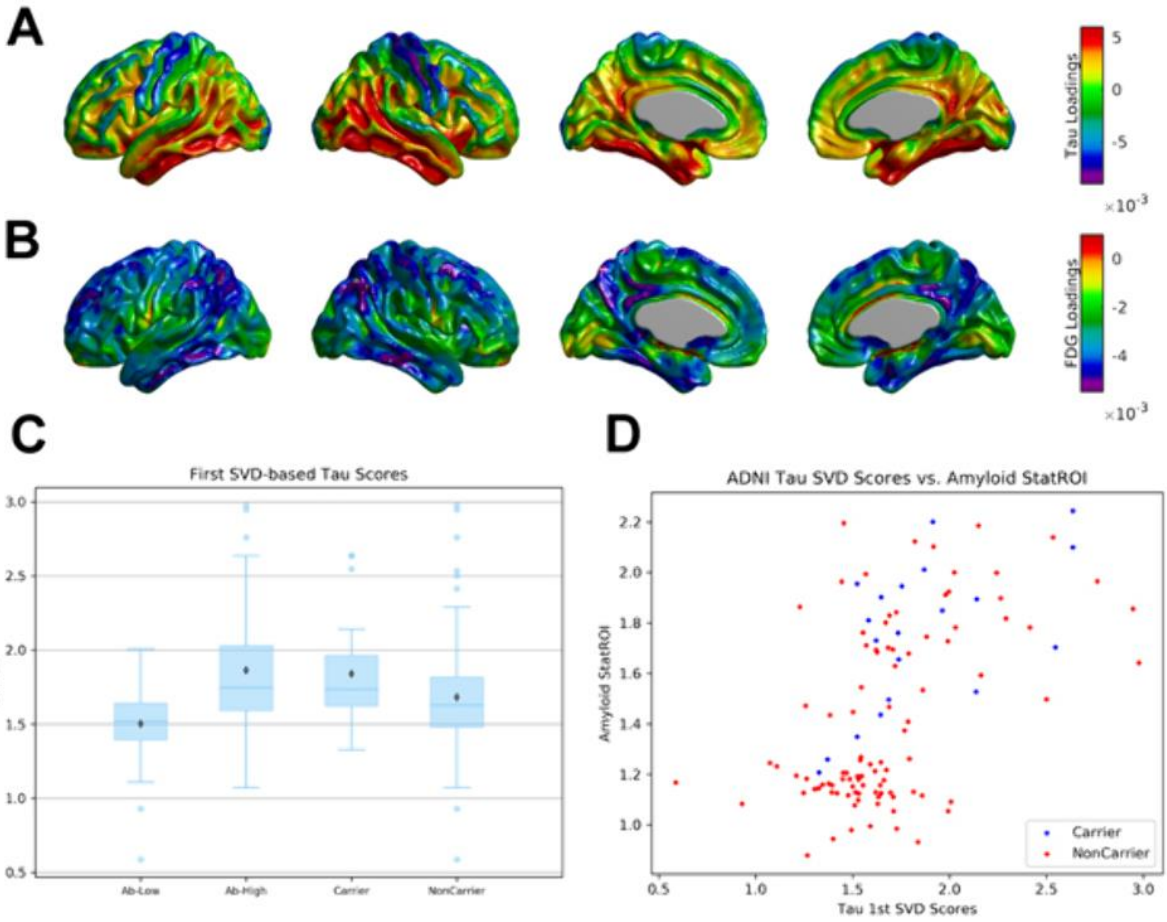
Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

TAU IS ASSOCIATED WITH REDUCED CEREBRAL GLUCOSE METABOLISM IN MCI INDEPENDENTLY OF BETA-AMYLOID AND APOEE4 GENOTYPE

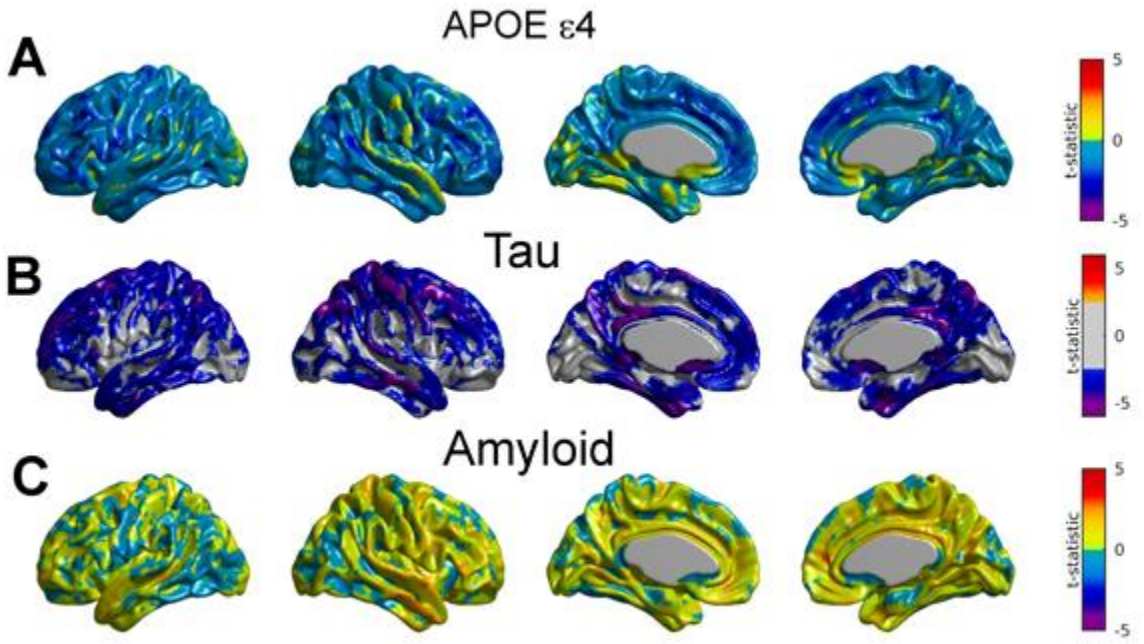
POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Felix Carbonell[1], Carolann Mcnicoll[1], Alex Zijdenbos[2], Barry Bedell[3]
[1]Biospective Inc., Clinical, Montreal, Canada, [2]Biospective Inc., Technology, Montreal, Canada, [3]Biospective Inc., Preclinical, Montreal, Canada

Aims: It has been shown that spatially distributed scores from Amyloid PET images are significantly correlated with glucose metabolism in MCI [1]. We hypothesize that analogous Tau PET scores are associated with a stronger reduction of glucose metabolism independently of the effects of beta-amyloid and APOE e4 genotype.
Methods: Our cross-sectional statistical analysis was applied to Tau, Amyloid, and FDG PET images from MCI subjects from the ADNI study. We employed a Singular Value Decomposition (SVD) approach to the cross-correlation matrix between Tau and the FDG images, as well as between Tau and Amyloid images [1]. The resulting SVD-based individual scores were used to fit voxelwise models for assessing the effect of the SVD-based tau, amyloid scores, and APOE ε4 status on the FDG images. [1] Carbonell *et al.*, *Journal of Alzheimer's Disease* **73**, 543–557, 2020.
Results: The first SVD component accounted for 21.49% of the total co-variability between FDG and Tau datasets. Figures 1A and 1B show a surface representation of the Tau and FDG spatial loadings, respectively. Figure 1C shows box plots of the Tau SVD-based scores, which are statistically different when segregated by amyloid status and significantly correlated with StatROI measurements of amyloid SUVR taken from an AD-signature ROI (Figure
1D).



Figures 2A, 2B, and 2C show the t-statistic maps for the APOE e4, tau, and amyloid effects on FDG PET.



Conclusions: We determined that only the distributed tau scores showed extended areas of statistical significance with FDG PET. More importantly, this relationship survives after controlling for the effects of distributed beta-amyloid and APOE ε4 genotype. Our results suggest that tau is associated with reduced glucose metabolism in MCI independently of beta-amyloid burden.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0002 / #346

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

AMINO-TERMINALLY ELONGATED ABETA-3-X PEPTIDES CAN BE GENERATED BY THE SECRETED METALLOPROTEASE ADAMTS4 AND DEPOSITS IN THE BRAIN OF A SUBSET OF ALZHEIMER'S DISEASE PATIENTS

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Merle Fricke[1], Christina Lehnen[1], Hans-Wolfgang Klafki[1], Barbara Morgado[1], Sandra Lehmann[2], Carolina Münch[2], Thomas Liepold[3], Jens Wiltfang[1], Olaf Jahn[3], Sascha Weggen[2], Oliver Wirths[1]
[1]University Medical Center Göttingen, Psychiatry And Psychotherapy, Göttingen, Germany, [2]Heinrich-Heine University, Department Of Neuropathology, Düsseldorf, Germany, [3]Max Planck-Institute for Multidisciplinary Science, Neuroproteomics Group, Department Of Molecular Neurobiology, Göttingen, Germany

Aims: The aggregation and deposition of amyloid-β (Aβ) peptides in the brain is thought to be the initial driver in the pathogenesis of Alzheimer's disease (AD). In addition to full-length Aβ peptides starting with an aspartate residue in position 1, both N-terminally truncated and elongated Aβ peptides are produced by various proteases from the amyloid precursor protein (APP), and have been detected in brain tissues and/or body fluids. We had demonstrated recently that the particularly abundant N-terminally-truncated Aβ4-x peptides are generated by ADAMTS4, a secreted metalloprotease that in the brain is exclusively expressed in the oligodendrocyte cell population.
Methods: We employed a previously developed electrochemical sandwich immunoassay and immuno-precipitation (IP) followed by mass spectrometry to determine Aβ-3-40 levels in the supernatants of a variety of cell lines, in addition to a detailed immunohistochemical analysis of human brain samples.
Results: In this study, we describe another ADAMTS4 cleavage site in APP N-terminal to Asp(1) between residues Glu(-4) and Val(-3), resulting in the release of N-terminally elongated Aβ-3-40 peptides, which serve as a component in a promising Aβ-based plasma biomarker assay. These elongated Aβ-3-40 peptides were detected in supernatants of various cell lines, and ADAMTS4 enzyme activity promoted the release of Aβ-3-x peptides. In addition, extracellular and vascular localization of N-terminally elongated Aβ-3-x peptides was identified in a subset of AD patient cases with immunohistochemistry. The results indicated that ADAMTS4 facilitates the generation of N-terminally elongated Aβ-3-x peptides, which were also identified in parenchymal and vascular deposits in brain samples of a subset of AD patients.
Conclusions: These findings implicate ADAMTS4 in both the pathological process of Aβ aggregation and in the early detection of amyloid pathology in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0003 / #827

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

ADVERSE EFFECT OF AMYLOID BETA OLIGOMERIZATION IN THE BRAIN CLEARANCE MECHANISMS

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Jorge Ghiso[1], Erwin Cabrera[1], Tammaryn Lashley[2], Agueda Rostagno[1]
[1]New York University Grossman School of Medicine, Pathology, New York, United States of America, [2]UCL Queen Square Institute of Neurology, Department Of Neurodegenerative Disease, London, United Kingdom

Aims: The mechanisms regulating the soluble-to-fibrillar conversion of amyloid beta (Abeta), the main component of parenchymal and vascular brain deposits in Alzheimer's disease (AD), remain a topic of intense scrutiny. Impaired brain clearance and abnormal Aβ degradation are considered key events for the formation and progressive accumulation of soluble neurotoxic oligomers and the development of synaptic pathology, one of the strongest correlates to cognitive impairment in AD. Our studies aimed to provide insight into the influence of Abeta oligomerization in brain elimination.
Methods: Stereotaxic cerebral injections in C57BL/6 mice were used to evaluate the brain clearance of well-defined radiolabeled monomeric and oligomeric assemblies of the main components of the AD brain deposits including full-length as well as N- and C-terminal truncated Abeta species. Proteomic approaches in combination with immunohistochemical studies using antibodies specifically recognizing different Abeta proteoforms were employed for identification and topographic localization in AD and transgenic models.
Results: Our data demonstrate that while soluble forms exhibited fast brain removal, oligomerization increased brain retention, a characteristic particularly evident in Abeta1-42 and enhanced in fragments truncated at Phe4. Consistent with these findings, the Abeta species with lower clearance propensity were found in the most insoluble parts of brain deposits, including plaque cores, as demonstrated by mass spectrometry, and immunohistochemical studies. On the contrary, Abeta species with low oligomerization proclivity, including C-terminally truncated derivatives, were easily eliminated from the brain consistent with their common presence in the interstitial and cerebrospinal fluids.
Conclusions: Overall, our data indicate that Abeta oligomerization negatively influences brain clearance mechanisms with the potential to exacerbate amyloid formation and self-perpetuate the amyloidogenic process, issues that should not be overlooked at the time of designing therapeutic strategies for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0004 / #2428

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

MOLECULAR BASIS OF CLINICAL ONSET IN FAMILIAL ALZHEIMER'S DISEASE.

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Sara Gutierrez[1], Lucía Chávez-Gutiérrez[1], Nick Fox[2], Natalie Ryan[3]
[1]VIB center for brain & disease research, Laboratory Of Proteolytic Mechanisms Mediating Neurodegeneration, Leuven, Belgium, [2]University College London, Dementia Research Centre, Queen Square Institute Of Neurology, London, United Kingdom, [3]Institute of Neurology, University College London, Dementia Research Centre, London, United Kingdom

Aims: Familial Alzheimer's disease (FAD), caused by mutations in Presenilin (PSEN1/2) and Amyloid Precursor Protein (APP) genes, is associated with an early age at onset (AAO) of symptoms of dementia. AAO is relatively consistent within families and between carriers of the same mutations, but differs markedly between individuals carrying different mutations. Gaining a mechanistic understanding of why certain mutations manifest several decades earlier than others is important in elucidating the foundations of pathogenesis and clinical onset. Pathogenic mutations affect the protease (PSEN/γ-secretase) and the substrate (APP) that generate amyloid β (Aβ) peptides. Altered Aβ metabolism has long been associated with AD pathogenesis. This study aims at understanding the molecular basis of pathogenicity and clinical onset. We hypothesize that Aβ profiles arising from the destabilizing nature of the FAD-linked mutations best reflect pathogenicity and define AAO.
Methods: We investigated this central aspect of AD pathophysiology via a comprehensive analysis of 25 PSEN1 and 25 PSEN2 mutations associated with a broad range of clinical onsets. We generated MEF cell lines stably expressing only wildtype or mutant PSEN1/2 γ-secretase complexes and infected these cell lines with APPC99. Secreted Aβ peptides where measured by ELISA.
Results: Our studies show that the Aβ (37 + 38 + 40) / (42 + 43) peptide ratio linearly correlates with AAO reported for carriers of PSEN1 and PSEN2 variants, and the correlative data offer predictive value in the assessment of variants of unclear pathogenicity in these genes.
Conclusions: This study delivers data and an experimental platform for AAO assessment valuable for fundamental, clinical and genetic research. Furthermore, it supports therapeutic interventions aimed at shifting Aβ profiles towards shorter Aβ peptides.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0005 / #519

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

STUDYING THE CONFORMATIONAL INTERPLAY OF DIFFERENT AMYLOID BETA PEPTIDES WITH NATIVE ION MOBILITY – MASS SPECTROMETRY

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Tanja Habeck, Silvana Zurmühl, Edvaldo Maciel, Frederik Lermyte
Technical University of Darmstadt, Clemens-schöpf-institute For Organic Chemistry And Biochemistry, Darmstadt, Germany

Aims: Amyloid beta (Aβ) peptides contribute to the formation of plaques and accordingly neurodegeneration. Due to variations in their biological production, different Aβ peptide isoforms exist. This study explores the distinct conformations of various Aβ species using native ion mobility combined with high-resolution mass spectrometry (IMMS). Additionally, we investigated how these peptides interact when mixed in solution. IMMS allows us to detect structural variability and examine the early stages of oligomerization.
Methods: A Waters Synapt XS with travelling wave ion mobility was used in this study. Prior to measurement stock solutions of all peptides were diluted to 30 µM in a 10 mM ammonium acetate solution. To investigate the influence of Aβ isoforms on each other, these peptides were mixed in equal proportions. Furthermore, we utilized non-pathogenic scrambled sequences and a less aggregation-prone rodent variant of Aβ42 as control samples.
Results: We observed clear distinctions in IMMS behaviour among the various Aβ monomers. Our high-resolution data revealed that a signal on the m/z axis, previously attributed to overlapping oligomeric species, actually originates from a conformationally diverse dimer, without contributions from higher-order oligomers. By studying the conformations of this dimer, we were able to differentiate between isoforms with different levels of toxicity associated with their aggregation. Furthermore, we identified hetero-oligomeric species, supporting the hypothesis that interactions between Aβ peptides influence the oligomerization processes.
Conclusions: To our knowledge this is the first study of the interplay between Aβ species on the conformational level with native IMMS. Additionally, the combination of different Aβ species gives new insights into early oligomerization processes. Considering hypotheses on Alzheimer's disease pathology that assign a key role to soluble oligomers, these insights potentially provide valuable information in better understanding the disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0006 / #1480

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

3D MAPPING DELIVERY AND PLAQUE CLEARING EFFICACY OF A BBB SHUTTLE-ENHANCED ADUCANUMAB BIOSIMILAR IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Jacob Hecksher-Sørensen[1], Marta Ramos Vega[2], Evi Alexiou[3], Allan Jensen[4], Camilla Stampe Jensen[4], Jacob Lercke Skytte[3], Casper Graversen Salinas[3], Sandra Vergo[4], Henrik H. Hansen[2]
[1]Gubra, Sales And Marketing, Hørsholm, Denmark, [2]Gubra, Sales And Marketing, Hørshom, Denmark, [3]Gubra, Ai Technology, Hørshom, Denmark, [4]Lundbeck, Biotherapeutic Discovery, Valby, Denmark

Aims: Accumulation of amyloid β (Aβ) in the brain is a neuropathological hallmark of Alzheimer's disease (AD). Recently approved Aβ-directed antibodies, including aducanumab, have demonstrated modest efficacy in AD, which may potentially be explained by poor blood-brain barrier (BBB) penetration. Transferrin receptor (TfR) mediated enhanced brain delivery of monoclonal antibodies across the BBB is a promising concept in drug development for CNS disorders. Using sheet fluorescence microscopy (LSFM) coupled with deep learning computational analysis, the present study aimed to visualize, map and quantify compound distribution and amyloid plaque load following long-term therapy with a BBB shuttle-enhanced Aβ-directed antibody in a mouse model of AD
Methods: APP/PS1 transgenic mice (32 ± 3 weeks of age, n=6-10 per group) were treated with an aducanumab biosimilar (AduBS, 10 or 50 nmol/kg), aducanumab biosimilar fused with a mTfR binder as BBB-shuttle (AduBS-BBB, 10 nmol/kg), control hIgG (Contr, 50 nmol/kg), or saline for 12 weeks. Whole-brains were stained with an antibody against hIgG (compound labelling) and hAβ (plaque labelling), respectively, cleared and scanned on a LSFM. A deep-learning image analysis algorithm was developed and validated for automated whole-brain visualization, segmentation, anatomical mapping and quantification of compound distribution and Aβ plaques at micrometre resolution using a custom mouse brain atlas.
Results: Both Aβ-directed antibodies, but not control hIgG, accumulated in brain areas with high Aβ plaque load, notably in cortical layers. Compared to AduBS, similar brain distribution pattern, compound fluorescent signal and Abeta plaque clearing efficacy was achieved using a five times lower dose of AduBS-BBB.
Conclusions: AduBS-BBB shows enhanced CNS accessibility and significant plaque-clearing efficacy, supporting the applicability of the TfR-shuttle concept to improve BBB penetrance of therapeutic antibodies in AD and other neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0007 / #1550

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

INHIBITION OF CU/ZN-SOD BY AB-INDUCED CO-AGGREGATION CAN BE PARTIALLY MITIGATED BY TRANSTHYRETIN

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Jan Homolak[1], Kristina Pavic[2], Melita Salkovic-Petrisic[3,4], Ana Babić Perhoč[4]
[1]University Of Zagreb School Of Medicine, Department Of Pharmacology And Croatian Institute For Brain Research, Zagreb, Croatia, [2]University of Zagreb, Faculty Of Pharmacy And Biochemistry, Zagreb, Croatia, [3]School of Medicine University of Zagreb, Department Of Pharmacology And Croatian Institute For Brain Research, Zagreb, Croatia, [4]University of Zagreb School of Medicine, Department Of Pharmacology And Croatian Institute For Brain Research, Zagreb, Croatia

Aims: Amyloid beta (Aβ) has been found to hinder the functioning of Cu/Zn-superoxide dismutase (Cu/Zn-SOD) through mechanisms that are not yet fully understood. This inhibitory effect of Aβ on Cu/Zn-SOD could be a crucial factor in the development of neurodegenerative conditions marked by the accumulation of protein aggregates, notably Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), where Aβ and Cu/Zn-SOD aggregation respectively play pivotal roles. Our primary goal was to clarify the mechanisms responsible for Aβ-induced inhibition of Cu/Zn-SOD in vitro. Furthermore, we sought to examine whether the presence of transthyretin (TTR), recognized for its ability to stabilize Aβ, could influence Aβ's inhibitory effects on Cu/Zn-SOD.
Methods: Cu/Zn-SOD activity was assessed using 1,2,3-trihydroxybenzene autoxidation. Aβ-Cu/Zn-SOD binding was studied through quantitative fluorescence adhesion assays and native polyacrylamide gel electrophoresis (PAGE) mobility shift assays using both standard and fluorescently labeled substrates. Co-aggregation was analyzed using Congo red spectral shift and binding-induced fluorescence.
Results: The inhibitory influence of Aβ on Cu/Zn-SOD is modulated by factors such as its aggregation status, the presence of Cu2+ and Zn2+, as well as the incubation conditions. A higher concentration of Cu/Zn-SOD within Aβ aggregates exhibits a negative correlation with the propensity for co-aggregation. Notably, TTR mitigates Aβ aggregation and its co-aggregation with Cu/Zn-SOD, thereby mitigating Aβ's inhibitory effect on Cu/Zn-SOD.
Conclusions: Aβ and Cu/Zn-SOD exhibit a propensity to co-aggregate, resulting in reduced total superoxide radical neutralization capacity. Enhanced Cu/Zn-SOD incorporation into Aβ aggregates represents a form of "suicide inhibition" halting further amyloid aggregation at the expense of the ability to neutralize free radicals, with potential implications for AD and ALS. The role of TTR in preventing Aβ-mediated inhibition of SOD in AD warrants further exploration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0008 / #2595

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

INTRANASAL DELIVERY OF THE SMOOTHENED AGONIST (SAG) ALLEVIATES ALZHEIMER'S DISEASE DEFICITS IN APPSWE/PS1DE9 MOUSE MODEL

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Yi-Heng Hsieh, Ding-I Yang
National Yang Ming Chiao Tung University, Institute Of Brain Science, Taipei City, Taiwan

Aims: We have reported that sonic hedgehog (SHH) expression is elevated in the Alzheimer's disease (AD) transgenic mouse brain (APPswe/PS1dE9; Hung et al., 2016). Further, we found that exogenous application of SHH exerts protective effects against transient focal cerebral ischemia (Huang et al., 2013). However, whether chronic activation of SHH signaling may affect AD phenotypes *in vivo* has been less well studied. The present work was therefore conducted to test whether the smoothened agonist (SAG), a SHH pathway activator, may recover the cognitive deficits and alleviate pathological aggression to exert beneficial effects in the animal model of AD.
Methods: Wild-type (WT) littermates and APPswe/PS1dE9 (AD) mice were intranasally given SAG for 12 weeks during 7-10 months of age. Three behavioral tests including novel object recognition test, Morris water maze, and fear conditioning were performed at the completion of drug delivery. Afterwards, cortical and hippocampal tissues were collected for biochemical analyses.
Results: We found that SAG restored the abilities of recognition and spatial memory in the AD mice based on the results of all three behavioral tests. Biochemical analyses revealed that SAG recovered synaptic plasticity, alleviated caspase-3-dependent apoptosis, decreased the formation of senile plaques and soluble Aβ1-42, mitigated the microgliosis, as well as alleviated oxidative stress in the AD mice.
Conclusions: We conclude that SAG can have beneficial effects in AD mice.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0009 / #2721

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

MEDIATION OF THE APOE ASSOCIATIONS WITH COGNITION THROUGH ALZHEIMER'S PATHOLOGY

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Jae-Won Jang
Kangwon National University, School Of Medicine, Chuncheon, Korea, Republic of

Aims: The ApoE ε4 allele of the apolipoprotein E (APOE) gene is a strong genetic risk factor for aging-related cognitive decline. However, the causal connection between ApoE ε4 allele and cognition is not well understood. The objective of this study was to identify the roles of Amyloid/Tau (AD pathology) in associations of APOE with cognition.
Methods: We studied mild cognitive impairment individuals from the Alzheimer's Disease Neuroimaging Initiative database The multiple linear regression analyses were conducted on 397 subjects(mean age of 71.9 years; 58.9% of female; 48.3% of APOE ε +4 allele carriers) (Table1) Serial mediation model of biomarker cascade hypotheses were performed using ApoE ε4 as predictor, CSF amyloid beta, phospho-Tau as Mediators and Cognition represented by CDR-SB across 36months as outcome adjusted by age, gender, education. Causal mediation analyses with 5,000 bootstrapped iterations were conducted to explore the mediation effects. Process R package was used for mediation analysis
Results: In MCI, APOE e+4 allele was not directly correlated with cognitive decline across 36months The effect of the APOE genotype on cognition was partly mediated by amyloid beta ($p<0.001$) but not by phopho-Tau ($p=0.212$) (Fig1 & Table2).
Conclusions: AD biomarker partially mediates the potential links between APOE genotype and cognition. Overall, the APOE ε4 allele may lead to a dysregulation of the AD cascade, which in turn leads to cognitive impairment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0010 / #1570

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

ZN-DEPENDENT AMYLOIDOSIS AND ITS REVERSAL

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Vladimir Mitkevich
Engelhardt Institute of Molecular Biology, Laboratory Of Protein Conformational Polymorphism In Health And Disease, Moscow, Russian Federation

Aims: The pathogenesis of Alzheimer's disease (AD) is associated with the formation of cerebral amyloid plaques, the main components of which are the modified beta-amyloid (Abeta) molecules as well as the metal ions. Aβ isomerized at Asp7 residue (isoD7-Abeta) is the most abundant isoform in amyloid plaques. We hypothesized that the pathogenic effect of isoD7-Abeta is due to the formation of zinc-dependent oligomers, and that this interaction can be disrupted by the rationally designed short peptides.
Methods: We utilized Surface Plasmon Resonance, Isothermal Titration Calorimetry, Dynamic Light Scattering and Molecular Dynamic simulation to demonstrate Zn^{2+}-dependent oligomerization of isoD7-Abeta and the formation of a stable isoD7-Abeta:Zn^{2+}:short peptide complex incapable of forming the oligomers. To demonstrate the physiological importance of zinc-dependent isoD7-Abeta oligomerization and the ability of short peptides to interfere with this process at the organismal level, we employed transgenic nematodes overexpressing human Abeta.
Results: We show that the presence of isoD7-Aβ in the medium triggers extensive amyloidosis that occurs in a Zn^{2+}-dependent manner, enhances paralysis, and shortens the animals' lifespan. Exogenous short peptides completely reverses these pathological effects of isoD7-Abeta.
Conclusions: We conclude that the synergistic action of isoD7-Abeta and Zn^{2+} promotes Abeta aggregation and that the selected small molecules capable of interrupting this process can potentially serve as anti-amyloid therapeutics. Supported by the Russian Science Foundation, grant #19-74-30007

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0011 / #2479

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

DECIPHERING THE PATHOLOGICAL SIGNIFICANCE OF SELF-PROPAGATING AB STRAINS IN DIFFERENT ANIMAL MODELS

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Rodrigo Morales[1], Nazaret Gamez[1], Claudia Duran-Aniotz[2], Ines Moreno-Gonzalez[3], Ruben Gomez-Gonzales[1]
[1]The University of Texas Health Science Center at Houston, Neurology, Houston, United States of America, [2]Universidad Adolfo Ibanez, Psychology, Santiago, Chile, [3]Universidad de Málaga, Departamento De Biologia Celular, Genética Y Fisiologia, Malaga, Spain

Aims: Alzheimer's disease (AD) is an heterogenous disorder characterized by the accumulation of amyloid-beta (Aβ) and tau. One possible explanation for the clinical and pathological variation in AD lies in the presence of distinct conformational strains of Aβ. Numerous studies provide compelling evidence for the existence of such strains as well as their ability to template their conformations in a prion-like manner. However, the interaction of such Aβ strains with different hosts has yet to be thoroughly examined. Here, we examined the host-seed interaction of different human brain-derived and synthetic misfolded Aβ strains in two different mouse models of amyloid pathology. We specifically explored the potential differences in amyloid propagation and pathological manifestations considering Aβ strains and animal models as variables
Methods: 50-day-old Tg2576 mice were intra-cerebrally challenged with mouse or human brain-derived Aβ seeds, or synthetic Aβ strains. Age-matched APP/PS1 mice were intra-cerebrally challenged with the biological Aβ-seeds as well. Cerebral pathology was assessed in 300-day-old Tg2576 mice, and in 180-day-old APP/PS1 mice
Results: Two structurally-defined synthetic misfolded Aβ strains induced remarkably different pathological features in Tg2576, including different rates of aggregation, tropism to specific brain regions, and differential recruitment of Aβ40/Aβ42 peptides. Moreover, the administration of human brain homogenates derived from AD patients, displaying unique patterns of amyloidosis, seeded distinct phenotypes in challenged APP/PS1 mice, as evaluated by their seeding activity, vascular pathology, and reactivity to thioflavin-S. Finally, we observed that the same human brain homogenate induced a different cerebral Aβ pathology when inoculated into Tg2576 and APP/PS1 mice.
Conclusions: Our findings support the concept of Aβ strains and demonstrate that they may drive different clinical and pathological outcomes in humans. Our work highlights the contribution of the host in pathological characteristics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0012 / #523

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

MOLECULAR STRUCTURAL CHANGES IN BRAIN TISSUE OF AN ALZHEIMER'S MOUSE MODEL: IMPACT OF POSTMORTEM DELAY

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Agnes Paulus[1], Sara Bachiller[2], Tomas Deierborg[3], Oxana Klementieva[1]
[1]Faculty of Medicine, Lund University, Experimental Medical Science, Lund, Sweden, [2]Institute of Biomedicine of Seville (IBiS), Virgen del Rocío University Hospital, Spanish Research Council (CSIC), University of Seville (US), Department Of Medical Biochemistry, Molecular Biology And Immunology, School Of Medicine, Sevilla, Spain, [3]Faculty of Medicine, Lund University, Experimental Medical Science,, Lund, Sweden

Aims: Understanding structural changes in brain tissue is a crucial pursuit for a deeper comprehension of molecular mechanisms during Alzheimer's disease (AD). The bedrock of such explorations rests upon human brain tissues, often acquired after a postmortem interval that can significantly vary from hours to days. Strikingly, the conceivable impact of postmortem delay (PMD) on molecular structures, including amyloids, remains to be unraveled. This study thus presents a question: Could PMD exert an influence on molecular structures? To address this, we employed Fourier-transform infrared (FTIR) spectroscopy, a label-free and non-destructive approach. Using FTIR we investigated changes in secondary structures of proteins and lipids in a mouse brain model of AD collected at different PMD.
Methods: Brains from 7-month-old APP^{NL-G-F} mice model of AD were collected at distinct time intervals: (I) immediately after sacrifice, (II) 6 hours, and (III) 24 hours post-sacrifice at room temperature. The brains were carefully extracted from the skulls and then preserved in paraformaldehyde, without undergoing perfusion. Subsequently, these brains were sectioned (15-micrometers thickness), and specifically employed for FTIR experiments.
Results: Our results indicate that PMD induces distinct modifications in the secondary structures of amyloid plaques and lipids. Specifically, we observed shifts in the characteristic beta-sheet structures of amyloid plaques, possibly contributing to changes in their aggregation patterns. Additionally, alterations in lipid composition and organization were detected, suggesting potential interactions between amyloid aggregates and lipid composition in the postmortem tissue of an animal model of AD.
Conclusions: In conclusion, our study highlights the impact of PMD on the protein structures within the amyloid plaques and lipid structures. These insights point to the refinement of experimental protocols and data interpretation for structural studies based on postmortem tissues.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0013 / #1609

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

CHARACTERIZATION OF SOLUBLE SYNTHETIC AMYLOID BETA AGGREGATES

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Alejandro Iván Ruiz Riquelme
University of Santiago de Compostela, Center For Research In Molecular Medicine And Chronic Diseases (cimus), Santiago de Compostela, Spain

Aims: Objective 1 – Biochemical characterization of soluble synthetic Aβ aggregates. Objective 2 – Structural characterization of soluble synthetic Aβ aggregates. Objective 2 – Toxicity assessment of soluble synthetic Aβ aggregates.
Methods: 1) Generation of soluble synthetic Aβ aggregates in different states of aggregation. Different aggregation protocols (monomers, oligomers, protofibrils, fibrils). Ultracentrifugation (100000 G). 2) Biochemical analysis. Native and SDS-PAGE. 3) Structural analysis. Transmission electron microscopy. 4) *In vitro* assessment of toxicity. Aβ cellular assay developed by Aoyagi et al. [1].
Results: Aβ aggregates of different size were generated and characterized both biochemically and structurally. We observed the existence of short fibrillar aggregates soluble at 100000 G with features different from insoluble Aβ fibrils. By native PAGE, short fibrils appeared as oligomers whereas insoluble fibrils got stuck in the wells, not entering the gels. Similar results were observed by SDS-PAGE. By transmission electron microscopy, we saw clear differences between soluble and insoluble fibrils with soluble fibrils being shorter and with a sharp morphology. After adding the fibrils to biosensor cells expressing Aβ, differences in the toxicity (measured as seeding activity) were observed.
Conclusions: Since soluble Aβ fibrils are the target of AD therapies such as the antibody lecanemab [2], synthetic soluble Aβ fibrils, easier to obtain than human soluble Aβ fibrils, can be used as a model to study the mechanism of antibodies targeting the initial stages of Aβ aggregation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0014 / #1435

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

THE AMYLOID BETA AGGREGATION MODULATOR GAL-201 IS UNDER DEVELOPMENT FOR ORAL AD TREATMENT: COGNITIVE IMPROVEMENT IN A TRANSGENIC AD MODEL

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Hermann Russ[1], Katrin Riemann[2], Jeldrick Ahsen[2], Gerhard Rammes[2]
[1]Galimedix Therapeutics Inc., 3704 Calvend Lane, Kensington, United States of America, [2]Klinik für Anaesthesiologie und Intensivmedizin der Technischen Universität München, Klinikum Rechts Der Isar, Munich, Germany

Aims: The small molecule GAL-201 has recently been characterized as a promising development candidate for oral treatment of AD (https://doi.org/10.3390/ijms23105794). It binds with high affinity (Ki=2.9 nM) to the misfolded form of monomeric amyloid beta and prevents the aggregation to the neurotoxic amyloid beta oligomers and protofibrils. These amyloid species have been validated by recent positive Phase 3 studies with antibody drugs, such as lecanemab as AD drug target. Prior to beginning clinical development, GAL-201 should also be investigated in an established transgenic (tg) model of AD for its neuroprotective and symptomatic potential.
Methods: The tgArcSwe mouse model of AD has been chosen since it carries, besides the Swedish mutation (APPswe), the amyloid beta-associated Arctic mutation (ArcAb). Tg and wild type mice (12 months) were tested for their cognitive performance in the water-cross maze after administration of 80 mg/kg GAL-201 subcutaneously on the day before the experiment.
Results: GAL-201 significantly improved the cognition in the mutants compared to placebo. The escape latency, which is the duration the animals need to perform the test, was clearly shorter since the transgenic mice showed a cognitive improvement when treated with GAL-201 (n=9-10 per group, p=0.06). In the accuracy experiment, the improvement of the GAL-201-treated transgenic mice was even more pronounced (n=9-10 per group, p=0.02). In addition, new in vitro data about the duration of the biological activity of GAL-201 will be presented.
Conclusions: The available results of the animal study in the Arctic mutation AD model further strengthen the profile of GAL-201 as a promising development candidate for oral Alzheimer therapy. The next step is the initiation of the IND enabling program, before starting a classic Ph 1 SAD/MAD study.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0015 / #2830

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

ELUCIDATION OF AMYLOID-BETA'S GAMBIT IN OLIGOMERIZATION.

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Adrien Schmid[1], Martin Zwahlen[1], Caroline Herron[2], Bea Gil[2]
[1]Arpeggio SA, Diagnostics & Therapeutics, Lausanne, Switzerland, [2]University College of Dublin, UCD, School Of Biomolecular And Biomedical Science, Dublin, Ireland

Aims: The modest therapeutic efficacy with some clinical antibodies as well as the ongoing, heated debate on viable, oligomeric amyloid-beta (Aβ) targets emphasizes the strong need for identifying specific Aβ «hotspots» for the improvement of next generation disease modifying-therapies for Alzheimer's disease (AD).
Methods: Targeted and quantitative mass spectrometry (MS), immuno-precipitation coupled with MS (IP-MS), SDS-PAGE and immunoblotting.
Results: Using advanced technologies in mass spectrometry, together with earlier developed antibody molecules against specific Aβ isoforms, we were able to shed light on an enigma associated with SDS-PAGE stable, low molecular weight (LMW) as well as large Aβ assemblies. Here we provide strong analytical proof of detection of specific Aβ isoforms (target hotspots) present in Aβ oligomers. This finding allows for an unprecedented, selective targeting of oligomeric assemblies, irrespective of the oligomer morphology. We show that the early appearance of specific Aβ isoforms rapidly seed the formation of small (≤17kDa), neurotoxic oligomers, which eventually leads to the formation of SDS-PAGE stable complexes of larger Aβ entities (>50kDa). We applied targeted and quantitative MS approaches to elucidate the composition of these meta-stable core Aβ structures and provide, for the first-time, quantitative data on the composition of Aβ oligomers.
Conclusions: We highlight here the strong need for identifying additional, molecular mechanisms associated with the early events of Aβ peptide aggregation during the long, insidious phase of AD. This in turn will allow the improvement of antibody-specific target engagement of early, pathological Aβ species present in the human AD brain and biofluids.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0016 / #2826

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

NATURAL ABETA OLIGOMERS THAT DIFFUSE OUT OF AD BRAIN IMPAIR HIPPOCAMPAL SYNAPSES AND ARE QUANTIFIED BY AN IMPROVED OLIGOMER IMMUNOASSAY

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Dennis Selkoe
Brigham and Women's Hospital, Neurology, Boston, United States of America

Aims: Objective: The Abeta oligomer hypothesis is a corollary of the amyloid hypothesis of Alzheimer's disease (AD) which posits that Abeta assemblies smaller and more diffusible than ~8 nm compacted amyloid plaque fibrils are principal bioactive forms of Abeta and contribute importantly to neurotoxicity and inflammation. Several forms of Abeta oligomers have been described or postulated, some of which are putatively soluble in aqueous fluids and others of which (often termed protofibrils) have been characterized as either soluble or particulate.
Methods: Methods: We used gentle aqueous soaking of typical AD cortex for 30 min without homogenization to avoid breaking up plaques. The soaking extracts were characterized by immunochemical assays, electrophysiology, transmission electron microscopy, and an improved oligomer-preferring ELISA.
Results: Results: Aqueous soaking extracts from AD cortex impaired synaptic plasticity (long-term potentiation) in both the Schaeffer collateral-CA1 pathway and the mossy fiber-CA3 pathway in wild-type mouse hippocampal slices. Immunodepletion of Abeta from the extract or simply co-incubating the extract with oligomer-preferring monoclonal antibodies (mAb) prevented this. High g-force ultracentrifugation (≥250,000g) of the aqueous extracts pelleted virtually all of the oligomeric Abeta signal as measured by an oligomer-preferring ELISA. Immunogold EM of the extracts demonstrated the presence of short, dispersed amyloid fibrils labeled by clinical mAbs, including lecanemab and donanemab. An improved, plate-based, oligomer-preferring ELISA (71A1 capture/3D6 detector) specifically quantified oAbeta in human and AD mouse brain extracts and human CSF and plasma.
Conclusions: Conclusions: A substantial portion of Abeta oligomers diffuse readily from AD cortex, are particulate (fibrillar) by immuno-EM and ultracentrifugation, and impair two forms of hippocampal synaptic plasticity, but the latter functions are prevented by FDA-approved therapeutic antibodies that bind both diffusible and plaque-associated amyloid fibrils.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0017 / #1789

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

IN SILICO INVESTIGATION OF THE ABILITY OF OCTOVESPIN AND FRATERNINE-10 IN DISAGGREGATION OF AB (1-42) AND A-SYNUCLEIN FIBRILS

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Yuri Só[1], Caio Costa[2], Luana Cristina Camargo[3], Márcia Renata Mortari[3], Ricardo Gargano[1]
[1]Universidade de Brasília, Physics, Brasília, Brazil, [2]University of Brasilia, Physics, Brasilia, Brazil, [3]Institute of Biological Science, Department Of Physiology, Brasília, Brazil

Aims: Beta-amyloid (Aβ) and α-synuclein fibrils are hallmarks of neurodegenerative diseases such as Alzheimer's and Parkinson's disease, respectively. Their presence in the brain leads to neurodegeneration and memory decline. Therefore, the search for new drugs that can decrease the formation of such deposits is of great interest. This study investigates two compounds: Octovespin, a peptide modified from Occidentalin-1202, which is a peptide isolated from *Polybia occidentalis* wasp venom, and fraternine-10, a peptide isolated from the venom of the social wasp *Parachartergus fraternus*. In *in vitro* assays, octovespin decreased the aggregation of Aβ. In *in vivo* trials, Octovespin reduced the cognitive deficits in Aβ-induced mice model. *In vitro* investigations of fraternine-10 are still ongoing. Here, we describe the computational approach for investigate the inhibitory activity of octovespin and fraternine-10 against Aβ fibrils (17-42 peptides) and α-synuclein fibrils (38-95 peptides).
Methods: We used molecular docking and molecular dynamics simulations (MD) with 100 ns to study the interactions.
Results: The results indicate that Octovespin and Fraternine-10 can interact with the fibrils for at least 100 ns, with the potential capacity to promote disaggregation.
Conclusions: Our findings can help us understand the characteristics and capabilities of these compounds, as well as their potential as derivatives of wasp venom for disrupting the fibril formation of Aβ and α-synuclein.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0018 / #684

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

TMP21 REGULATES BACE1 MATURATION AND AMYLOIDOGENESIS

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Xiaojie Zhang[1], Zhao Wang[2], Zhe Wang[3], Weihong Song[2]
[1]Central South University, Psychiatry, Changsha, China, [2]Wenzhou Medical University, Institute Of Aging, Wenzhou, China, [3]Xuanwu Hospital, The National Clinical Research Center For Geriatric Disease, Beijing, China

Aims: Amyloid β protein (Aβ) is derived from amyloid precursor protein (APP) by β- and γ-secretase cleavages. BACE1, the β-secretase, cleaves APP at Asp-1 and Glu-11 site to release amyloidogenic C99 and non-amyloidogenic C89, respectively. Transmembrane protein 21 (TMP21) is required for intracellular protein trafficking and maturation. This study aimed to examine the role of TMP21 in AD pathogenesis and its underlying mechanism.
Methods: APP processing was analyzed by Western blot and Aβ level was measured by ELISA. Adeno-associated virus and stereotactic injection were used to express or knockdown TMP21 gene. Behavioral tests were performed to examine the cognitive function of AD transgenic model mice.
Results: TMP21 overexpression increases Aβ generation. Mechanistically, TMP21 overexpression restricts BACE1 maturation by binding to immature BACE1 and retaining it in the endoplasmic reticulum or lipid raft, and then shifts the BACE1 cleavage preference towards Asp-1 to increase amyloidogenic C99 and subsequent Aβ production. Abnormal TMP21 expression lead to accumulation of immature BACE1, increased Aβ secretion and neuritic plaque formation, and exacerbates cognitive dysfunction in AD mice.
Conclusions: Our results demonstrate that TMP21 is a trafficking receptor regulating BACE1-mediated amyloidogenesis and dysregulation of its disorders contribute to AD pathogenesis through affecting BACE1 intracellular trafficking and maturation. Together, our findings reveal a novel mechanism of TMP21 in BACE1 maturation and APP processing, and highlight a close involvement of the lipid raft in AD pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0019 / #304

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

QUANTITATIVE PROTEOMICS REVEALS NOVEL AMYLOID BETA 42 COLLABORATORS ORCHESTRATING AGGREGATION AND TOXICITY

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Arun Upadhyay[1], Deepak Chhangani[2], Nalini Rao[1], Julia Kofler[3], Robert Vassar[1], Diego Rincon-Limas[2], Jeffrey Savas[1]
[1]Feinberg School of Medicine, Northwestern University, Neurology, Chicago, United States of America, [2]University of Florida, Neurology, Gainsville, United States of America, [3]University of Pittsburgh, Pathology, Pittsburgh, United States of America

Aims: Amyloid beta 42 (Aβ42) is the most-studied amyloid forming protein. Aβ42 aggregates are considered most outstanding factor instigating downstream changes in pathways leading to Alzheimer's disease (AD). Aβ42 aggregation primarily is a self-driving phenomenon. However, we do not understand how presence of other proteins affect the aggregation and toxicity of Aβ peptides. Our aim is to identify proteins interacting at very early stage of amyloid aggregation pathway.
Methods: We recently got breakthrough in developing a novel biochemical amyloid purification protocol from mouse or human brain tissues. We used highly pure amyloid fibril cores from multiple sources, including human, mouse, primary rat neurons, and Drosophila, for quantitative (MS3) mass spectrometry analyses followed by a battery of complimentary biochemical and proteomic studies.
Results: Our robust proteomics pipeline identified proteins present in amyloid fibrils obtained from multiple sources. Using different age groups of animal, we can delineate early interaction partners from late binding proteins. Using metabolically labelled (N15) tissue, we can also filter out non-specifically bound proteins as contaminants. To confirm our MS findings we utilized biochemical assays, immunoblots, immunohistochemistry, and ELISA, and immunogold labelling. Additionally, we subjected some of the most interesting protein partners to further investigation using in vitro studies. Many of the proteins can also modify amyloid aggregation and associated toxicity in Aβ42 overexpressing fly models.
Conclusions: Although Aβ peptides can readily aggregate in vitro, their oligomerization and aggregation in human brain is unquestionably influenced by several factors. Very early protein interaction partners collaborating with small Aβ peptides may affect the trajectory and profile of amyloid aggregation and thus the downstream AD-associated pathological changes.

P0020 / #182

Poster Topic: *Theme A: β-Amyloid Diseases / A01.a. Disease Mechanisms, Pathophysiology: Abeta aggregation, protein misfolding*

DEAMIDATION PROTEINS AND AUTOANTIBODIES AGAINST THEM AS NOVEL AD BLOOD BIOMARKERS

POSTERS: A01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ABETA AGGREGATION, PROTEIN MISFOLDING

Roman Zubarev
Karolinska Institutet, Medical Biochemistry & Biophysics, Stockholm, Sweden

Aims: What causes aggregation of Aß and Ptau, the most prominent AD hallmarks? The underlying cause could be the disregulation of protein homeostasis, in particular, of the defence against accumulation of deamidation products. Deamidation is a spontaneous posttranslational modification, in which asparagine residues lose ammonia and attach a water molecule. In the majority of cases, this leads to the formation of the damaging isoaspartyl residue. In isoaspartyl, the backbone is extended by the CH2 group compared to normal amino acid, which destabilizes the native protein structure. This, in turn, decreases the protein solubility, and results in aggregation of long-lived molecules, such as albimin (lifetime in blood ca. 3 weeks). Human serum albumin (HSA) is the most abundant blood protein, and its a major carrier of Aß and Ptau from blood brain barrier to clearance centers (liver and kidneys). Accumulation of deamidated HSA should lead to a bottleneck in clearance, and contribute to aggregation of these damaging molecules in brain. Here we hypothesized that in AD the level of HSA deamidation is significantly higher than in normal blood, while the amount of antibodies against deamidated HSA is significantly lower.
Methods: We used proteomics analysis to measure the isoaspartate level in AD and normal blood. Then created a monoclonal antibody (mAb) sensitive to isoaspartyl in a key position in the HSA molecule, and designed an ELISA based on this mAb. We also artificially aged HSA, inducing extensive deamidation in it, and used this aged HSA (aHSA) as a bait to measure the level of antibodies in blood against it.
Results: Hypothesis was confirmed.
Conclusions: We produced a novel diagnostic tool for early detection of AD risk in form of two complementary ELISAs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0021 / #909

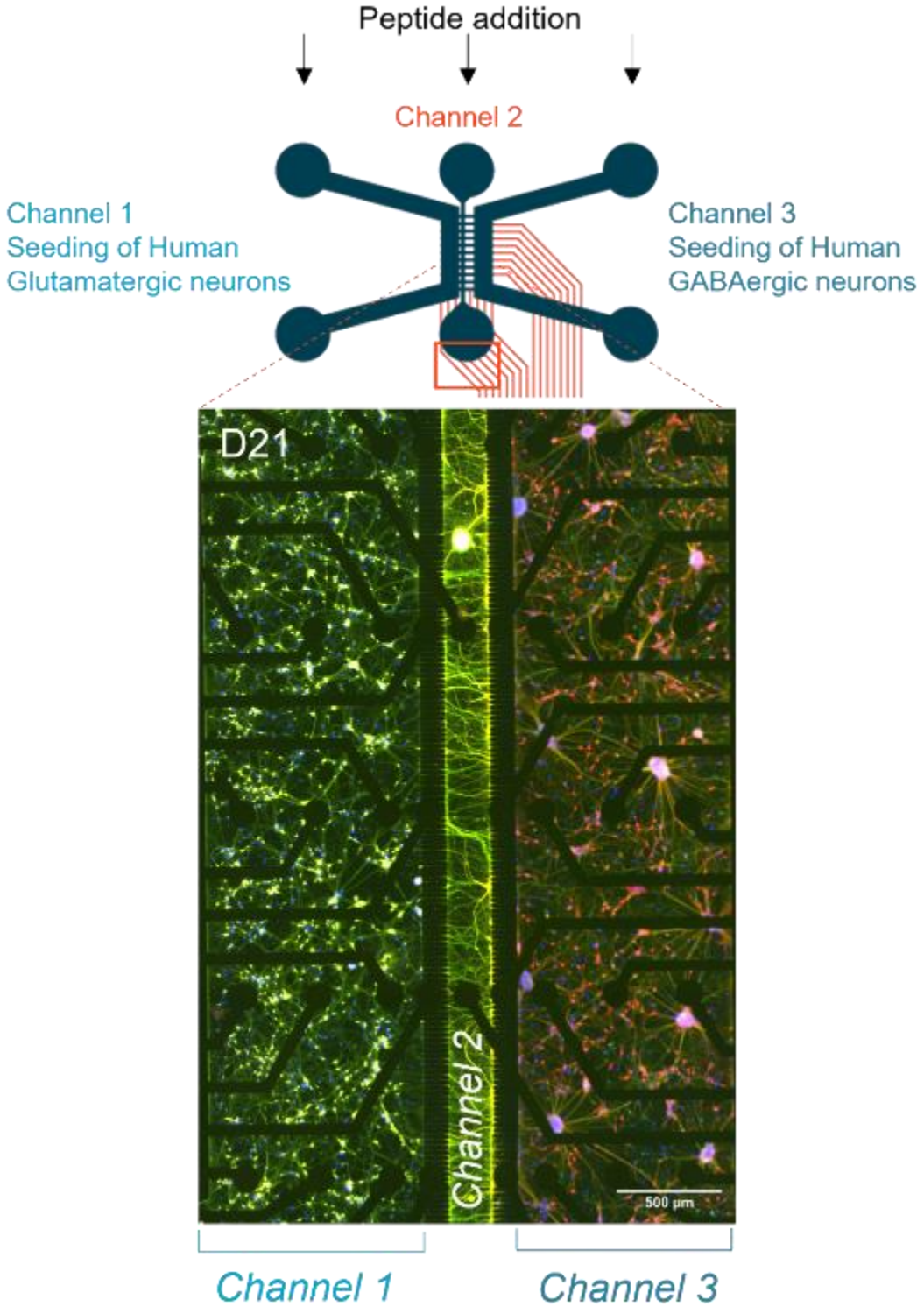
Poster Topic: *Theme A: β-Amyloid Diseases / A01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

BIO-DIAMOND PROJECT: ADVANCING ALZHEIMER'S DISEASE MODELS FOR TARGET VALIDATION AND DRUG DISCOVERY

POSTERS: A01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Ahmad Allouche[1], Louise Miny[2], Sonia Kridi[1], Jessica Rontard[2], Julie Colin[1], Benoît Maisonneuve[2], Nicolas Violle[1], Thibault Honegger[2]
[1]ETAP-Lab, Meurthe Et Moselle, Vandœuvre-lès-Nancy, France, [2]NETRI, Rhône, Lyon, France

Aims: Here, we present a full characterization of the reproducibility of a microfluidic-based hiPSC culture, an essential tool toward developing models of AD that are both physiologically relevant and up to the industry's standards.
Methods: We employed NETRI's DuaLink Shift microfluidic system for co-culture of hiPSC-derived glutamatergic and GABAergic neurons. This innovative device, depicted in the figure, features three compartments for precise isolation of soma, neurites, and synapses via microchannels. In collaboration with ETAP-Lab, we introduced AβO and TauO into a microfluidic co-culture of hiPSC-derived neurons. These oligomers, known for their neurotoxicity, were added at various concentrations and developmental stages. Our approach assesses their impact on different neuron types, replicating key aspects of Alzheimer's
pathology.



Results: We propose a comprehensive characterization of the neuronal populations maintained for several weeks in microfluidic devices, using a range of analytical methods, including immunoassays, immunostaining, and electrophysiological activity assessments. These preliminary data highlight the impacts of the addition of peptides on neuronal activity.

Conclusions: This represents a crucial step in the development of highly relevant, industry-standard models for AD. Such models can serve as indispensable resources for academic research teams and pharmaceutical industries alike, facilitating the elucidation of the pathological mechanisms of Alzheimer's disease and the screening of new effective treatments.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0022 / #415

Poster Topic: *Theme A: β-Amyloid Diseases / A01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

INFLUENCE OF THE APP-BCTF (C99) OLIGOMERIZATION AND EXOSOMAL SPREAD IN ALZHEIMER'S DISEASE

POSTERS: A01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Céline Badot, Inger Lauritzen, Frédéric Checler
CNRS, Ipmc, Sophia Antipolis, Valbonne, France

Aims: The accumulation of C99 was found to cause early Aβ-independent lysosomal-autophagic pathology. Recently, our lab showed that exosomes, small endocytic extracellular vesicles, isolated from AD models are also enriched with both monomeric and oligomeric C99, but the role of C99 oligomerization remains unknown. Since exosomal secretion is known to increase when lysosomal-autophagic degradation is compromised, but also to participate to prion-like transmission of neurotoxic proteins, we hypothesize that particularly C99 oligomers spreading could be neurotoxic. Thus, my aim is to characterize the neo-oligomerization of C99, its toxicity and the exosomal spread of C99 oligomers.
Methods: The bimolecular fluorescence complementation (BiFC) method is a protein interaction assay based on the principle that a fluorescent protein (Venus) is reassembled from its two complementary non-fluorescent N-terminal (VN) or C-terminal (VC) fragments when an interaction occurs between two proteins (C99 tagged with VN or VC) thus giving rise to a yellow fluorescence.
Results: By using biochemical approaches and high-resolution microscopy, we validated inducible C99 BiFC constructs allowing the visualization of C99 neo-oligomerization. Oligomers were found to be formed in the trans-Golgi network and to be trafficked to the endolysosomal system, in which they accumulate in enlarged autophagic compartments reflecting clearance deficits. Moreover, C99 oligomers were less prone to γ-secretase cleavage, supporting a potentiation of Aβ-independent toxicity of oligomers.
Conclusions: Our new BiFC tool allowed us to specifically detect *de novo* C99 oligomerization and a link between oligomers trafficking into the late endosomal system and lysosomal-autophagic toxicity. These results support the perspective of visualizing the exosomal propagation of C99 fluorescent oligomers and their related neurotoxicity. Hopefully, the outcomes of this project will be a step forward in understanding the role of C99 in AD pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0023 / #224

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

INDUCTION OF NEUROINFLAMMATION BY THE DISRUPTION OF GUT MICROBIOTA IN NEURODEGENERATIVE DISEASES.

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Benjamin Adebisi
Institute of Anatomy, Cell Biology, Brain and Neurodegeneration., Functional And Molecular Neurobiology, Osogbo, Nigeria

Aims: The research aims to link how the disruption of gut microbiota triggers proteinopathies in the brain. Impairment of protein metabolism in the brain, such as alpha synuclein and beta amyloid, is responsible for the aggregation. Aggregated proteins alter neuronal functions and such alterations have been indicted in neuronal cell loss in most patients with neurodegenerative diseases such as Parkinson's and Alzheirmer's diseases.
Methods: Literature reviews on the several pathological mechanisms elucidating on the aggregation of proteins were researched and one of such notable biological process is neuroinflammation, which is mediated by the microglia. Microglia are activated in response to immune triggers to foreign materials in the brain.
Results: The triggers responded to by the microglia are Lipopolysaccharides, LPS, a major components in the outer membrane of gram-negative bacteria. These bacteria are migrated from the mucosa of the gastrointestinal tract through the blood stream, endocrine pathways or vagal networks. The gut has several millions of bacteria, which activities maintain the physiological state of system; howbeit, disruption of the microorgasms results in leaky gut, giving allowance for the migration of several bacteria to the central nervous system, bacteria also crosses the blood-brain barrier, giving room for eliciting immune responses, which alter mitochondrial functions and invariably protein aggregation seen in many neurodegenerative diseases. Mitochondrial disruptions have been connected with impairment of lysosomal and proteasomal degradation pathways, causing accumulation of aged organelles and proteinopathies.
Conclusions: Since the culminative effects of neuroinflammation, mitochoindrial dysfunction and protein aggregation are pathological processes in neuodegenerative diseases linked to the microbial components and balance in the gut, it is imperative that management of these diseases are looked into through maintaining healthy microbial population in the gastrointestinal system by the use of probiotics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0024 / #1848

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

EXTRACELLULAR ATP AS DETERMINANT OF MICROGLIA ACTIVATION AND NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Nikita Arnst[1], Martina Bedetta[1], Simonetta Falzoni[2], Dorianna Sandonà[1], Nelly Redolfi[1], Annamaria Lia[1], Elisa Greotti[1,3,4], Francesco Di Virgilio[2], Paola Pizzo[1,3,5]
[1]University of Padova, Department Of Biomedical Sciences, Padua, Italy, [2]University of Ferrara, Department Of Medical Sciences, Ferrara, Italy, [3]Italian National Research Council (CNR), Neuroscience Institute, Padua, Italy, [4]University of Padova, Padova Neuroscience Center (pnc), Padua, Italy, [5]University of Padova, Centro Studi Per La Neurodegenerazione (cesne), Padua, Italy

Aims: Alzheimer's disease (AD) is a neurodegenerative disease that still lacks an effective cure. Recently, the presence of activated microglia in histological samples of AD brains supports the hypothesis that inflammation might play a central role as a trigger of neuronal damage. In this context, microglia are one of the main targets of extracellular ATP (eATP), a molecule involved in the activation and propagation of neuroinflammation. To establish the role of eATP as a determinant of microglia activation and neuroinflammation we started by characterizing both microglia reactivity and the inflammatory state of the PS2APP (line B6.152H) mouse model of AD.
Methods: We performed a morpho-functional analysis of microglia in the somatosensory cortex (SSCx) of WT and AD mice at 2-, 6-, and 9 months using confocal microscopy and Imaris software. We used Iba1 to stain microglia, coupled with Lamp2 and vGLUT1/2 staining to assess microglia pruning activity. We performed also a western blot analysis of NLRP3 to assess a possible early activation of the inflammasome.
Results: 3D images of microglia stained with Iba-1 showed less branching morphology in AD mice at all time points. Also, LAMP2-positive structures volume, as well as vGLUT1/2 volume in Iba-1 positive cells in AD mice, were increased, indicating higher microglia pruning activity during the early disease stages. We found a significant increase in NLRP3 levels in 2-month-old AD mice.
Conclusions: We reveal an early activation of microglia in the SSCx of PS2APP mice. Indeed, Iba-1 reactivity and microglia pruning activity are higher in AD mice at 2 months of age, thus well before the surge of both plaque deposition and cognitive deficits. We aim to measure eATP in the brain at the same time points.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0025 / #792

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

THE PROGRESSION OF ALZHEIMER'S DISEASE IN THE HUMAN BRAIN: RNA DYNAMICS IN INFLAMMATION, NEUROTRANSMISSION AND OLIGODENDROCYTES

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Aurélien Badina[1], Stergios Tsartsalis[1,2], Kelly Ceyzériat[2,3,4], Alexandre Tresh[1], Léa Guenat[1], Quentin Amossé[1,2], Laurene Abjean[2,3,4], Philippe Millet[1,2], Benjamin Tournier[1,2]
[1]University of Geneva, Psychiatry, Geneva, Switzerland, [2]University Hospitals of Geneva, Psychiatry, Geneva, Switzerland, [3]University of Geneva, Cibm Center For Biomedical Imaging, Geneva, Switzerland, [4]University of Geneva, Laboratory Of Child Growth And Development, Geneva, Switzerland

Aims: We are investigating the human brain's adaptive response to Alzheimer's Disease (AD) progression by examining the dynamics of specific pathways and gene expressions, integrating RNA quantification and protein analyses across two distinct cohorts.
Methods: The first cohort comprises 30 fresh-frozen human post-mortem hippocampal samples, divided into age- and sex-matched groups of non-neurological controls (n=7), early AD (Braak 4, n=12), and advanced AD (Braak ≥5, n=11). We analyzed 770 RNA strands using a NanoString nCounter panel and explored neuroinflammation, neurotransmission, and myelin metabolism pathways. Western Blot analyses were conducted on hippocampal proteins from the same subjects. The confirmation cohort encompasses 30 FFPE human hippocampi (n=6/group, age- and sex-matched), with young controls, controls with and without Amyloid-β deposits, Braak 4, and Braak 6 subjects. Immunofluorescence on the confirmation cohort is being performed to investigate cross-pathway gene involvement.
Results: Comparing RNA levels of Braak 4 to Controls revealed 36 differentially expressed genes (11 up and 25 downregulated, with 4 overlapping with GWAS), whereas Braak 6 to Braak 4 showed 278 (54 up and 224 downregulated, 21 overlapping with GWAS) and Braak 6 to Controls revealed 349 (87 up and 262 downregulated, 24 overlapping with GWAS). Early AD showed an upregulation of inflammatory pathways and a downregulation of myelin synthesis pathways. These pathways were inversely altered in advanced AD without reverting to control levels. Neurotransmission pathways were consistently downregulated.
Conclusions: We show a strong inflammatory response in early AD stages that diminishes as the disease progresses, while the myelin metabolism pathways show the opposite pattern. It suggests an association between the two pathways, supported by GWAS data, and could shed light on damages of neuroinflammatory's peak response and diminution. [SNSF grant: 310030_212322]

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0026 / #213

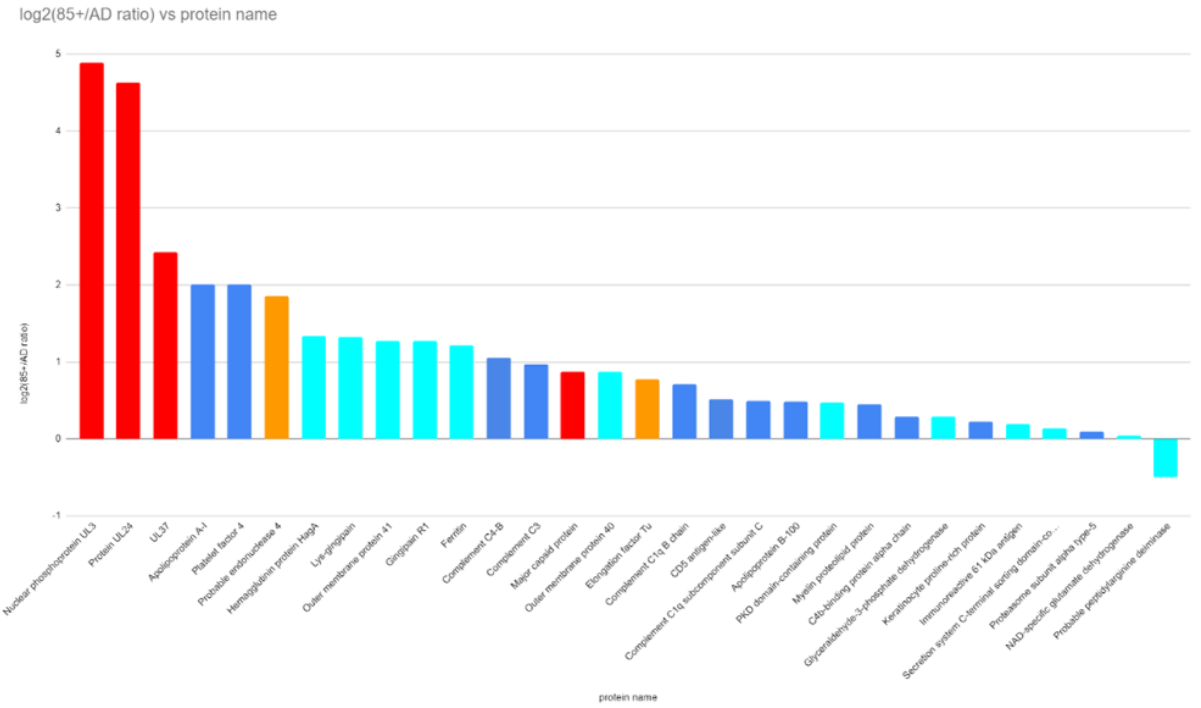
Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

PROFILING IMMUNOLOGIC RESPONSE TO PATHOGENS IN POPULATIONS: ELDERLY POPULATION WITH OR WITHOUT ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Omer Bender, Daniel Bar
Tel Aviv University, Faculty Of Medicine, Tel Aviv, Israel

Aims: Alzheimer's disease (AD) has been associated with several pathogens. Specifically, Herpes simplex 1 virus (HSV-1), Chlamydia Pneumoniae (CP) and the periopathogenic bacteria Porphyromonas gingivalis (PG) has been demonstrated in the brain of AD patients and causally linked to pathological cleavage of the APP to form the insoluble Aβ1–42 peptides, one of the pathological hallmarks in AD. While exposure to PG and HSV-1 are prevalent, only a portion of affected individuals will develop AD. We propose that specific immune responses modulate the risk of developing AD following exposure to CP, PG, HSV-1 or other AD-associated pathogens.
Methods: We will test this hypothesis by screening blood for antibodies against CP, PG, HSV-1 and brain tissue auto-antibodies. The immune response of No-AD, AD patients and younger controls to various pathogens will be measured. We will identify which pathogenic proteins are recognized by the immune system of each subject, using proteomics, and test for a differential immune response to surface markers and virulence proteins and build a predictive model of immune-dependent AD-avoidance.
Results: Among the proteins identified by the adaptive immune system are those found by previous studies to penetrate the blood brain barrier and novel proteins associated with AD (Figure1).



Conclusions: We had shown differential immune response virulence proteins preferentially bound by the AD group suggesting an immune protective role for antibodies to these pathogens' proteins. The low and ineffective antibody counts of the AD patients might enable the pathogens to colonise brain tissue and promote local inflammation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0027 / #731

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

THE INFLUENCE OF FORMYL PEPTIDE RECEPTORS ON AMYLOID BETA SENSING IN GLIA AND IMMUNE CELLS

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Lukas Busch, Bernd Bufe
University of Applied Sciences Kaiserslautern, Department Of Informatics And Microsystems Technology, Zweibrücken, Germany

Aims: Recent research on Alzheimer's Disease (AD) discovered over 100 structurally diverse Aβ peptides, of which so far only $Aβ_{1-42}$ and $Aβ_{1-40}$ are well characterized. We could recently identify $Aβ_{1-42}$, $Aβ_{1-40}$ but also $Aβ_{11-40}$ and $Aβ_{17-40}$ as sensitive activators of formyl peptide receptors (FPRs), a small gene family of immune receptors, comprising three members. In this study we investigated the biological effects and structural basis of Aβ interactions on FPRs in glia and primary human immune cells.
Methods: • Calcium imaging experiments • Chemotaxis assays • ERK phosphorylation assays
Results: FPR1 displayed over tenfold higher sensitivity to $Aβ_{11-40}$ and $Aβ_{17-40}$ than to $Aβ_{1-42}$. Glial U87 cells strongly responded to $Aβ_{11-40}$ and $Aβ_{17-40}$ in calcium imaging experiments, driven by FPR1 activation. In chemotaxis assays, only $Aβ_{11-40}$ but not $Aβ_{17-40}$ induced cell migration, indicating functional bias among Aβ peptides. In primary human neutrophils and mouse astrocytes $Aβ_{11-40}$ and $Aβ_{17-40}$ elicited FPR-dependent signaling, arguing for a physiological significance of FPRs in Aβ sensing. To investigate the structural basis of the biased Aβ signals, we systematically screened fragmented peptides spanning the complete Aβ sequence and identified two motifs that induced subtype-specific responses through FPR1 and FPR3. Both motifs prompted ERK-phosphorylation in U87 cells, but only the FPR1-specific agonist initiated chemotaxis, highlighting FPR-subtype dependent differences in signal transduction of glia responses.
Conclusions: We here identified $Aβ_{11-40,}$ and $Aβ_{17-40}$ as novel activators of FPR1 in glia and immune cells. We show that Aβ binding motifs differ between FPR-subtypes and trigger Aβ variant-selective effects. Given that the composition of Aβ variants can drastically differ in-between patients non-canonical Aβ sensing by FPRs may contribute to the complexity of glial cell responses and the strong variance in the pathological progression of AD between patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0028 / #818

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

INVESTIGATING THE REGULATION OF THE NLRP3 INFLAMMASOME IN ASC-DEPENDENT AND ASC-INDEPENDENT PATHWAYS OF ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Shilauni Dadwal[1,2], Michael Heneka[2]
[1]University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Esch-Belval Esch-sur-Alzette, Luxembourg, [2]Université du Luxembourg, Lcsb, Belvaux, Luxembourg

Aims: The inflammasome is a protein complex that activates caspases, leading to inflammation in response to various stimuli, including microorganisms and protein aggregates of e.g. amyloid-β, and tau. Among the numerous studied inflammasomes, NLRP3 has been extensively investigated due to its well-described activation mechanism. To develop targeted therapies for inflammatory disorders, it is crucial to fully understand how various molecules and signaling pathways activate and regulate the assembly of NLRP3 inflammasomes. So far in literature kinases like NEK7, MARK4, GBP5, PKR, AKT, and BTK are known to regulate the NLRP3 inflammasomes. In our project, we are focusing on the interactions between these kinases and what are the other factors involved in the activation, inhibition, and regulation of NLRP3. We are also focusing on the potential interactions of these regulatory factors within ASC-dependent and ASC-independent pathways. So far, data shows the increased expression of NLRP3 upon external stimuli which is the very first step towards studying the regulation of NLRP3 inflammasome in murine and human models.
Methods: In our study, we assessed the expression of NLRP3, ASC, interleukins (IL-1beta and IL-18), and kinases (NEK7, MARK4, GBP5, PKR, AKT, BTK) in various models, like primary microglia, Raw macrophages 264.7, THP-1, BV2 cell lines, iPSCs and APP mouse models upon treatment with lipopolysaccharide (LPS) and nigericin. Subsequently, we employed immunocytochemistry, ELISA, and Western blot techniques for further analysis.
Results: Our investigations have so far demonstrated an increased expression of NLRP3 and ASC in samples subjected to LPS and nigericin treatments compared to controls across primary microglia, Raw macrophages, THP-1, and BV2 cell lines.
Conclusions: Our ongoing studies have revealed an upregulation of NLRP3 and ASC expression. Additionally, we are exploring the expression of interleukins and kinases after the treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0029 / #2022

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

POLYUNSATURATED FATTY ACID METABOLISM IN THE ALZHEIMER'S BRAIN AND THE INFLUENCE OF APOE4

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Brandon Ebright[1], Dante Dikeman[1], Isaac Asante[1], Shaowei Wang[2], Stan Louie[1], Hussein Yassine[2]
[1]USC Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences, Clinical And Experimental Therapeutics, Los Angeles, United States of America, [2]University of Southern California, Neurology, Los Angeles, United States of America

Aims: To determine how fatty acid metabolism in the brain changes with Alzheimer's disease (AD) progression, the influence of the APOE4 allele, and how it contributes to neuroinflammation.
Methods: In postmortem human brains from the Religious Order Study (n=198), polyunsaturated fatty acids (PUFA) and their eicosanoid metabolites were quantified using a targeted LC-MS/MS assay. The brain levels of bioactive lipids were compared between persons with no cognitive impairment (NCI), mild cognitive impairment (MCI) and AD dementia, and stratified by APOE genotype and sex.
Results: Lipidomic analysis of human cortex tissue revealed higher levels of n-6 arachidonic acid (AA) and lower levels of n-3 PUFAs such as eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA) in APOE4-carriers with AD (**Figure 1**). The endogenous precursors to n-3 PUFAs, α-linolenic acid (ALA) and stearidonic acid, were significantly higher in APOE4 non-carriers with AD but did not change in APOE4-carriers (**Figure 2**). Downstream AA metabolites formed through lipoxygenase (LOX) activity such as 5-HETE and 15-HETE were lowest in brains with AD and consistently lower in APOE4-carriers regardless of disease state (**Figure 3**). This downregulation in LOX-mediated metabolism also appeared to be influenced by sex, where males had the greatest reduction in LOX metabolites. Alternatively, the cyclooxygenase (COX) pathway was promoted with disease progression, evidenced by higher levels of the inflammatory mediator thromboxane B2 (TXB2) in brains with MCI and APOE4-carriers with AD. **Figure 1:**

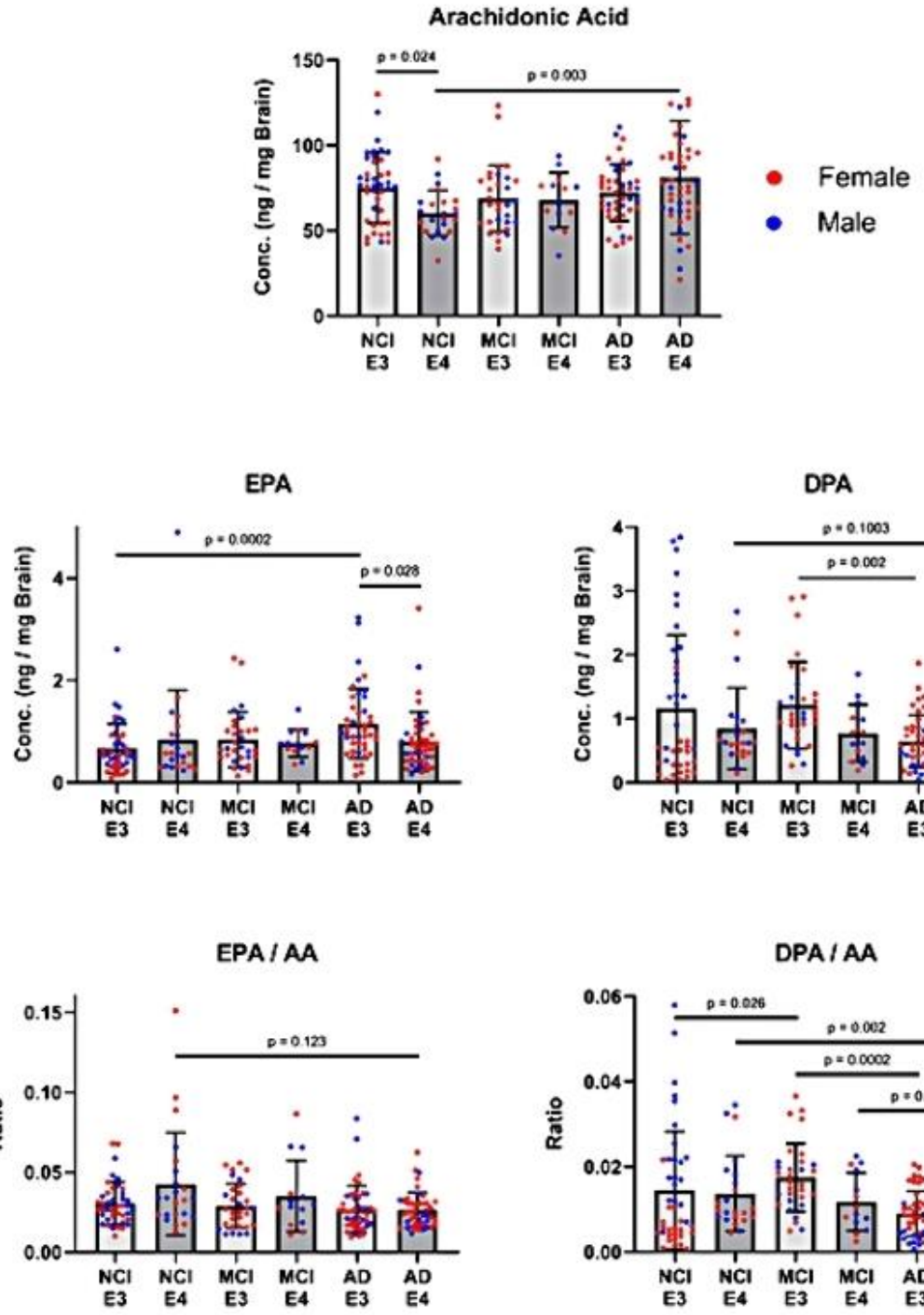

Arachidonic Acid
Conc. (ng / mg Brain)
p = 0.024
p = 0.003
Female
Male
EPA
p = 0.0002
p = 0.026
DPA
p = 0.1003
p = 0.002
EPA / AA
Ratio
p = 0.123
DPA / AA
p = 0.026
p = 0.002
p = 0.0002
p = 0.093
NCI E3
NCI E4
MCI E3
MCI E4
AD E3
AD E4

Figure 2:

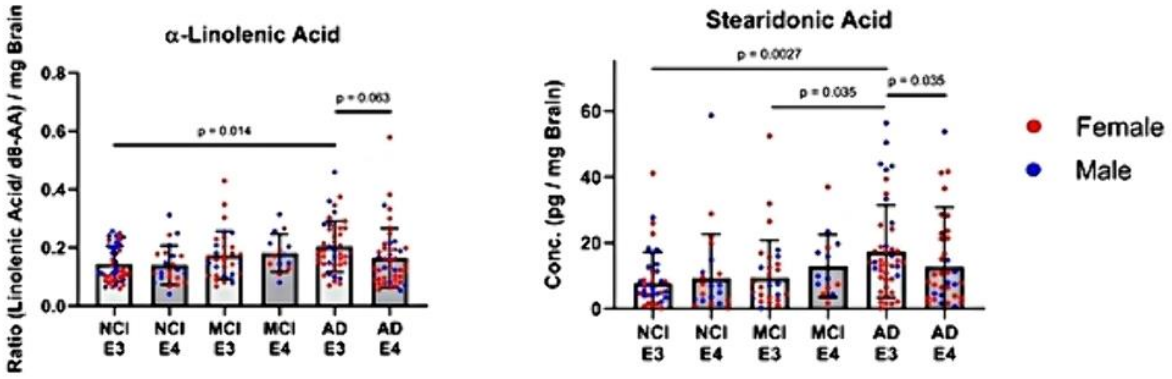
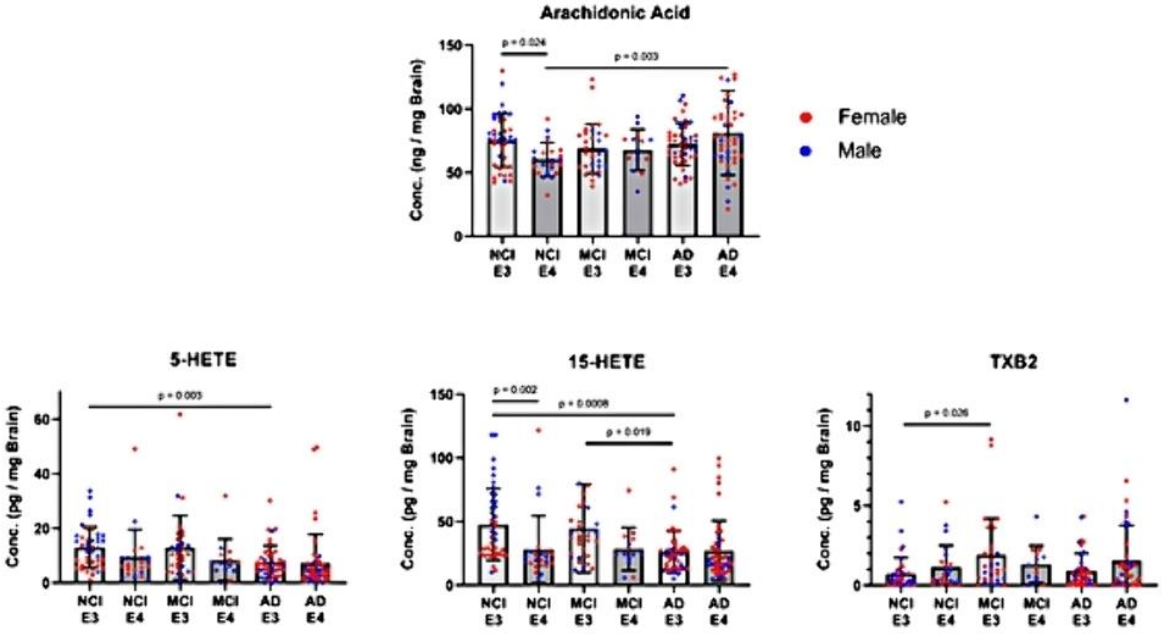


Figure 3:



Conclusions: These findings suggest that brains with AD have increased calcium-dependent phospholipase A2 (cPLA2) activation, promoting higher levels of AA and inflammatory eicosanoids. Furthermore, the cPLA2 activation, suppression of endogenous n-3 PUFA production, and suppression of LOX activity are exacerbated in APOE4-carriers and appear to be influenced by sex.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0030 / #2602

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

TREM2 IS DOWN-REGULATED BY HSV1 IN MICROGLIA AND INVOLVED IN ANTIVIRAL DEFENSE IN THE BRAIN.

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Stefanie Fruhwürth[1], Line Reinert[2], Carl Öberg[1], Marcelina Sakr[1], Marcus Henricsson[3], Henrik Zetterberg[4], Sören Paludan[2]
[1]Sahlgrenska Academy, Institute of Neuroscience and Physiology, Department Of Psychiatry And Neurochemistry, Göteborg, Sweden, [2]Aarhus University, Department Of Biomedicine, Aarhus, Denmark, [3]AstraZeneca, Biomarker Discovery And Development, Mölndal, Sweden, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: The aim of this study was to explore how herpes simplex virus type 1 (HSV1) modulates gene expression in human microglia and to determine the functional impact on control of HSV1 infection.
Methods: Here, we have used human induced pluripotent stem cell (hiPSC)-derived models of microglia and cortical neurons as well as Trem2-/- mice to study innate immune sensing of HSV1 by microglia, antiviral mechanisms, and control of HSV1 infection.
Results: Here, we report that HSV1 infection of hiPSC–derived microglia down-regulates expression of genes in the TREM2 pathway. TREM2 was found to be important for virus-induced *IFNB* induction through the DNA-sensing cGAS-STING pathway in microglia and for phagocytosis of HSV1-infected neurons. Consequently, TREM2 depletion increased susceptibility to HSV1 infection in human microglia–neuron cocultures and in the mouse brain. Thus, TREM2 is important for the antiviral immune response in microglia.
Conclusions: Our data further support the idea of the essential role for microglia in early antiviral defense and provide mechanistic insight into the virus-cell interactions that govern the outcome of HSV1 infection in the brain. Since *TREM2* loss-of-function mutations and HSV1 serological status are both linked to Alzheimer's disease, this work poses the question whether genetic or virus-induced alterations of TREM2 activity predispose to post-infection neurological pathologies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0031 / #2083

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

DECIPHERING THE ROLE OF A BRAIN-SPECIFIC LNCRNA IN AD-RELATED NEUROINFLAMMATION

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Ulrike Fuchs[1], Sophie Schröder[1], André Fischer[2]
[1]German Center for Neurodegenerative Diseases, Epigenetics And Systems Medicine, Göttingen, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), University Medical Center Göttingen, Psychiatry And Psychotherapy, Göttingen, Germany

Aims: Long non-coding RNAs (lncRNAs) are emerging as important regulators of neuronal plasticity and have recently been linked to the onset and progression of neurodegenerative diseases. However, our knowledge about the role of lncRNAs in neuronal and non-neuronal cells is still limited. The aim of this project was to identify cell type-specific expression changes of non-neuronal lncRNAs in the context of AD-related neuroinflammation and to characterize their function.
Methods: To this end, we performed an RNA sequencing-based screening of differentially expressed lncRNAs in primary astrocytes following their activation. We identified multiple candidate lncRNAs for further analysis and studied their role via loss of function approaches.
Results: Our data reveal that one brain-specific lncRNA candidate is de-regulated in amyloid-beta activated astrocytes and regulates inflammatory pathways and synapse homeostasis. Knockdown of this lncRNA was sufficient to induce a neuroinflammatory phenotype in primary astrocytes. Furthermore, we found that this lncRNA was also de-regulated in human AD data sets.
Conclusions: Since lncRNAs are often cell-type and tissue specific, they provide an optimal therapeutic target with less side effects, compared to other target structures. Thus, our lncRNA candidate could serve as a novel biomarker for AD-related neuroinflammation and a target for therapeutic interventions via RNA-based medicines.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0032 / #2064

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

AMYLOID-BETA EVASION BY NEUROTROPIC PATHOGENS BORRELIA BURGDORFERI AND STREPTOCOCCUS PNEUMONIAE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Pavel Uvarov[1], Lilith Heiland[1], Alexander Moir[2,3], Anna Maaser-Hecker[2,3], Daan Cox[1], Taru Meri[4], Deepak Kumar[2,3], Rudolph Tanzi[2,3,5,6], Karita Haapasalo[1,2,3]
[1]University of Helsinki, Bacteriology And Immunology, Helsinki, Finland, [2]Mass General Institute for Neurodegenerative Disease, Massachusetts General Hospital, Genetics And Aging Research Unit, Department Of Neurology, Charlestown, United States of America, [3]Harvard Univeristy, Harvard Medical School, Boston, United States of America, [4]University of Helsinki, Faculty Of Biological And Environmental Sciences, Helsinki, Finland, [5]Massachusetts General Hospital, Mccance Center For Brain Health, Boston, United States of America, [6]Henry and Allison McCance Center for Brain Health, Department Of Neurology, Boston, United States of America

Aims: Amyloid-beta is toxic to neurons and, in excess, can trigger Alzheimer's disease. It has also been shown to protect the brain from infectious agents invading the central nervous system. Pathogenic microbes have, however, evolved to evade the innate immune system facilitating microbial spread in host tissues. While evasion of the complement system has been described to be a common trait on pathogens, little is known about microbial amyloid-beta evasion. The aim of this study is to determine whether microbes have evolved strategies to evade this emerging mechanism of innate immunity involving host defense peptides such as amyloid-beta.
Methods: Binding of synthetic and cell derived amyloid-beta to bacteria and several microbial molecules was assessed by ELISA, Western blotting, and electron microscopy. Bacterial culturing was used to study survival of *Borrelia* when challenged with amyloid-beta 1-42. 3D human neural cell cultures were used for modeling the effect of multiple interactions between amyloid-beta, bacteria and innate immune molecules in a pathological microenvironment.
Results: We identified novel putative amyloid-beta-binding proteins from multiple bacterial species. Binding of synthetic amyloid-beta 1-42 to *Borrelia hermsii* reduced its survival. However, *Borrelia burgdorferi,* responsible for Lyme neuroborreliosis, exhibited resistance to synthetic amyloid-beta and amyloid-beta in 3D cultures. Increases in cytokine levels and reduction of soluble amyloid-beta in 3D cultures were detected in the presence of several pathogens but not in cultures infected with neurotropic pathogens, *B. burgdorferi* and *Streptococcus pneumoniae*.
Conclusions: Results indicate amyloid-beta's target specificity in binding to microbial molecules and reducing their survival. The molecular mechanism by which some pathogens evade amyloid-beta entrapment and whether this trait, exploited by restricted species of bacteria, could be related to neuroinflammation and amyloid-beta plaque formation characteristic to Alzheimer's disease warrants further investigation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0033 / #3008

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

APOE4 INDUCES AN ADAPTIVE IMMUNE RESPONSE IN MICE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Sem Halters, Elga De Vries, Jan Van Den Bossche, Lynn Van Olst, Daniëlle Wessels, Willem Van De Zande, Carla Rodriguez-Mogeda, Juan Garcia-Vallejo
Amsterdam UMC, location VU, Medical Cell Biology And Immunology, Amsterdam, Netherlands

Aims: Recent studies indicated that the peripheral immune system is dysregulated in early stages of Alzheimer's disease (AD). APOE4 is the most important known genetic risk factor for developing late-onset AD. The role of APOE4 on the central immune system has been studied extensively, whereas we don't know its effect on the peripheral immune system yet. Therefore, we wanted to study the peripheral immune landscape of APOE3 and APOE4 targeted replacement mice.
Methods: We performed mass cytometry on the splenocytes of 6 month old APOE3 and APOE4 targeted replacement (TR) mice. By using immunohistochemistry, we checked for the presence of immune cells in the brain and changes on the brain vasculature of APOE3-TR and APOE4-TR mice.
Results: We observed an adaptive immune response in APOE4-TR mice, based on increased numbers of activated B cells and a shift from naïve and effector $CD8^+$ T cells towards memory CD8 T cells. On top of that, both regulatory $CD4^+$ T and regulatory B cell populations were enriched in APOE4-TR mice. Interestingly, memory $CD8^+$ T cells in APOE4-TR also expressed lower levels of the checkpoint inhibitors, PD-1, PD-L1, and LAG-3, and higher levels of the tissue-resident marker CD103. In APOE4-TR mice, $CD8^+$ T cells were also able to infiltrate the brain via the corpus callosum. Potentially mediated by a decrease in the tight junction molecule Claudin-5 on the brain vasculature.
Conclusions: Taken together, we discovered that human APOE4 induces an adaptive immune response in mice. APOE4 induced changes in memory $CD8^+$ T cells are mainly associated with tissue-residency and lower T cell exhaustion. It seems that changes on the brain vasculature in APOE4-TR mice allow $CD8^+$ T cells to accumulate in the corpus callosum.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0034 / #1767

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

DEVELOPMENT OF NEW HUMAN MODELS TO STUDY THE ROLE OF COMPLEMENT IN NEURODEGENERATION

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Ashley Comer[1], Fabrizio Pontarelli[1], Gregory Wirak[1], Soumya Nair[2], Vaishnavi Rajagopal[2], Dimitry Ofengeim[1], Timothy Hammond[1]
[1]Sanofi, Rare And Neurologic Diseases, Cambridge, United States of America, [2]Sanofi, Immunology And Inflammation, Cambridge, United States of America

Aims: Complement overactivation has emerged as a key mechanism in neurodegenerative disease, and in mouse models of Alzheimer's disease genetic or therapeutic inhibition of the complement pathway reduces synapse loss, prevents neuron death and improves cognition. Despite this data, the mechanisms driving complement-induced neural dysfunction in the human brain are not fully understood.
Methods: Complement proteins vary substantially between rodent and humans, so we have developed human *in vitro* iPSC models and humanized *in vivo* mouse models to bridge the gap.
Results: We show in a human iPSC-derived brain tri-culture system with motor neurons, microglia and astrocytes that complement deposition on neurons disrupts firing as measured by calcium imaging and MEA recordings, and that this effect is caused by complement sub-lytic activation of membrane attack complex (MAC) pores. In addition, complement activation increased human synaptosome engulfment by iPSC microglia, suggesting a dual role for the pathway in disrupting neural connectivity. We also developed a humanized complement mouse model in which human complement-preserved serum is injected into the mouse striatum. We show that serum injection into the mouse brain leads to human complement activation and deposition on mouse neurons. This model will be critical to test human-specific complement inhibitors in the mouse brain, where additional functional readouts can be measured.
Conclusions: Modulating complement components or their regulators holds promise for controlling neuroinflammation and preserving neuronal function in neurodegenerative disease, and these models will help pave the way for novel therapeutic development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0035 / #1123

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

THE CHOROID PLEXUS IS AN IMMUNOLOGICAL RHEOSTAT FOR THE HUMAN CENTRAL NERVOUS SYSTEM

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Ryan Hobson, Samuel Levy, Andrew Teich, Neil Shneider, Elizabeth Bradshaw, Wassim Elyaman
Columbia University, Neurology, New York, United States of America

Aims: Analyze the phenotype of adaptive and innate immune cells and their dynamics at the brain's borders in directly modulating neuroinflammation in neurodegenerative diseases.
Methods: Here, we performed single-cell RNA and T cell receptor (TCR) sequencing on 142,521 immune cells isolated from fresh human postmortem choroid plexus and paired leptomeninges and brain parenchyma from several neurodegenerative conditions including late-onset Alzheimer's disease (LOAD), Parkinson's and amyotrophic lateral sclerosis (ALS) (n=67 sequenced samples).
Results: Comparing the TCR repertoires between meninges and choroid plexus from the same donor revealed completely independent resident T cell TCR sequences, suggesting that T cells in these two tissues respond to different antigen triggers and likely serve divergent functions. Indeed, comparing the RNA expression profiles of key immune populations across the meninges and choroid plexus revealed divergent roles and a preference for wound-healing and regulatory gene programs in the choroid plexus. Interestingly, we also found that choroid plexus CD8 T cells are a prominent source of IFNγ and likely contribute to choroid plexus barrier disruption and immune cell chemotaxis across the blood-CSF barrier. Importantly, we identified a population of tissue resident NK cells in the choroid plexus that may play a role in eliminating IFNγ-producing CD8 T cells and therefore maintaining barrier integrity.
Conclusions: These results suggest that unlike the meninges which supply T cells to the brain from a population of tissue resident T cells, the choroid plexus immune interface serves as a local rheostat for immune cell migration across the blood-CSF barrier. Work is currently underway to identify the factors that drive immune cell residency in the choroid plexus, especially tissue resident NK cells and CD8 T cells, which could reveal druggable targets for broadly controlling neuroinflammation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0036 / #803

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

USING SINGLE-MOLECULE AND SUPER-RESOLUTION METHODS TO INVESTIGATE THE LINK BETWEEN ASC AND AMYLOID-B IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Beatrix Huissoon[1], Giulia Albertini[2], Emre Fertan[1], John Danial[1], Jeff Lam[1], Bart De Strooper[2], David Klenerman[1]
[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]KU Leuven & VIB, Center For Brain & Disease Research, Leuven, Belgium

Aims: It is now believed that small, 'oligomeric' aggregates of amyloid β (Aβ) are the primary sources of toxicity and responsible for neuronal loss in Alzheimer's disease. Understanding of how these aggregates cause toxicity and how the brain responds to them is still limited. We investigated the effect of injected oligomers of human Aβ on inflammatory responses in mouse brains. This could provide further insight into the amyloid cascade and oligomeric toxicity.
Methods: The left ventricles of 2-month-old wild-type C57BL/6 mice were injected with human Aβ1-42 oligomers (oAβ) or scr, a scrambled form of Aβ. They were then sacrificed at 2, 6, 12, 24, 48, 72 and 96 hours (n≥3). Another set of mice were first fed a diet containing Pexidartinib (PLX3397) for 3 weeks to deplete their microglia, then injected as before and sacrificed at 6, 24, 72 and 96 hours. Single molecule imaging using SiMPull assays were performed, alongside super-resolution analysis with DNA-PAINT to assess differences in size and shape of aggregates.
Results: Single molecule imaging methods were able to show a microglia-dependent increase in ASC (inflammasome adapter) levels in response to injection of oAβ, with a subsequent increase in endogenous Aβ production. Also, evidence has been found that microglia are responsible for the clearance of oAβ. Using super-resolution techniques, a higher proportion of larger Aβ aggregates are seen with oAβ injection compared to the control, with differences in ASC size and shape also found.
Conclusions: These data provide evidence to support the idea that small, oligomeric aggregates of Aβ can trigger inflammatory responses in mouse brains, which is largely dependent on the presence of microglia. The associated increase in mouse Aβ production also provides some support for the amyloid cascade hypothesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0037 / #249

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

LONGITUDINAL EFFECTS OF CAREGIVING BURDEN ON INFLAMMATORY BIOMARKERS IN SPOUSAL CAREGIVERS OF INDIVIDUALS WITH COGNITIVE IMPAIRMENTS

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

So Yeon Jeon[1,2]
[1]Chungnam National University College of Medicine, Psychiatry, Daejeon, Korea, Republic of, [2]Chungnam National University Hospital, Psychiatry, Daejeon, Korea, Republic of

Aims: Caring for spouses with cognitive impairments presents significant emotional and physiological challenges. This study longitudinally examined the correlation between neuropsychiatric symptoms, as assessed by the Neuropsychiatric Inventory (NPI), and the levels of the inflammatory biomarker Oxidized Low-Density-Lipoprotein Receptor-1(OLR1) in spousal caregivers.
Methods: From May 2020 to May 2023, patients visiting the Chungnam National University Hospital Geriatric Neuropsychiatric Clinic with their spouses underwent clinical evaluations and blood tests. The study involved twenty spousal caregivers of individuals with diagnosed cognitive impairments, who completed baseline and one-year follow-up assessments. NPI scores were utilized to evaluate neuropsychiatric symptoms at baseline and after 12 months. Correspondingly, blood samples were collected at both time points to measure OLR1 levels. Longitudinal analyses, adjusted for age, sex, and baseline cognitive status, were utilized to scrutinize the evolving relationship between NPI scores and OLR1 levels.
Results: Preliminary data indicate a significant positive correlation between baseline NPI scores and OLR1 levels (p=0.038). Moreover, over a year, alterations in NPI scores were positively correlated with fluctuations in OLR1 levels (p=0.017). Spousal caregivers who reported an escalated care-recipient burden demonstrated a consistent increase in OLR1 levels throughout the 12-month observation period.
Conclusions: The results indicate that the neuropsychiatric challenges associated with caregiving might be linked with heightened inflammatory responses, as reflected by OLR1 levels. This correlation provides a deeper understanding of the physiological pathways potentially influenced by the stressors associated with caregiving for spouses with cognitive impairments. The potential ramifications on caregivers' cognitive and cardiovascular health necessitate further investigation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0038 / #2418

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

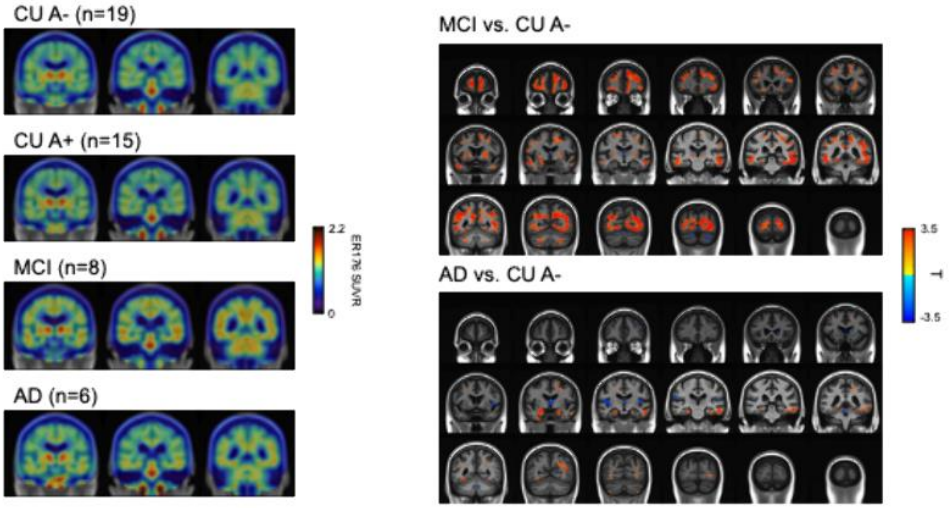
NEUROINFLAMMATION IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Mahathi Kandimalla[1], Jeyeon Lee[1], Paul Min[1], Hugo Botha[2], Jonathan Graff-Radford[2], David Jones[2], Prashanthi Vemuri[1], Kejal Kantarci[1], David Knopman[2], Clifford Jack[1], Ronald Petersen[2], Val Lowe[1]
[1]Mayo Clinic, Department Of Radiology, Rochester, United States of America, [2]Mayo Clinic, Department Of Neurology, Rochester, United States of America

Aims: Neuroinflammation leads to the direct demise of neurons, reduced synaptic activity, and suppression of neurogenesis in the hippocampus— making inflammation a critical factor in the progression of Alzheimer's Disease (AD). ER176 is a 3rd generation, PET neuroinflammation radiotracer that may help identify suitable candidates for specialized treatment when adversely impacted by neuroinflammation. ER176 has advantages over other radiotracers with its increased specific binding, reduced variability between subjects, capability to image low-affinity binders, and low radio metabolites entering the brain. We assessed ER176 detection of neuroinflammation in selected participant groups.
Methods: Participants from the Mayo Clinic Study of Aging were recruited for this study. The study included four participant groups: cognitively unimpaired with normal amyloid (CU A-, n=19), cognitively unimpaired with high amyloid (CU A+, n=15), mild cognitive impairment with increased amyloid (MCI A+, n=8), and AD dementia (AD, n=6). We explored the variations in Neuroinflammation PET results among different groups.
Results: Neuroinflammation was more elevated in the MCI and AD patients compared to both CU groups. Group averages showed that inflammation locality (MCI in frontal lobe, thalamus, basal ganglia, temporal lobe, & the occipital lobe and AD in temporal lobe) levels varied between the different groups. A voxel-wise comparison using a two-sample t-test revealed that the MCI and AD groups exhibited greater neuroinflammation than the CU groups. No differences were seen between CU A- vs CU A+.
Conclusions: Our findings suggest that the progression of neuroinflammation corresponds with cognitive decline rather than amyloid deposition

alone.


CU A- (n=19)
CU A+ (n=15)
MCI (n=8)
AD (n=6)
2.2
0
ER176 SUVR
MCI vs. CU A-
AD vs. CU A-
3.5
-3.5

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0039 / #1396

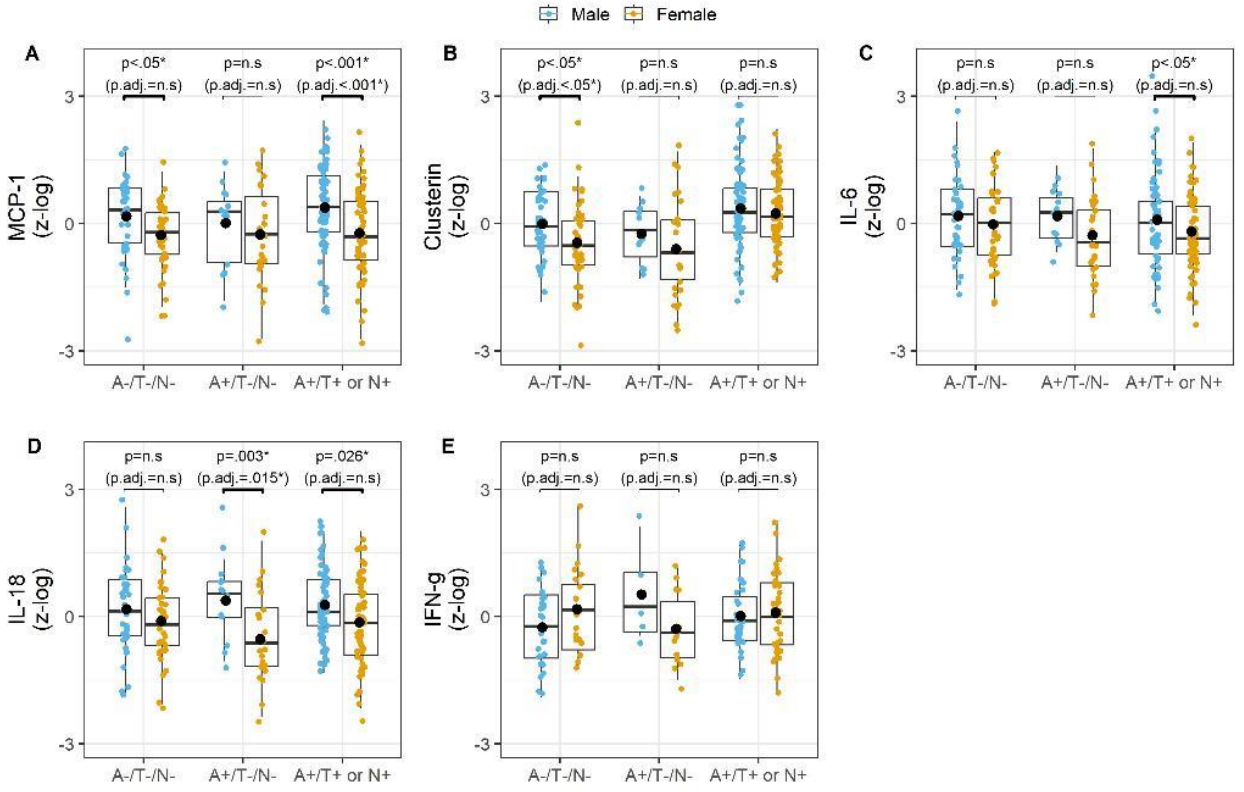
Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

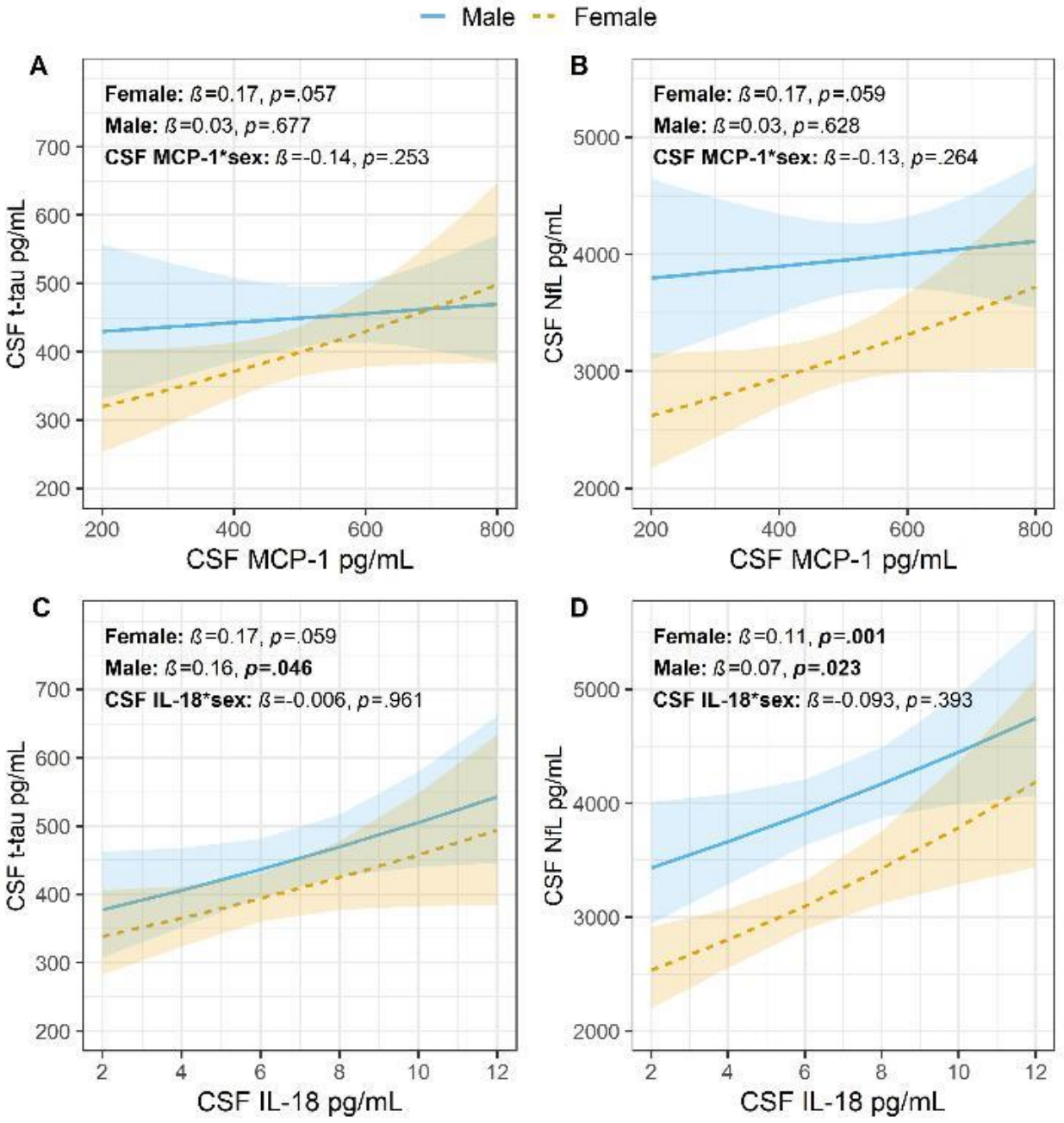
SEX DIFFERENCES IN CSF IMMUNE ACTIVATION MARKERS IN PREDEMENTIA ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Stephanie Knudtzon[1], Kaja Nordengen[2], Per Selnes[3], Lene Pålhaugen[3], Knut Waterloo[1], Berglind Gísladóttir[3], Tormod Fladby[3], Bjørn-Eivind Kirsebom[1]
[1]Department of Neurology, University Hospital of North Norway, Neurology, Tromsø, Norway, [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, Institute Of Clinical Medicine, Oslo, Norway, [3]Akerhus University Hospital, Neurology, Oslo, Norway

Aims: Alzheimer's disease (AD) is more commonly seen among females than males. The innate immune system plays an important role in the development of AD, and different immunological responses may account for some of the sex differences observed in the development of AD. To elucidate possible sex differences in AD-linked innate immune activity, concentrations of five innate immune biomarkers in the cerebrospinal fluid (CSF) were compared between males and females in cognitively normal (CN) cases with normal AD biomarkers, as well as predementia AD cases as defined by the A/T/N classification.
Methods: A total of 251 participants were included in the study. CSF amyloid beta $_{42/40}$ ratio (A), phosphorylated-tau181 (T), and total tau (N) concentrations were used to define the A/T/N classification. The included groups were CN without AD pathology (A-/T-/N-, n=75, 49.3% female), and two predementia AD groups comprising A+/T-/N- (n=38, 65.8% female) and A+/T+ or N+ (n=136, 53.7% female). Sex differences in CSF monocyte chemoattractant protein 1 (MCP-1), interleukin (IL)-6, IL-18, clusterin and Interferon-γ (INF-γ) and their association with total-tau (t-tau) and neurofilament light chain (NfL) were assessed with linear regression. Adjustments for multiple comparisons were performed with false discovery rate.
Results:


Male
Female
A
MCP-1 (z-log)
p<.05* (p.adj.=n.s)
p=n.s (p.adj.=n.s)
p<.001* (p.adj.<.001*)
B
Clusterin (z-log)
p<.05* (p.adj.<.05*)
p=n.s (p.adj.=n.s)
p=n.s (p.adj.=n.s)
C
IL-6 (z-log)
p=n.s (p.adj.=n.s)
p=n.s (p.adj.=n.s)
p<.05* (p.adj.=n.s)
D
IL-18 (z-log)
p=n.s (p.adj.=n.s)
p=.003* (p.adj.=.015*)
p=.026* (p.adj.=n.s)
E
IFN-g (z-log)
p=n.s (p.adj.=n.s)
p=n.s (p.adj.=n.s)
p=n.s (p.adj.=n.s)
3
0
-3
A-/T-/N-
A+/T-/N-
A+/T+ or N+



CSF concentrations were higher in males than females for the following biomarkers: clusterin in the A-/T-/N- group (p.adjusted=.045), IL-18 in the A+/T-/N- group (p.adjusted=.015), and MCP-1 in the A+/T+ or N+ group (p.adjusted<.001). There were no significant sex differences in the associations between CSF neurodegeneration markers (t-tau or NfL) to MCP-1 or IL-18.

Conclusions: Higher concentrations of CSF immune biomarkers in males may indicate sex-related differential immune activation pattern across A/T/N stages. However, these differences seem not to relate to markers of neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0040 / #1726

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

ROLE OF INTERLEUKIN-1B IN SHORT- AND LONG-TERM EFFECTS OF HERPES SIMPLEX VIRUS TYPE-1 INFECTION IN MOUSE MODELS OF ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Domenica Donatella Li Puma[1,2], Roberto Piacentini[1,2], Bruno Bandiera[1], Giovanna De Chiara[3], Anna Teresa Palamara[4,5], Claudio Grassi[1,2]
[1]Università Cattolica del Sacro Cuore, Department Of Neuroscience, Rome, Italy, [2]Fondazione Policlinico Universitario, A. Gemelli Irccs, Rome, Italy, [3]National Research Council (CNR), Institute Of Translational Pharmacology, Rome, Italy, [4]Istituto Superiore di Sanità, Department Of Infectious Diseases, Rome, Italy, [5]Sapienza University of Rome, Department Of Public Health And Infectious Diseases, Laboratory Affiliated To Istituto Pasteur Italia - Cenci Bolognetti Foundation, Rome, Italy

Aims: In previous studies we demonstrated that when Herpes Simplex virus type 1 (HSV-1) reaches the CNS its replication triggers accumulation of Alzheimer's disease (AD) hallmarks leading to synaptic and memory deficits in C57/Bl6 mice. Here we investigated the contribution of interleukin-1β (IL-1β) to the HSV-1-induced AD-like phenotype after multiple cycles of viral reactivation.
Methods: Molecular, electrophysiological and behavioral analyses were performed in C57/Bl6, APP$^{-/-}$ and Tau$^{-/-}$ mice infected with HSV-1 and subjected to either two (2TS) or six (6TS) thermal stress-induced viral reactivations, along with or without treatment with the IL-1 receptor antagonist, anakinra (30 mg/kg, i.p.).
Results: After 2TS, HSV-1-infected C57/Bl6 mice exhibited increased levels of IL-1β negatively affecting synapse structure and function leading to memory deficits. This AD-like phenotype was fully rescued by mice treatment with anakinra, that also counteracted the hyperphosphorylation of glycogen synthase kinase 3β at Tyr216 and amyloid precursor protein (APP) at Thr668, we observed in infected mice. In HSV-1-infected APP-/- and Tau-/- mice undergone 2TS we also found upregulation of IL-1β mRNA (+1.8 and +1.7 folds vs. mock-infected mice, respectively, $p<0.05$) that correlated with deficits of long-term potentiation (74.9±6.7% vs. 102.3±10.2% in Tau-/- mice and 67.2±5.7% vs. 90.8±9.8% in APP -/- mice; $p<0.05$ vs mock-infected). After 6TS brain accumulation of amyloid-β (Aβ) and pTau was far greater than at 2TS and anakinra treatment failed to ameliorate the synaptic and memory deficits in HSV-1-infected mice.
Conclusions: Collectively, our findings suggest that IL-1β-mediated neuroinflammation is a major determinant of the AD-like phenotype that we observed at early stages of our mouse model of sporadic AD. At later stages Aβ and pTau accumulation makes our model no more responsive to pharmacological treatments blocking the molecular cascade downstream the IL receptor.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0041 / #2254

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

ACTIVATED CGAS-STING PATHWAYS COORDINATE NEUROINFLAMMATION AND MITOCHONDRIAL IMPAIRMENT IN THE APP KNOCK-IN MICE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Sifang Liao[1], Makoto Shimozawa[2], Li-Peng Mao[3], Per Nilsson[4], Evandro Fang[1]
[1]University of Oslo and Akershus University Hospita, Department Of Clinical Molecular Biology, Lørenskog, Norway, [2]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, SOLNA, Sweden, [3]Institute of Geriatric Immunology, School of Medicine, Jinan University, Department Of Microbiology And Immunology, School Of Medicine, Guangzhou, China, [4]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden

Aims: Alzheimer's disease (AD) is the primary form of late-onset dementia with the hallmarks of amyloid-β plaques and tau aggregates deposition. Mitochondrial dysfunction and neuroinflammation play crucial roles in the development of AD. The cGAS enzyme detects cytosolic DNA, especially leaked mtDNA, leading to the activation of STING and the expression of genes that cause inflammation. TANK-binding kinase 1 (TBK1) is located downstream of the cGAS-STING pathway and is responsible for regulating the expression of type-I interferons and other cytokines; interestingly, TBK1 also plays a role in the autophagy/mitophagy to maintain mitochondrial quality. We aim to investigate how TBK1 coordinates its double-side roles in AD using a cross-species approach in the APP knock-in mice.
Methods: Hippocampus tissues were collected from 2, 6, and 12-month-old APP knock-in mice and their controls. Then RNA-seq, electron microscope, and Immunohistofluorecense were utilized to examine the changes in neuroinflammation and mitochondrial morphology in the APP knock-in mice and their controls.
Results: Our RNA-seq data suggest that signaling pathways related to neuroinflammation were elevated in the APP^{NL-G-F} AD mice in an age-dependent manner. Compared with WT mice, we observed altered mitochondrial homeostasis and a high accumulation of damaged mitochondria in the hippocampal tissue of the 12-month-old APP^{NL-G-F} mice paralleled by activation of the cGAS-STING signaling in this AD mouse. We then analyzed the genes related to lysosomal function and found that these genes are significantly affected in the APP^{NL-G-F} mice.
Conclusions: Our data suggest that APP KI mice displayed strong neuroinflammation, and it may be due to the accumulation of damaged mitochondria. We are now manipulating the expression and activity of TBK1 and monitoring the effects on neuroinflammation and mitophagy in AD animals of different ages.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0042 / #715

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

NEUROINFLAMMATION IN ALZHEIMER'S DISEASE: EVIDENCE OF ELEVATED INFLAMMASOMES SIGNALLING CASCADE IN POSTMORTEM NEOCORTEX

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Frances Lim[1], Yuek Chai[1], Thiruma Arumugam[2], Michelle Tan[1,3], Mitchell Lai[1]
[1]National University of Singapore/Yong Loo Lin School of Medicine, Pharmacology, Singapore, Singapore, [2]La Trobe University, Microbiology, Anatomy, Physiology & Pharmacology, Melbourne, Australia, [3]Singapore General Hospital, Clinical Translational Research, Singapore, Singapore

Aims: Inflammasomes are cytosolic pattern recognition receptors that play a vital role in host innate immune response to pathogen infections and in tissue repair upon cellular damage. *In vitro* and animal experimentations showed that early build-up of Alzheimer's disease (AD)-associated proteins, namely β-amyloid plaques and neurofibrillary tangles, may trigger the activation of the inflammasomes. Upon activation, inflammasome forms a protein complex and elicits a signalling cascade involving the cleavage and activation of pro-inflammatory cytokines, leading to neuroinflammation, and contributing to AD pathophysiology. However to date, there is no comprehensive study of the inflammasomes-related pathway signalling cascade in human cases of AD. Hence, this study aims to investigate the key inflammasomes-related genes in postmortem AD brains.
Methods: Expression profiling of inflammasomes-related genes NLRP1, NLRP3, AIM2, PYCARD, CASP1, IL1B, IL18 and GSDMD were performed in two neocortical areas (Brodmann areas [BA] 9 and 21) in a cohort of 48 neuropathologically confirmed AD patients and 33 controls. Mann-Whitney U test and False Discovery Rate were used to compare the relative expression levels of each gene between AD and control groups.
Results: In both BA9 and BA21, CASP1, PYCARD and GSDMD relative gene expression levels were significantly increased in AD compared to controls. IL18 gene expression level was significantly increased in BA9 of AD compared to controls, while NLRP1, NLRP3, AIM2 and IL1B gene expression levels were significantly increased in BA21.
Conclusions: AD neocortex showed both region-specific and non-specific upregulation of genes related to inflammasome activation. Given that activated inflammasomes play an instrumental role in the instigation of neuroinflammation which may subsequently exacerbate the neurodegenerative process in conditions such as AD, inflammasomes may be considered as a potential treatment target in alleviating neuroinflammation in AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0043 / #384

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

REGULATION OF ASTROCYTE REACTIVITY BY THE ALZHEIMER'S DISEASE RISK GENE CLU

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Alexandra Lish[1], Elyssa Grogan[1], Hyo Lee[2], Nancy Ashour[1], Seeley Fancher[1], Gwen Orme[1], Nicholas Seyfried[3,4,5], Courtney Benoit[1], Richard Pearse Ii[1], Tracy Young-Pearse[1]
[1]Brigham and Women's Hospital, Neurology, Boston, United States of America, [2]Icahn School of Medicine at Mount Sinai, Genetics And Genomic Sciences, New York City, United States of America, [3]Emory University School of Medicine, Center For Neurological Disorder, Atlanta, United States of America, [4]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [5]Emory University School of Medicine, Neurology, Atlanta, United States of America

Aims: Genetic studies have implicated CLU in the pathogenesis of Alzheimer's disease (AD). CLU is implicated in heterogeneous biological processes, but the precise molecular mechanisms by which CLU alters disease risk remain unclear. We aimed to interrogate the cell autonomous and non-autonomous consequences of CLU loss-of-function.
Methods: CRISPR/Cas9 editing was employed to generate CLU iPSC isogenic sets of lines (WT, HET, and KO). After differentiating these lines to neurons and astrocytes, we performed unbiased proteomic profiling to identify candidate cell-type specific mechanisms impacted by CLU loss. Top findings were validated using a combination of methods, including western blotting, ELISA measurements, and qPCR. Finally, astrocyte-neuron-microglia co-cultures were used to elucidate how astrocyte-derived CLU influences the homeostasis of other cell types.
Results: Based on our proteomics screen, we focused on an intriguing finding that the loss of CLU induces an inflammatory response in astrocytes in the absence of other AD-relevant stressors. This resulted in the upregulation of IL-6 and C3. We determined that NfkB signaling is strongly upregulated in CLU KO astrocytes. Activating NfkB signaling in astrocytes increases CLU expression, suggesting a compensatory feedback loop. Using microglia-astrocyte-neuron co-cultures, we found that astrocytic CLU affects neuronal synaptic vesicle release
Conclusions: Taken together, our data provide a mechanistic link between CLU expression in astrocytes and NfkB signaling, both of which are strongly implicated in AD pathogenesis. In AD, there is significant degeneration of neurons and microglial overactivation, and our unique experimental approach allows us to capture whether and how the loss of CLU in human astrocytes contributes to pathological changes in other brain cell types.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0044 / #970

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

A MULTI-PRONGED RESPONSE OF XENOGRAFTED HUMAN MICROGLIA TO ALZHEIMER'S DISEASE AB PATHOLOGY

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Renzo Mancuso
VIB-University of Antwerp, Vib-center For Molecular Neurology, Antwerp, Belgium

Aims: Analyzing human microglia cell states relevant to Alzheimer's Disease (AD) in human brain samples is challenging due to genetic diversity, postmortem delay and admixture of pathologies.
Methods: We therefore collected 138,577 single cell expression profiles of human microglia derived from a well-controlled xenotransplantation model of AD.
Results: Human microglia adopt a disease-associated (DAM) profile similar to mouse microglia but display a more pronounced HLA state, likely related to antigen presentation in response to amyloid plaques. The human response is in addition characterized by a pro-inflammatorycytokine/chemokine CRM response raised to oligomeric Aβo. Expression of AD risk genes is distributed over this multi-pronged response to amyloid pathology. Genetic deletion of TREM2 or APOE, as well as APOE polymorphisms and TREM2R47H expression modulate these responses differentially.
Conclusions: Therapeutic strategies targeting microglia need to assess how they affect not only DAM responses but all different cell states, as this will define their therapeutic outcome.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0045 / #571

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

DESIGNING, DEVELOPMENT , SYNTHESIS AND NEUROPROTECTIVE ACTIVITY ASSESSMENT OF A NOVEL HYBRID CONJUGATE OF L-DOPA AND CURCUMIN AS AN EFFICACIOUS THERAPEUTIC AGENT FOR PARKINSON'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Krishna Misra[1], M.M., Bharath[2], Unnati Soni[3], Manoj Shrivas[1,2], Sarika Singh[2,4], M.D. Pandareesh[3,4]
[1]Indian Institute of Information Technology, Applioed Science, Allahabad, India, [2]Indian Institute of Information Technology,Allahabad, Applioed Science, Allahabad, India, [3]Indian Institute of Information Technology, Applied Science, Allahabad, India, [4]Indian Institute of Information Technology,Allahabad, Applied Science, Allahabad, India

Aims: The concept of hybrid molecules incorporating pharmacophores of herbal drugs and commercial ones is novel and promising that can effectively target multifactorial diseases . In the present work a hybrid molecule has been prepared containing the pharmacophores of L-Dopa and Curcumin, so that it serves dual purpose of release of Dopamine as well as protection of surviving neurons .
Methods: We have designed , synthesized and tested a hybrid molecule containing pharmacophores of L-Dopa , the commercial drug for Parkinson,s disease and Curcumin. . Curcumin protects neuronal mitochondria against oxidative/nitrosative stress, induces glutathione synthesis in cell and animal models of Parkinson's disorder. The composition was designed through in silico methods .The hybrid molecule has been synthesized in one step .In vitro tests on N27 Neuronal cell line and study conducted in neurotoxin 6-hydroxydopamine induced sporadic Parkinson's disease rat model show positive results.
Results: The synthetic hybrid molecule was obtained in quantitative yield .It was characterized by IR, H^1, ^{13} C NMR and Mass spectra. *In-silico* studies show that this modified Curcumin - L-DOPA drug can serve as a highly efficient inhibitor of both i.e. Parkin (c-Abl) as well as α-Synuclein, the two neuronal proteins implicated in Parkinson disease. In vitro tests on N27 Neuronal cell line and study conducted in neurotoxin 6-hydroxydopamine induced sporadic Parkinson's disease rat model show enhanced activity vis-a vis L-Dopa.
Conclusions: The Conjugate containing pharmacophores of L-Dopa and Curcumin is expected to serve dual purpose i.e. release Dopamine as well as offer protection to surviving neurons in case of Parkinson's disease. The hybrid approach has potential future in drug discovery, since it can combine the basic concept of Ayurveda with perspective of modern medicine . .

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0046 / #2171

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

HERPES SIMPLEX VIRUS-1 INFECTION INDUCES COMPLEMENT PROTEINS UPREGULATION IN BRAIN CELLS: POSSIBLE ROLE IN SYNAPTIC DAMAGE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Mariya Timotey Miteva[1], Virginia Protto[1,2], Maria Elena Marcocci[1], Roberto Piacentini[3], Domenica Donatella Li Puma[3], Anna Teresa Palamara[1,2], Giovanna De Chiara[4]
[1]Sapienza University of Rome, Department Of Infectious Diseases And Public Health, Rome, Italy, [2]Istituto Superiore di Sanità, Department Of Infectious Diseases, Rome, Italy, [3]Università Cattolica del Sacro Cuore, Department Of Neuroscience, Rome, Italy, [4]National Research Council (CNR), Institute Of Translational Pharmacology, Rome, Italy

Aims: Several pieces of evidence suggest that recurrent herpes simplex virus-1 (HSV-1) infection reaching the brain is one of the risk factors for Alzheimer's disease (AD). Numerous studies suggest that abnormal upregulation of the complement cascade, a key component of the innate immune system, is involved in the pathogenesis of AD, also concurring to synaptic elimination in the brain (Hong et al, 2016). This study aims to investigate if HSV-1 infection triggers complement protein activation in brain cells and to evaluate if this event leads to synaptic loss, a process recently demonstrated for other viral brain infections, but still unexplored for HSV-1.
Methods: We mock- and HSV-1 infected primary neuron-glia co-cultures isolated from rat brain embryos and analyzed cells 24h post-infection. Cells were assayed by Western Blot and RT-PCR for the expression of complement components C1q, C3, and C4 and synaptic markers PSD-95 and synaptophysin, postsynaptic and presynaptic markers, respectively. Immunofluorescence analyses (IF) were also carried out to detect specifically C3 and C1q expression. A Neutralisation Assay was performed infecting cells in the presence or absence of an anti-C3 antibody, or with Compstatin, an inhibitor of C3 convertase.
Results: HSV-1 infection in cultured rat brain cells induces a significant increase of C1q, C3, and C4 at both mRNA and protein levels. ELISA Assay shows a significant C3 increase in supernatants of HSV-1 infected cells. The C3 and C1q increase after HSV-1 infection was also confirmed by IF. Finally, neutralization of C3, in both strategies, leads to partial rescue of the HSV-1-induced decrease of PSD-95 and synaptophysin.
Conclusions: Overall, these results suggest a possible complement-dependent synaptic damage triggered by HSV-1 brain infection, thus strengthening the causal link between HSV-1 and neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0047 / #391

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

INHIBITION OF AN OXIDIZED CONFORMER OF MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) AS A STRATEGY AGAINST SPORADIC ALZHEIMER´S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Andreas Müller-Schiffmann[1], Felix Torres[2], Anatolly Kitaygorodskyy[3], Argyro Alatza[4], Sarah Tschirner[1], Annemieke Rozemuller[5], Selina Wray[4], Roland Riek[3], Vishwanath Lingappa[3], Carsten Korth[6]
[1]University of Düsseldorf, Neuropathology, Düsseldorf, Germany, [2]ETH Zurich, Physical Chemistry, Zurich, Switzerland, [3]Prosetta Biosciences, Chemistry, San Francisco, United States of America, [4]University College London, Neurodegenerative Diseases, London, United Kingdom, [5]VUMC Amsterdam, Neuropathology, Amsterdam, Netherlands, [6]Heinrich Heine University of Düsseldorf, Neuropathology, Düsseldorf, Germany

Aims: The molecular factors connecting epidemiologically established systemic risk factors such as subchronic inflammation, obesity, diabetes and others to sporadic Alzheimer's disease (AD) are unknown. Eventually, these risk factors converge on trigger proteins upstream of the amyloid beta cascade and tau phosphorylation.
Methods: We used small molecule compounds inhibiting cellular host factors necessary for herpes virus replication as a discovery tool to identify such molecular interfaces upstream of AD cellular pathology. The target of the lead compound was identified via drug affinity chromatography. Validation was done in cellular and animal models of AD-like pathology.
Results: Our lead compound inhibited the conversion of macrophage migration inhibitory factor (MIF) to the oxidized conformer (oxMIF) in the presence or absence of herpes virus infection. This led to decreased downstream Akt and GSK signaling, as well as decreased tau phosphorylation and aggregation *in vitro* and *in vivo* in the tgTau58/2 model. Novel monoclonal antibodies specific to oxMIF enabled improved characterization of its induction and conformational conversion.
Conclusions: oxMIF is a powerful molecular target in the pharmacotherapy of sporadic AD and apparently a converging point of external systemic factors triggering or accelerating AD-like neuropathology. Its inhibition is a highly promising avenue for sporadic AD pharmacotherapy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0048 / #912

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

NEUROINFLAMMATION, NEURODEGENERATION, AND MITOCHONDRIAL DYSFUNCTION IN THE PATHOGENESIS OF COGNITIVE DECLINE IN ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Domenico Plantone[1], Matteo Pardini[2], Delia Righi[1], Carlo Manco[1], Miriana D'Alessandro[1], Virginia Pelagotti[3], Federico Massa[3], Elena Bargagli[1], Nicola De Stefano[1]
[1]University of Siena, Department Of Medicine, Surgery And Neurosciences, Siena, Italy, [2]University of Genova, Department Of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal And Child Health, Genova, Italy, [3]University of Genoa, Department Of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal And Child Health (dinogmi),, Genoa, Italy

Aims: The role of transactive response DNA binding protein-43 (TDP-43), immune response, and mitochondrial damage in the pathogenesis of Alzheimer's disease (AD) is under investigation. TDP-43 has been studied in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with ubiquitin-positive inclusions, but several data support its role in AD. Neurofilament light chain (NfL) is a well-established biomarker of neuroaxonal injury in neurodegenerative diseases. Growth differentiation factor-15 (GDF-15) represents a validated marker for mitochondrial dysfunction and has interesting associations with disability in AD. The aim of this study is to assess the CSF concentrations of NfL, GFAP, GDF-15, TDP-43, and 13 different cytokines in a cohort of AD patients, and to explore their association with clinical disability and pathological burden.
Methods: We used the commercially available immunoassay kits for NfL, GFAP, and TDP-43 run on the ultrasensitive SR-X Biomarker Detection System (Quanterix). Concentrations of selected cytokines were determined by multiplex bead-based flow cytometry assay (LEGENDplex, Biolegend, San Diego, CA). GDF-15 concentrations were assessed using Abcam's GDF-15 Human ELISA kit.
Results: 58 patients were enrolled in this study. Patient median age (IQR) was 75 years (71.75-78.25) and 35% were males. The median MMSE score (IQR) was 24 (21.15-26). MMSE was correlated with beta-amyloid CSF concentration (R 0.44;p<0.001), with GDF-15 CSF concentration (R =0.44;p<0.001), with IL-17A (R=0.37;p=0.006). TDP-43 CSF concentration correlated with IL-1beta (R=-0.32;p=0.015), with IL-6 (R=-0,27;p=0.041) and with IL-12p70 (R=-0.27;p=0.042). GDF-15 CSF concentration was also inversely correlated with beta-amyloid CSF concentration (R=-0.47;p<0.001). CSF NfL concentration was correlated with age (R=0.28;p=0.032), IP-10 (R=0.27;p=0.04), IL-1beta (R=0.27;p=0.041), TNF-alpha (R=0.29;p=0.02), IL-6 (R=0.35;p=0.007) and IL-8 (R=0.28;p=0.036).
Conclusions: The findings of this study, support the notion of a link between neuroinflammation, neurodegeneration, and mitochondrial dysfunction in the pathogenesis of cognitive decline in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0049 / #1405

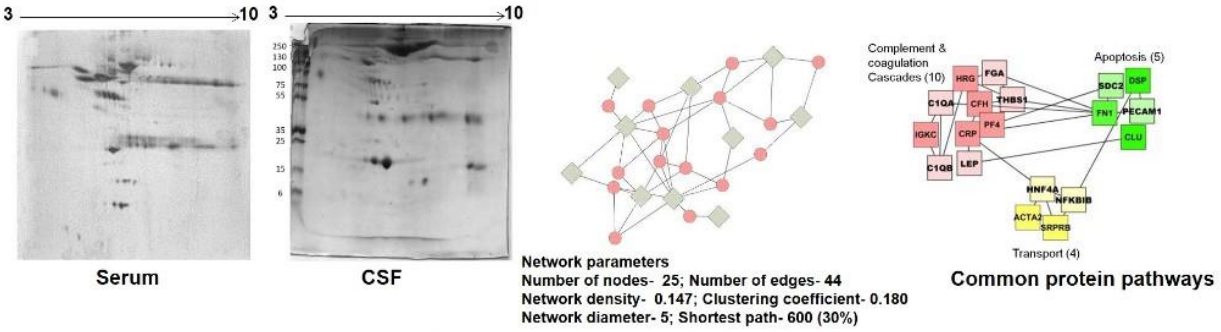
Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

BIOLOGICAL PROTEIN INTERACTION STUDY OF AMYLOID BETA PEPTIDE INTERACTIONS WITH BLOOD AND CSF: ROLE IN ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Pratibha Sharma[1,2], Alagiri Srinivasan[1], Rajinder Dhamija[3]
[1]All India Institute of Medical Sciences, Biophysics, New Delhi, India, [2]Institute of Human Behaviour and Allied Sciences, Human Behaviour Department, Delhi, India, [3]Institute of Human Behaviour and Allied Sciences, Director And Professor Neurology, Delhi, India

Aims: Background: Alzheimer's disease (AD) is a complex and age-dependent neurodegenerative disorder that results in dementia, causing cognitive impairment and memory decline. The pathology and etiology of this disease are quite complicated. Amyloid beta (1-42) is known to play a central role in the disease by forming fibrils. Plaque refers to the loose tangle of fibers deposited outside neurons. Many CSF and blood proteins interact with Aβ and plaques through the blood-brain barrier. An interactive analysis of their functions is necessary to describe the disease status. **Objective:** To identify the blood and CSF protein interactions specific to oligomer Aβ.
Methods: Aβ peptide monomer and oligomer forms were separated using gel-filtration chromatography. These were allowed to pull-down separately with blood serum and CSF proteins from Wister albino rat using affinity chromatography in proteins native form. Interacting proteins were digested in-gel and in-solution by trypsin and identified using Mass spectrometry. Gene ontology and pathway analysis were performed for classification and interactions of proteins with respect to AD pathways.
Results:



Proteomics analysis results of blood serum and CSF proteins from Wister Albino rat interacting with Amyloid beta (1-42) peptide

The results of the pathway analysis indicate that the complement pathway has an essential role to play in AD, depicted in below images.

Conclusions: The circulatory proteins play a crucial role in the transport and clearance of Aβ, which can trigger inflammation pathways and apoptosis pathways.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0050 / #1327

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

SPECIFIC SERUM AUTOANTIBODIES PREDICT THE DEVELOPMENT AND PROGRESSION OF ALZHEIMER'S DISEASE WITH HIGH ACCURACY

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Lu Shen[1], Liangjuan Fang[1], Bin Jiao[2]
[1]Xiangya Hospital, Central South University, Department Of Neurology, Changsha, China, [2]87 Xiangya Road Xiangya Hospital, Central South University, Department Of Neurology, Changsha, China

Aims: Autoimmunity plays a key role in the pathogenesis of Alzheimer's disease (AD). However, whether autoantibodies in peripheral blood can be used as biomarkers for AD has been elusive.
Methods: Serum samples were obtained from 1,686 participants, including 767 with AD, 146 with mild cognitive impairment (MCI), 255 with other neurodegenerative diseases, and 518 healthy controls. Specific autoantibodies were measured using a custom-made immunoassay. Multivariate support vector machine models were employed to investigate the correlation between serum autoantibody levels and disease states.
Results: Seven candidate AD-specific autoantibodies were identified, including MAPT, DNAJC8, KDM4D, SERF1A, CDKN1A, AGER, and ASXL1. A classification model with high accuracy (area under the curve (AUC) = 0.94) was established. Importantly, these autoantibodies could distinguish AD from other neurodegenerative diseases and out-performed amyloid and tau protein concentrations in cerebrospinal fluid in predicting cognitive decline ($P < 0.001$).
Conclusions: This study indicated that AD onset and progression are possibly accompanied by an unappreciated serum autoantibody response. Therefore, future studies could optimize its application as a convenient biomarker for the early detection of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0051 / #2223

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

RATIONAL TARGETING OF NLRP3 INFLAMMASOME IN MICROGLIA: A CRSIPR TILING SCREEN BASED APPROACH FOR DEVISING A NOVEL NEURO-IMMUNOMODULATORY THERAPY FOR AD

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Falak Sher
Columbia University, Neurology, New York City, United States of America

Aims: The NLRP3 inflammasome is crucial in Alzheimer's disease (AD) inflammation and progression, with microglia playing a key role. Targeting NLRP3 can reduce AD-associated inflammatory markers and pathologies. Current NLRP3 inhibitors often lack specificity, leading to side effects. A more precise inhibitor would address these issues, making it a promising therapeutic avenue for AD. We are actively exploring this direction through following aims: 1). Investigate the role of the NLRP3 inflammasome in AD's pathogenesis and progression. 2). Identify the subunits of microglial inflammasome and importantly 3). Develop a rational NLRP3 inhibitor that offers increased specificity and reduced side effects.
Methods: 1. Utilization of pooled CRISPR-tiling to disrupt inflammasome protein-coding sequences in human microglial model systems. 2. Functional mapping of high-throughput CRISPR perturbations to identify critical protein interfaces. 3. Employing CRISPR-mediated homology-directed repair (HDR) for high-throughput variant classification, combined with a haploidization strategy, to assess over 500 variants for altered inflammasome activation.
Results: 1. Identified a crucial, non-redundant subcomplex of the NLRP3 protein family essential for inflammasome activation. 2. Revealed in-frame alleles causing inflammasome subunit loss-of-function due to destabilization or functional alteration. 3. Pinpointed specific amino acids in NLRP3 ideal for developing rational small molecules to regulate inflammasome activity.
Conclusions: 1. The NLRP3 inflammasome plays a significant role in AD's pathogenesis, and interventions targeting it can alleviate AD-related pathological hallmarks. 2. Many current NLRP3 inhibitors lack specificity and come with side effects, emphasizing the need for more targeted inhibitors. 3. The research introduces a robust methodology that illuminates specific amino acids in NLRP3 for intervention and advances the understanding of the inflammasome, offering potential therapeutic applications in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0052 / #2834

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

RAB10 IN NEURO-IMMUNE CROSS-TALK ASSOCIATED WITH ALZHEIMER'S DISEASE

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Erzsebet Szatmari[1], Wyatt Bunner[1], Lauren Grodi[1], Alessandro Didonna[2], Jonathan Jacob Carver[2], Debajit Bhowmick[2]
[1]East Carolina University, Physical Therapy, Greenville, United States of America, [2]East Carolina University, Anatomy And Cell Biology, Greenville, United States of America

Aims: Objectives: Reduced activity of Rab10, a small Rab GTPase involved in vesicular trafficking was found to confer resilience against Alzheimer's disease (AD) even for high-risk individuals. To identify the mediators of Rab10-dependent neuroresilience, we developed heterozygous knockout mice for Rab10 ($Rab10^{+/-}$). The objective of this study was to elucidate the role of Rab10 in the AD-dependent activation of central and peripheral immune responses.
Methods: Methods: Immunofluorescence staining: for Iba1 and GFAP on coronal sections from 4-month-old $Rab10^{+/}$ and $Rab10^{+/+}$ mice. Flow cytometry: to evaluate the activation state and the immunophenotype of specific immune cells isolated from the spleen of 4-month-old $Rab10^{+/}$ and $Rab10^{+/+}$ mice. Treatment of $Rab10^{+/-}$ and $Rab10^{+/+}$ organotypic hippocampal slices with oligomeric amyloid (oAβ) or scrambled Aβ peptide as control, followed by measurement of pro-inflammatory cytokine release into the culture medium using a Luminex multiplex assay.
Results: Results: In the $Rab10^{+/-}$ hippocampus, the baseline activation status of the microglia (Iba1-immunoreactivity) was significantly reduced. Flow cytometry analysis of peripheral immune cells indicated reduction in natural killer (NK) cells in the spleen of $Rab10^{+/-}$ mice. There was no difference between genotypes in the total CD8 and CD4 lymphocytes. However CD8 effector cells % was significantly lower, while CD4 effector cells were higher in $Rab10^{+/-}$ mice. Treatment of $Rab10^{+/-}$ and $Rab10^{+/+}$ organotypic hippocampal slices with oAβ42 or scAβ followed by measurement of cytokine release indicated a significant reduction in the production of IL1-β, TNFα and IFNγ in $Rab10^{+/-}$ slices.
Conclusions: Conclusions: Our data suggest a role for Rab10 in innate immunity that has been shown to contribute to AD progression. Through attenuating neuroinflammation and modulating immune cell phenotypes, Rab10 reduction might offer a promising therapeutic avenue for prevention or treatment of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0053 / #870

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

BETA-AMYLOID IS A CYTOKINE AND ALZHEIMER'S IS AN INNATE AUTOIMMUNE DISEASE REGULATED BY AMINO ACID (TRYPTOPHAN, ARGININE, BETA-ALANINE, TAURINE) METABOLISM

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Autumn Meek, Yanfei Wang, Mark Reed, Christopher Barden, Donald Weaver
Krembil Brain Institute, Neurobiology, Toronto, Canada

Aims: There is a need for a model of AD that unifies current divergent theories into a harmonized mechanistic explanation. Incorporating protein aggregation processes into a broadly-encompassing immunopathic model of AD by repositioning Aβ as an immunopeptide (cytokine) achieves this goal. Our study comprehensively evaluates Aβ as a cytokine, conceptualizing AD as an innate autoimmune disease subject to endogenous homeostatic regulation by four amino acids (tryptophan, arginine, β-alanine, taurine).
Methods: We performed a comprehensive series of in silico, in vitro, and in vivo studies to rigorously analyze the molecular mechanisms of Aβ-mediated neurotoxicities in AD, comparing Aβ to known cytokines and AD to known autoimmune diseases.
Results: Triggered by diverse stimuli (infection [viral, bacterial], trauma, ischaemia, air pollution), Aβ is released as a cytokine initiating an innate immunity cascade in which Aβ demonstrates immunomodulatory and antimicrobial properties (whether or not bacteria are present), resulting in a misdirected attack upon host neurons. This mistaken attack occurs because of similar membrane electrotopologies between neurons and bacteria; *i.e*. Aβ cannot differentiate neurons (particularly the synaptic zone) from bacteria. This neuron-bacterium misidentification is a key aetiopathogenic step in AD. After the misdirected-attack, the resulting necrotic neuronal products (Aβ-GM1 aggregates) diffuse to nearby neurons causing ongoing release of Aβ, leading to a chronic innate autoimmune cycle. AD is therefore a brain-centric autoimmune disorder of innate immunity; a subsequent screening program identified four amino acids (tryptophan, arginine, β-alanine, taurine) and their metabolites as key homeostatic regulators on brain innate immunity capable of downregulating neuroinflammation.
Conclusions: Positioning Aβ as a cytokine, conceptualizing AD as an innate autoimmune disease, and identifying endogenous regulatory molecules (L-tryptophan, L-arginine, β-alanine, taurine) which homeostatically influence innate autoimmunity constitutes an innovative mechanistic and therapeutic approach to AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0054 / #732

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

CXCL16-CXCR6 AXIS INVOLVEMENT IN ALZHEIMER'S DISEASE-SPECIFIC CD8+T-CELLS RECRUITMENT TO THE BRAIN

POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Marco Zattoni[1], Sabine Bernegger[1], Sofia Weinbender[1], Rodolphe Poupardin[2], Barbara Altendorfer[1], Heike Mrowetz[1], Ludwig Aigner[1]
[1]Paracelsus Medical University Salzburg, Institute Of Molecular Regenerative Medicine, Salzburg, Austria, [2]Paracelsus Medical University Salzburg, Institute Of Experimental And Clinical Cell Therapy, Salzburg, Austria

Aims: Together with brain amyloid depositions, astrogliosis and microglia activation, Alzheimer´s disease (AD) progression has been recently associated with infiltration of $CD8^+$ T-cells into brain parenchyma. $CD8^+$ T-cells tightly associate with microglia and neurons in brain of AD-affected humans and APP/PS1 animals, a widely used AD mouse model. Although the mechanism involved in parenchymal $CD8^+$ T-cells accumulation remains unknown, recent studies suggested a potential role of the Cxcl16-Cxcr6 axis in their recruitment to the brain. Therefore, we aim to assess the interplay between $Cxcr6^+CD8^+$ T-cells and Cxcl16-producing cells in APP/PS1 brain.
Methods: Public available single cell RNA sequencing (scRNA seq) datasets helped us to identify the cellular source of Cxcl16 and its receptor. Quantitative PCR (qPCR) and immunohistochemical (IHC) analysis of brain tissue from microglia-depleted mice allowed us to investigate the role of Cxcl16-expressing cells in the recruitment of $Cxcr6^+CD8^+$ T-cells.
Results: scRNA seq datasets revealed that *Cxcr6* is mainly expressed by effector $CD8^+$ T-cells, while *Cxcl16* expression is characteristic of microglial cells. qPCR analysis indicated a significant overexpression of *Cxcl16* and *Cxcr6* in diseased-animals compared to controls. Furthermore, we observed slightly reduced *Cxcl16* and *Cxcr6* levels in microglia-depleted APP/PS1 mice compared to untreated animals, indicating microglia as the main source of Cxcl16 in AD-affected brains and a putative role of this chemokine in the recruitment of Cxcr6-expressing T-cells. Interestingly, IHC analysis of microglia-depleted APP/PS1 brain tissue showed an increased number of $Cxcr6^+CD8^+$ cells in close contact to remaining $Iba1^+$ cells.
Conclusions: Overall, these results suggested an involvement of Cxcl16-Cxcr6 axis in the recruitment of $CD8^+$ T-cells in APP/PS1 animals. Further functional analysis of microglia and T-lymphocytes cross talk may pave the way for novel therapies targeting Alzheimer´s and other related neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0055 / #1134

Poster Topic: *Theme A: β-Amyloid Diseases / A01.c. Disease Mechanisms, Pathophysiology: Inflammation*

SLEEP QUANTITATIVE MEASURES ASSOCIATED WITH FLUID INFLAMMATION MARKERS IN COGNITIVELY UNIMPAIRED ADULTS

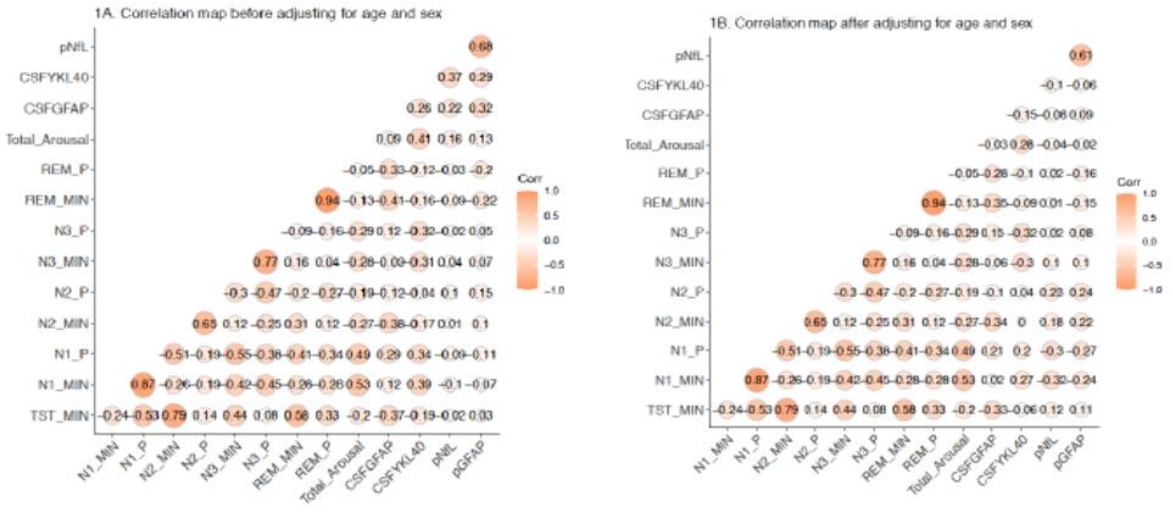
POSTERS: A01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Nuole Zhu[1,2], Miren Altuna[3,4], Javier Arranz[1], Maria Saudinós[2], Laura Videla[2,5], Sílvia Valldeneu[2], Susana Clos[1], Sandra Gimenez[6,7], Juan Fortea[5], Daniel Alcolea[1,2], Alberto Lleó[1,2]
[1]Biomedical Research Network Center for Neurodegenerative Diseases, CIBERNED, Spain, Memory Unit, Barcelona, Spain, [2]Sant Pau Biomedical Research Institute, Universitat Autònoma de Barcelona, Sant Pau Memory Unit, Department Of Neurology, Barcelona, Spain, [3]CITA-Alzheimer Foundation, Donostia-San Sebastián, Spain, Alzheimer Foudation, Donostia, Spain, [4]Osakidetza, Organización Sanitaria Integrada (OSI) Debabarrena, Spain, Neurology, Euskadi, Spain, [5]Hospital de la Santa Creu I Sant Pau, Sant Pau Biomedical Research Institute, Barcelona, Spain, Catalan Foundation For Down Syndrome,, Barcelona, Spain, [6]Hospital de la Santa Creu I Sant Pau, Sant Pau Biomedical Research Institute, Barcelona, Spain, Multidisciplinary Sleep Unit, Respiratory Department, Barcelona, Spain, [7]Atlantic Fellow for Equity in Brain Health, Global Brain Health Institute, Multidisciplinary Sleep Unit, Respiratory Department, Barcelona, Spain

Aims: The relationship between neuroinflammation and sleep in cognitively unimpaired individuals has been scarcely studied. We aimed to explore the relationship between markers of neuroinflammation in cerebrospinal fluid (CSF) and plasma and sleep quantitative measures.
Methods: A total of 55 CU without sleep disorders underwent a nocturnal polysomnography (PSG) followed by morning blood collection. Additionally, 51 participants also underwent morning lumbar puncture to collect CSF. We assessed the concentrations of Glial Fibrillary Acidic Protein in CSF (CSFGFAP), in plasma (pGFAP), CSFYKL40 and plasma neurofilament (pNfL) for associations with PSG-derived quantitative sleep parameters using Spearman tests. Sleep parameters included total sleep time (TST), NREM (N1, N2, N3) and REM duration (MIN) and percentage (P), as well as total arousal events. Considering the influence of age and sex on biomarker concentrations, we also conducted analyses adjusted for these factors using linear regression models.
Results: Demographic, clinical and biomarker data are summarized in Table1. The mean age was 56 (13) years, with 32% being male. CSFGFAP showed significant negative correlation with TST, N2 duration; REM sleep duration, and percentage (all $p<0.05$). Similarly, CSFYKL40 positively correlated with N1 duration and percentage, and negatively correlated with N3 duration, percentage, and total arousal events (all $p<0.05$) (Figure 1.A). After adjusting for age and sex, we continued to observe negative correlation between CSFGFAP and TST, REM sleep ($p<0.05$), as well as between CSFYKL40, N3 sleep and total arousal events ($p<0.05$). Additionally, pNfL displayed an inverse correlation with N1 duration and percentage (both $p<0.05$) (Figure 1B).

Table 1. Sociodemographic, Clinical and fluid data from study Group (N=55)	
Age , Mean (SD), years	56 (13)
Male sex, n(%)	17 (31%)
APOE4+, n (%)	16 (32%)
MMSE, mean (SD)	29.4 (1)
TST, mean (SD), min	353 (65)
REM duration, mean (SD), min	63 (24)
N1 duration, mean (SD), min	39 (24)
N2 duration, mean (SD), min	175 (41)
N3 duration, mean (SD), min	73 (33)
Total arousal events, mean (SD)	17.5 (14)
CSFGFAP, median (IQR), pg/mL	6519 (4117)
CSFYKL40, median (IQR), pg/mL	191 (89)
pGFAP, median (IQR), pg/mL	108 (93)
pNfL, median (IQR), pg/mL	8 (4.7)

Figure1. Spearman Correlation Map between Sleep parameters and Inflammation Biomarkers



Conclusions: In CU individuals, the duration and quality of sleep associated with concentration of neuroinflammation and axonal damage biomarkers. This association is more pronounced in CSF neuroinflammation biomarkers. The nature and impact of these associations deserves further investigation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0056 / #1581

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

SLEEP-DEPENDENT MODULATION OF BRAIN HOMEOSTASIS IN ALZHEIMER'S DISEASE

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Sara Calafate[1], Bart De Strooper[2], Tiago Gil Oliveira[3], Joris De Wit[2]
[1]Life and Health Sciences Research Institute (ICVS), School Of Medicine, Braga, Portugal, [2]KU Leuven & VIB, Center For Brain & Disease Research, Leuven, Belgium, [3]University of Minho, School Of Medicine, Braga, Portugal

Aims: In Alzheimer's disease (AD), early accumulation of amyloid-β (Aβ) causes deficits in episodic memory, leading to cognitive impairment. Moreover,hippocampal hyperactivity and increased susceptibility for seizure emerges, placing synapse dysfunction is at the basis of AD pathogenesis. Remarkably, neuronal hyperactivity is prominent during sleep and sleep disturbances are accompanied by silent epileptic-like discharges in individuals with AD during the prodromal phase. Moreover, early sleep disturbance coincides with aberrant neuronal activity and neuroinflammation, in patients and mouse models.
Methods: Recently, using spatial transcriptomics and bulk RNAsequencing, I found that the sleep-active Melanin Concentrating Hormone (MCH) decreases the expression of immediate early genes and restrains synaptic activity of hippocampal neurons (Calafate et al, 2023). MCH-neurons located in the lateral hypothalamic area (LHA), regulate duration of rapid-eye movement (REM) sleep and project to the hippocampus modulating hippocampal-dependent memory. Moreover, we took advantage of techniques such as EEG/EMG, electrophysiology and others.
Results: My work identified an early impairment of the MCH-system in AD patients and in the AppNL-G-F mice (a mouse model for early stages of AD) at the time point that aberrant hippocampal activity, impaired REM sleep and higher susceptibility for seizures emerge. Moreover, my work showed that MCH peptide is sufficient to rescue increased hippocampal excitatory synaptic transmission in the AppNL-G-F mice. This suggests that MCH, released during sleep, protects neurons from aberrant excitation placing the MCH-system as a key modulator of neuronal activity and homeostasis. However, brain homeostasis depends on complex interaction between cell-types. My preliminary data identifies that MCH-system has the capacity to modulate microglia response and therefore has the potential to orchestrate microglia-neuron communication.
Conclusions: I hypothesize that the failure of the sleep-related MCH-system contributes to loss of neuronal homeostasis by different but complementary mechanisms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0057 / #2330

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

LICOCHALCONE A PREVENTS ALZHEIMER'S DISEASE DEVELOPMENT IN APPSWE/PS1DE9 MICE

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Marina Carrasco[1], Jordi Olloquequi[2], Ester Verdaguer[3], Carme Auladell[3], Jesus Ureña[3], Antoni Camins[1], Miren Ettcheto[4]
[1]universitat de Barcelona, Pharmacology, Toxicology And Therapeutic Chemistry, Barcelona, Spain, [2]university of Barcelona, Biochemistry And Physiology, barcelona, Spain, [3]universitat de Barcelona, Cellular Biology, Physiology And Immunology, Barcelona, Spain, [4]University of Barcelona, Pharmacology, Toxicology And Therapeutic Chemistry, barcelona, Spain

Aims: Alzheimer's Disease (AD) is the main form of dementia with no effective treatment available. Multiple studies have demonstrated the multifactorial character of the disease, suggesting that multi-target drugs could be a potential therapeutical treatment. Licochalcone A (LCA), a chalcone that comes from *Glycyrrhiza glabra,* has shown an anti-inflammatory and anti-diabetic effect among others, positioning as a promising drug to stop AD. Accordingly, the aim of this study was to evaluate the neuroprotective role of LCA to prevent AD development.
Methods: To perform this study, six-month-old C57BL/6J and double transgenic APPswe/PS1dE9 (APP/PS1) male mice were used. At five-month-old, animals were treated with LCA at a dose of 15 mg/kg/day or saline intraperitoneally three times per week/4 weeks, dividing them into 4 different groups; WT Saline, WT LCA, APP/PS1 Saline and APP/PS1 LCA. Afterwards, Novel Object Recognition Test (NORT) and Morris Water Maze (MWM) were performed to evaluate memory loss. Finally, several hallmarks of AD such as dendritic spine loss, β-amyloid (βA) plaques and chronic neuroinflammation, among others were evaluated.
Results: Our study demonstrated a protection against memory loss after LCA treatment in APP/PS1 mice in NORT and MWM behavioural tests. Additionally, these results correlate with the preservation of dendritic spine number in the animals previously treated with LCA comparing to the saline-treated transgenic mice. Altogether, the biochemical assays demonstrate a synaptic deterioration and βA plaques deposition in APP/PS1, which is significantly ameliorated due to LCA administration, enhancing synapsis and βA plaques clearance. Finally, LCA reported an amelioration of neuroinflammatory processes such us a reduction of microglial activation.
Conclusions: In conclusion,our results demonstrated that LCA ameliorates memory loss in APP/PS1 mice by the maintenance of dendritic spines, the reduction of βA plaques deposition and neuroinflammation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0058 / #2643

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

ALTERED ACTIVITY-DEPENDENT NEURONAL GENE EXPRESSION IN ALZHEIMER'S DISEASE

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Xavier Fernandez-Olalla, Carles Vendrell-Tornero, Arnaldo Parra-Damas, Carlos A. Saura
Institut de Neurociencies, Departament De Bioquímica I Biologia Molecular, Bellaterra, Spain

Aims: Changes in gene expression programs in memory-related neural circuits are associated with cognitive decline in normal and pathological aging, including Alzheimer's disease (AD). However, the specific genes and the transcriptional regulatory mechanisms underlying synapse and cognitive dysfunction during AD progression are largely unknown. Our previous studies have revealed impairment of activity-induced CREB/CRTC1-regulated transcription at early and intermediate AD pathological stages. The aim of this study is to examine the mechanisms of activity-dependent gene changes during AD pathological progression.
Methods: We identified potential activity-regulated genes by analyzing published RNA-seq and CREB/CRTC1 ChIP-seq datasets obtained from depolarized mouse cultured neurons. We applied biochemical and molecular biology approaches to assess the differential expression of gene transcripts and proteins induced by neuronal activity and potentially altered in human hippocampus of AD. Furthermore, we used lentiviral transduction to modulate CREB signaling in mouse neuronal cultures.
Results: Our results revealed that specific activity-dependent immediate-early-genes (IEGs) as well as synaptic function and plasticity-related genes were transcriptionally regulated by CREB/CRTC1 signaling. Accordingly, pharmacological and lentiviral modulation of the CREB/CRTC1 signaling pathway confirmed differential modulation of these activity-dependent genes in primary neurons. Importantly, some of these genes were deregulated in the human hippocampus at distinct AD pathological stages.
Conclusions: These results indicate that altered expression of activity-dependent neuronal genes regulated by CREB/CRTC1 in memory-related neural circuits may contribute to early cognitive dysfunction in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0059 / #1138

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

DIRECT VISUALIZATION OF PROTEIN AGGREGATES IN SYNAPTOSOMES

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Shekhar Kedia[1], Emre Fertan[1], Yunzhao Wu[1], Yu Zhang[1], John Danial[1], Maria Grazia Spillantini[2], David Klenerman[1]
[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]University of Cambridge, Clinical Neurosciences, Cambridge, United Kingdom

Aims: Pathological protein aggregation and synaptic dysfunction are major contributors to neurodegenerative disorders. However, understanding disease-relevant protein aggregation, such as Beta-amyloid, Alpha-synuclein and Tau aggregation within synapses, remains limited. To address this, we present a novel method for visualizing protein aggregates in individual synaptosomes.
Methods: We combined Single-molecule Pull Down (SiMPull) and direct Stochastic Optical Reconstruction Microscopy (dSTORM), to immobilize individual synaptosomes and characterize single aggregates within them with ~20nm spatial resolution.
Results: We validated the method with mouse models of neurodegenerative diseases and post-mortem human brain tissues.
Conclusions: Our method offers a valuable tool for decoding molecular triggers underlying neurodegeneration at an early stage and provides new insights into developing earlier therapeutic strategies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0060 / #1626

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

ROLE OF PLD IN TAUOPATHIES: MECHANISTIC UNDERSTANDING FOR TARGETED THERAPEUTICS.

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Balaji Krishnan[1], Sravan Gopalkrishna Shetty Sreenivasamurthy[1], Chandramouli Natarajan[1], Shaneilahi Budhwani[1], Klarissa Garza[1], Sarah Bosworth[1], Marlene Juarez[1], Malav Mallipudi[1], Joshua Currie[1], Helen Onuorah[1], Nikhil Manuel[1], Jared Dornak[1], Kyle Sheth[1], Evan Wong[1], Charles Cook[1], Karthik Ramaswamy[1], Kamil Khanipov[2], Steven Widen[3], Aditi Fnu[4], Parimal Samir Fnu[4], Ananth Kumar Kammala[5], Ram Kumar Menon[5], Agenor Limon[1]
[1]The University of Texas Medical Branch at Galveston, Mitchell Center For Neurodegenerative Diseases, Neurology, Galveston, United States of America, [2]The University of Texas Medical Branch at Galveston, Pharmacology, Galveston, United States of America, [3]The University of Texas Medical Branch at Galveston, Biochemistry And Molecular Biology, Galveston, United States of America, [4]The University of Texas Medical Branch at Galveston, Microbiology And Immunology, Galveston, United States of America, [5]The University of Texas Medical Branch at Galveston, Basic Science And Translational Research, Galveston, United States of America

Aims: Phospholipase D1, a multimodal signaling element is aberrantly modulated in neurodegenerative states. Using multidisciplinary functional and morphological assessments, we have attempted a thorough approach and provide some key observations that highlight the importance of PLD1 signaling mechanisms as very viable and tolerated therapeutic target in different neurodegenerative states**.** Recently we have optimized the mechanistic action of PLD in both temporal and spatial manner to provide a clear insight into developing targeted therapeutics that will have minimal side-effects. We provide our recent advances in this presentation.
Methods: Human clinical samples of postmortem brains from Alzheimer's Disease (AD) patients, behavioral variant frontotemporal dementia (bvFTD or FTD) patients, and age-matched controls (CTRL) were used to study co-localization of PLD1 with various markers in the autophagy, neuroinflammation, microglial and synaptic neurotransmission pathway to outline the clinical relevance of the disease. These studies were replicated in the 3xTg-AD, hTau, P301S and adeno-associated viral vector (AAV)-based human PLD1 overexpression (hPLD1OXP) or PLD1 inhibition (PLD1 shRNA) in wildtype and transgenic mouse models at 6-months, 12-months or 18-months of age to understand whether the signaling mechanism underlying human clinical condition was faithfully replicated in our functional models. Lastly, RNAseq and protoemics study were conducted to refine the therapeutic approaches. Preliminary studies were conducted to understand the targeted delivery of our lead compound.
Results: Behavioral, electrophysiological, biochemical results of PLD1 expression in healthy and diseased states will be discussed along with an emphasis on how the cellular expression differs. Signaling partners will be discussed with respect to synaptic neurotransmission and aberrant cellular processes in astrocytes and microglia.
Conclusions: Targeted therapies against aberrant PLD1 in distinct cellular milieu will be critical in promoting the resilience to cognitive decline

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0061 / #574

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

ALPHA-SYNUCLEIN INDUCES COFILIN PATHOLOGY AND DENDRITIC SPINE IMPAIRMENT VIA A CELLULAR PRION PROTEIN (PRPC)/CHEMOKINE RECEPTOR 5 (CCR5)-DEPENDENT PATHWAY

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Marina Oliveira Da Silva[1], Miguel Santejo[1], Isaac Babcock Babcock[2], Ana Magalhães[3], Laurie Minamide[2], Erika Castillo[4], Raymond Swanson[4], Tiago Outeiro[5], Ricardo Taipa[6], Michael Ruff[7], James Bamburg[2], Márcia Liz[1]
[1]i3S - Instituto de Investigação e Inovação em Saúde da Universidade do Porto – Associação, Nerve Regeneration Group, Porto, Portugal, [2]Colorado State University, Department Of Biochemistry And Molecular Biology, Fort Collins, United States of America, [3]i3S - Instituto de Investigação e Inovação em Saúde da Universidade do Porto – Associação, Addiction Biology Group, Porto, Portugal, [4]University of California, San Francisco, Institute For Neurodegenerative Diseases, Department Of Neurology, Ucsf Weill Institute For Neurosciences, San Francisco, United States of America, [5]University Medical Center Gottingen, Department Of Experimental Neurodegeneration, Göttingen, Germany, [6]Centro Hospitalar Universitário de Santo António, Neuropathology Unit, Porto, Portugal, [7]Creative Bio-Peptides Inc, Creative Bio-peptides, Rockville, United States of America

Aims: Cognitive dysfunction and dementia are critical symptoms in Lewy Body dementias (LBD). Specifically, alpha-synuclein (αSyn) accumulation in the hippocampus leading to synaptic dysfunction was linked to cognitive deficits in LBD. Here, we investigated the cellular and molecular impact of αSyn on hippocampal neurons by focusing on cofilin pathology and dendritic spine impairment, aiming at defining a novel therapeutic target for synaptic and cognitive deficits in LBD.
Methods: Cofilin pathology and the underlying molecular mechanisms were assessed *in vitro* by analyzing hippocampal neurons either overexpressing αSyn or subjected to the exogenous addition of αSyn pre-formed fibrils (PFFs). We have validated our findings in a mouse model of human αSyn neuronal overexpression, the Thy1αSyn mice, in an additional one of brain injection of αSyn PFFs, and in post-mortem brain samples from LBD patients.
Results: We observed that either αSyn overexpression or αSyn PFFs treatment triggered the formation of cofilin-actin rods, synapse disruptors, in cultured hippocampal neurons and in the hippocampus of synucleinopathy mouse models and of LBD patients. *In vivo*, cofilin pathology was present concomitantly with synaptic impairment and cognitive dysfunction. Rods generation prompted by αSyn involved the co-action of the cellular prion protein (PrP^C) and the chemokine receptor 5 (CCR5). Importantly, we showed that CCR5 inhibition, with a clinically relevant peptide antagonist, reverts dendritic spine impairment promoted by αSyn.
Conclusions: Our findings show that αSyn disrupts hippocampal synaptic structure by inducing the formation of cofilin-actin rods via PrP^C and CCR5. Importantly, we identify CCR5 as a novel therapeutic target to prevent synaptic impairment and cognitive dysfunction in LBD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0062 / #303

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

M1 MELANOPSIN GANGLION CELL DEGENERATION IN THE 3XTG MOUSE MODEL

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Luis Perez De Sevilla Muller, Brandy Recio, Amirreza Toloei, Nicholas Brecha
UCLA, Neurobiology, Los Angeles, United States of America

Aims: Objectives: This study aimed to investigate M1 melanopsin ganglion cell degeneration in the 3xTg mouse retina using specific melanopsin antibodies and morphological analysis. With circadian rhythm disruption observed in Alzheimer's disease (AD), our objectives were to test if melanopsin ganglion cell-related cellular changes, which are known to contribute to sleep disorders and circadian dysfunction, occurs in this mouse model of AD.
Methods: Methods: We examined M1 melanopsin ganglion cell degeneration in 3xTg mouse retinas using specific antibodies and a morphological analysis of wholemount retinas. Analysis focused on quantifying cell loss, and dendritic morphology. A range of ages of 6- to 12-month-old were studied to establish the temporal progression of degeneration.
Results: Results: Immunohistochemistry revealed progressive melanopsin ganglion cell degeneration in 3xTg mice. Morphological analysis demonstrated significant cell loss, and dendritic retraction. Notably, the degenerative process was more pronounced with increasing age, suggesting an age-dependent pattern.
Conclusions: Conclusions: Our study shows a degeneration of M1 melanopsin ganglion cells in the 3xTg mouse retinas, suggesting a link between circadian rhythm disruption and AD. The observed morphological changes underscore the connection between retinal degeneration and the circadian rhythm disturbances and sleep disorders seen in AD. Understanding the cellular basis of these changes may guide future therapeutic strategies aimed at mitigating circadian rhythm dysfunction and sleep disturbances associated with AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0063 / #1982

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

SUBTLE INFLAMMATORY CHANGES AND SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Andrea Pilotto[1], Virginia Quaresima[1], Alice Galli[2], Marta Parigi[2], Chiara Tolassi[2], Chiara Trasciati[2], Elena Marcello[3], Salvatore Caratozzolo[2], Alberto Benussi[2], Clara Tirloni[2], Silvia Pellucchi[3], Monica Di Luca[3], Alessandro Padovani[1]
[1]University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy, [2]University of Brescia, Neurology Unit, Department Of Clinical And Experimental Sciences, Brescia, Italy, [3]university of milan, Department Of Pharmacology, milan, Italy

Aims: Aim of the study was to evaluate the correlation between subtle inflammatory alterations and synaptic dysfunction in Alzheimer's disease.
Methods: : sixty AD patients and 20 age-matched controls underwent CSF analyses for neurogranin, Tau, P-tau and Abeta amyloid, NfL, GFAP, and inflammatory markers as well as an extensive cognitive, behavioral and motor assessment. Correlations between CSF biomarkers were evaluated using partial correlation adjusted for the effect of age, sex and disease duration.
Results: AD patients exhibited higher levels of neurogranin and inflammatory CSF markers compared to controls. Neurogranin showed a strong correlation with inflammatory markers in CSF, independently from the relationship with neuronal and amyloid related.
Conclusions: this study suggested a shared mechanism linking synaptic dysfunction and subtle inflammatory alterations in early Alzheimer disease that need to be confirmed in on going longitudinal studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0064 / #1267

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

EFFECT OF OLIGOMERIC AMYLOID BETA ON GLUTAMATERGIC EXOCYTOSIS IN IPSC-DERIVED CORTICAL NEURONS

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Ajay Pradhan[1], Max Lindberg[2], Hanna Karlsson-Fernberg[3], Sandra Roselli[1], Stefanie Fruhwürth[1], Sara Linse[4], Jörg Hanrieder[1,5], Ann-Sofie Cans[3], Henrik Zetterberg[1,5,6,7,8,9]
[1]University of Gothenburg, Department Of Psychiatry & Neurochemistry, Gothenburg, Sweden, [2]Lund University, Department Of Biochemistry And Structural Biology, Lund, Sweden, [3]Chalmers University of Technology, Department Of Chemistry And Chemical Engineering, Gothenburg, Sweden, [4]Lund University, Biochemistry And Structural Biology, Lund, Sweden, [5]Department of Neurodegenerative Disease, Ucl Institute Of Neurology, London, United Kingdom, [6]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [7]UK Dementia Research Institute, Ucl Institute Of Neurology, London, United Kingdom, [8]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China, [9]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America

Aims: Alzheimer's disease is characterized by amyloid beta accumulation, leading to synaptic dysfunction. Although oligomeric amyloid beta is implicated in synaptic impairment and neurodegeneration, the underlying mechanisms remain a topic of debate. Our current research project focuses on elucidating the specific effects of amyloid beta on glutamate exocytosis in induced pluripotent stem cell (iPSC)-derived cortical neurons.
Methods: Mature human iPSC-derived neurons were exposed to either 100 nM recombinant monomeric amyloid beta or a combination of 100 nM monomers and 1 nM mature amyloid fibrils for 10 minutes to promote the formation of oligomeric species. To assess synaptotoxicity at the neurites, we employed ultrafast amperometric glutamate biosensors. Exocytotic release of glutamate from discrete synaptic vesicles at the neurites was stimulated by the application of a high-concentration potassium chloride solution. Glutamate release was then recorded electrochemically with a high sampling rate of 100 kHz in both treated and non-treated neurons.
Results: In this ongoing project, our observations to date indicate that a brief 10-minute incubation of iPSC-derived neurons with a solution containing 100 nM amyloid beta monomers and 1 nM mature fibrils led to a dramatic reduction in glutamate exocytosis. Conversely, incubation with 100 nM amyloid beta monomers alone for 10 minutes did not result in impaired glutamate release. However, a 1-hour incubation with the same solution resulted in a noticeable reduction in glutamate exocytosis.
Conclusions: Preliminary data suggests that iPSC-derived neurons are highly sensitive to the synaptotoxic effects of amyloid beta aggregates. Even a brief exposure time can affect glutamate release, as evidenced by electrochemical detection.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0065 / #947

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

BLOOD-BASED SNAP-25, GFAP AND NFL IN ALZHEIMER'S DISEASE; RELATION TO COGNITION, ATROPHY AND SYNAPTIC DENSITY

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Mathias Sauer[1], Charlotte De Rocker[2], Lana Grötschel[1], Julie Goossens[3], Andréa L. Benedet[1], Michael Schöll[4], Johanna Nilsson[1], Ann Brinkmalm[5], Shorena Janelidze[6], Erik Stomrud[6], John O'Brien[7], Leonidas Chouliaras[7], Maura Malpetti[8], James Rowe[8], Henrik Zetterberg[9], Kaj Blennow[9], Oskar Hansson[6], Eugeen Vanmechelen[3], Nicholas Ashton[10]
[1]Gothenburg University, Department Of Psychiatry & Neurochemistry, Molndal, Sweden, [2]ADx NeuroSciences, Neuroscience, Gent, Belgium, [3]AdX, Neurosciences, Gent, Belgium, [4]University of Gothenburg, Wallenberg Centre For Molecular And Translational Medicine, Gothenburg, Sweden, [5]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, Gothenburg, Sweden, [6]Lund University, Department Of Clinical Sciences, Lund, Sweden, [7]University of Cambridge, Department Of Psychiatry, Cambridge, United Kingdom, [8]University of Cambridge, Clinical Neurosciences, John Van Geest Centre For Brain Repair, Cambridge, United Kingdom, [9]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [10]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden

Aims: Blood biomarkers related to neurodegeneration have shown association with cognitive decline and brain atrophy. Recently, the detection of synaptic pathology in blood may offer additional value to a blood-based relationship of neurodegeneration. In this study, we investigated the additional value of blood SNAP25 to blood GFAP and NfL.
Methods: We examined 110 participants (54 AD and 56 healthy controls) from the Swedish BioFINDER pilot study. The mean age of patients was 75.9 years (7.1 SD) and there was an even distribution of sex. We examined group differences by the Wilcoxon rank sum test and associations between the blood markers and MRI and MMSE were determined by linear regression, adjusting for age and sex, and in combination with each other. GFAP and NFL were measured by commercial Simoa assays 4-Plex E kit and SNAP25 with a prototype Simoa assay, developed from a previously validated in-house CSF assay.
Results: All blood biomarkers were significantly increased in patients with AD as compared to controls. These three biomarkers significantly correlated with each other (R=0.42-0.56; p=<0.001). SNAP-25 and GFAP associated with cortical thickness (β=-0.05, p=0.009; β=-0.09, p=<0.001) but not NFL. The biomarkers associated with MMSE (SNAP-25 β=-6.69, p=0.001; GFAP β=-2.46, p=<0.001; NFL β=-1.52, p=0.007). Only GFAP associated with cortical thickness and MMSE in the AD group alone (β=-0.08, p=0.002; β=-1.99, p=<0.015). GFAP is the only marker contributing to the model when combining the markers to predict cortical atrophy and MMSE.
Conclusions: In this pilot study, blood SNAP25, NfL, and GFAP were significantly associated with cognition and brain atrophy. Yet only GFAP was associated with these measures in the symptomatic group. In a multivariate model, SNAP25 did not add additional value in the association of blood biomarkers and neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0066 / #582

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

ASTROCYTIC-TO-MICROGLIAL ENDOZEPINE SIGNALING REGULATES SYNAPTIC PRUNING IN ALZHEIMER'S DISEASE

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Yuan Shi[1,2,3], Mochen Cui[1,2,4], Juan Zu[1,2,4], Viktoria Ruf[1], Qiang Huang[1,2], Jochen Herms[1,2,3]
[1]Ludwig-Maximilians-Universität München, Center For Neuropathology, Munich, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Department Of Translational Brain Research, Munich, Germany, [3]Ludwig-Maximilians-Universität München, Munich Cluster For Systems Neurology (synergy), Munich, Germany, [4]Ludwig-Maximilians-Universität München, Munich Medical Research School, Munich, Germany

Aims: Astrocytes and microglia have been demonstrated to independently engulf synapses in Alzheimer's disease (AD), employing various mechanisms. However, whether they communicate with each other and jointly modulate synapses is less well defined. Endozepine diazepam binding inhibitor (DBI) is primarily produced and released by astrocytes and prominently binds to microglia which is pivotal in engulfing synapses. Here, we aimed to investigate whether the synaptic loss in AD is dependent on DBI-mediated astrocyte-microglia communication.
Methods: Synaptic plasticity of eGFP-labeled apical dendrites in *APPswe/PS1dE9* mice are monitored using longitudinal 2-photon *in vivo* imaging. DBI expression is acquired and analyzed using super-resolution confocal microscopy coupled with 3D reconstruction. Furthermore, spatial transcriptomic and single-cell RNA sequencing are employed to determine the astrocytic subpopulations based on their relative locations to plaques. Besides animal models, we assessed alterations of plaque-surrounding astrocytes and microglia in human postmortem brain tissues from patients with AD.
Results: We observed a gradually decreased synaptic density in *APPswe/PS1dE9* mice around amyloid plaques, coupled with heightened astrocytic DBI as well as their transmission into microglia. Moreover, microglia in *APPswe/PS1dE9* mice show promoted synaptic engulfment. These effects were mitigated by interfering with DBI signaling using shRNA or genetic depletion. Similar to *APPswe/PS1dE9* mice, we observed elevated astrocytic DBI and microglial synaptic engulfment in postmortem brain tissues from AD patients, compared to healthy controls.
Conclusions: These results collectively reveal that the astrocyte-microglia communication is dysregulated in AD via aberrantly activated DBI signaling, leading to excessive synaptic loss that can be ameliorated by DBI suppression. Our finding supports endozepine DBI as a potential therapeutic target for rescuing AD-related synaptic loss, and glial communication as an intriguing aspect for developing new strategies for treating neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0067 / #1151

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

COMPLEXINS AND THE DEVELOPMENT OF EARLY AD PATHOLOGIES IN PARVALBUMIN INTERNEURONS

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Kelly South Pham[1], Sneha Malepati[1], Matthew Rowan[2]
[1]Emory University, Department Of Cell Biology, Atlanta, United States of America, [2]Emory University School of Medicine, Cell Biology, Atlanta, United States of America

Aims: The cellular and proteomic complexity of the mammalian brain contributes to differential vulnerabilities to pathology development during preclinical Alzheimer's disease (AD). The group of presynaptic proteins called complexins (Cplx) have been identified as "pro-resilient" against cognitive decline in human tissues. Cplx also appears to be preferentially expressed in inhibitory cells, with our group recently identifying that Cplx proteins are extremely enriched in the parvalbumin interneuron-specific proteome with respect to excitatory neurons. Here we investigate the distribution of complexin-positive parvalbumin interneurons across multiple brain regions and how modifying the abundance of complexins contributes to the emergence of AD pathologies.
Methods: We stereotaxically injected a parvalbumin interneuron-specific fluorescent marker into the primary somatosensory (SS) cortex and lateral entorhinal cortex (LEC) and performed immunohistochemistry (IHC) to characterize the quantity of co-localization of parvalbumin interneurons and complexins in different brain regions. We then used an adult-onset, region-specific AAV approach in conjunction with a CRISPR/Cas9 construct to knockdown complexins in parvalbumin interneurons in a cell-type- and region-specific manner. We then performed IHC to characterize any pathological amyloid and tau species produced as a result of the complexin knockdown.
Results: We quantified the amount of complexin-positive parvalbumin interneurons in the LEC, a highly vulnerable region in AD. We further quantified the extent of amyloid and tau pathologies which occur in response to the knockdown of complexins in parvalbumin interneurons in the LEC compared to controls.
Conclusions: These results confirm some of the "pro-resilient" qualities of complexins in protecting a highly vulnerable neuron and brain region, revealing a potential therapeutic genetic intervention for preclinical AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0068 / #829

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

SIGNALING MECHANISMS OF GLUTAMATERGIC SYNAPSE MAINTENANCE AND DEGENERATION

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Yimin Zou
University of California, San Diego, Neurobiology, La Jolla, United States of America

Aims: The synapses are the computational unit of neural circuits. Reduction of synaptic numbers and decline of synaptic functions, which occur early in Alzheimer's disease and Parkinson's disease, are closely correlated with and may be a key underlying mechanism of the decline of brain function.
Methods: Work from our lab showed that the planar cell polarity (PCP) signaling pathway plays an essential and direct role in glutamatergic synapses formation in development and glutamatergic synapse maintenance in adulthood (Thakar et al., 2017) (Zou, 2020) (Ban et al., 2021) (Feng et al., 2021). The PCP proteins are localized in the developing and adult synapses and interact with synaptic scaffold proteins and glutamate receptors and are responsible for the formation and stability of the vast majority of glutamatergic synapses in the brain.
Results: Our lab found that planar cell polarity is the key signaling mechanism for synapse maintenance and the direct target for amyloid β induced synapse degeneration (Feng et al., 2021). Oligomeric Aβ binds to Celsr3 and weakens the interaction between Celsr3 and Frizzled3 and assists Vangl2 in disassembling synapses. A regulator of PCP signaling, Ryk, is also required for Aβ-induced synapse loss functioning together with Vangl2. In the 5XFAD mouse model of Alzheimer's disease, Ryk conditional knockout in neurons or intracerebroventricular infusion of a function-blocking monoclonal Ryk antibody protected synapses and preserved cognitive function (Feng et al., 2021).
Conclusions: Therefore, the PCP pathway has emerged as a key regulatory mechanism for synapse degeneration and provides novel target to understand and intervene with neurodegeneration. I will present new progress in understanding how oligomeric Aβ and phosphorylated tau lead to glutamatergic synapse degeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0069 / #1006

Poster Topic: *Theme A: β-Amyloid Diseases / A01.d. Disease Mechanisms, Pathophysiology: Synaptic plastcity & synapse pathology*

EXERCISE DAMPENS MICROGLIAL SYNAPTIC ENGULFMENT IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY

Juan Zu[1,2,3], Mochen Cui[1,2,3], Fang Zhang[2], Gerda Mitteregger[1], Yuan Shi[1,2,4], Jochen Herms[1,2,4]
[1]Ludwig-Maximilians-Universität München, Center For Neuropathology, Munich, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Department Of Translational Brain Research, Munich, Germany, [3]Ludwig-Maximilians-Universität München, Munich Medical Research School, Munich, Germany, [4]Ludwig-Maximilians-Universität München, Munich Cluster For Systems Neurology (synergy), Munich, Germany

Aims: Emerging evidence substantiates the effects of exercise in ameliorating cognitive impairment in Alzheimer's disease (AD). However, the precise mechanisms engendered by exercise in AD remain elusive. Microglia play a central role in AD-associated dementia via eliminating synapses. Here we aim to investigate whether and how long-term voluntary exercise affects microglial synaptic engulfment in the AD context.
Methods: We utilized three-month-old *APPswe/PS1dE9* (*ΔE9*) mice that emulate the amyloid plaque profile of AD and housed them individually with either operational or blocked running wheels. After three months of voluntary exercise, the brains from both cohorts were harvested. We conducted multiplex immunostaining, super-resolution microscopy, and 3D-reconstruction-based analysis to measure the engulfed synaptic materials spatially localized in microglial lysosomes.
Results: We ascertained that exercise reduces microglial lysosomal content (CD68) and their phagocytosis of synaptic materials (PSD95). With this altered functionality, we uncovered a notable elevation in microglial α7 nicotinic acetylcholine receptors (nAchRα7) – the principal microglial acetylcholine receptors, generally reduces in the AD context – following long-term exercise in *ΔE9* mice. Furthermore, under the stimulation of *ΔE9* mice brain extraction, we observed that primary microglia exposed to acetylcholine chloride revealed heightened nAchRα7 expression and significantly reduced synaptosomes phagocytosis, both of which were blocked by a nAchRα7 antagonist – methyllycaconitine citrate.
Conclusions: In summary, our results furnish evidence that long-term exercise mitigates excessive microglial phagocytosis of synaptic materials through nAchRα7 modulation, providing a prospective therapeutic target for the modification of AD pathophysiology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0070 / #1063

Poster Topic: *Theme A: β-Amyloid Diseases / A01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

CAMKIIALPHA IS OXIDIZED AND ACTIVATED BY OLIGOMERIC AMYLOID-BETA

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Hugo Fanlo-Ucar[1], Pol Picón-Pagès[2], Víctor Herrera-Fernández[2], Sira Ausellé-Bosch[2], Lorena Galera-López[2], Daniela Gutiérrez[3], Andrés Ozaita[2], Alejandra Álvarez[3], Baldomero Oliva[2], Francisco J. Muñoz[2]
[1]UPF-MELIS (PRBB), Department Of Medicine And Life Sciences, Barcelona, Spain, [2]Universitat Pompeu Fabra, Melis, Barcelona, Spain, [3]Pontificia Universidad Católica de Chile, Centro Uc De Envejecimiento Y Regeneración (care), Santiago, Chile

Aims: Memory function relies on hippocampal formation through long-term potentiation (LTP), which involves NMDA receptors activation, the subsequent autophosphorylation of CaMKIIα and the nuclear translocation of the transcription factor CREB. In addition, it is known that amyloid beta-peptide oligomers (oAβ) lead to synaptic loss, dramatically affecting memory. Nonetheless, how this pathological mechanism occurs is not well understood. Therefore, we examined the impact of oAβ on CaMKIIα.
Methods: i) *In vitro* biochemical kinase assays, ii) molecular/cellular biology studies with SH-SY5Y cells, murine hippocampal neurons, brain samples from control and AD individuals and control and AD transgenic mice and iii) modelling by bioinformatic analysis.
Results: Our findings show that oAβ generates reactive oxygen species (ROS), which significantly oxidize CaMKIIα (ox-CaMKIIα), which is also significantly present in AD brain samples. Additionally, we demonstrated that oxidation induces a conformational change in the structure that hinders the recovery of the native conformation, promoting an activated state of CaMKIIα. We also discovered that its phosphorylation is mutually exclusive with oxidation. In both AD transgenic mouse brains and primary cultures of murine hippocampal neurons, we demonstrated that the oxidation of CaMKIIα leads to the phosphorylation of CREB and its translocation to the nucleus. We also found that oAβ induces an increase in the transcription of the pro-survival CREB target genes ARC and BDNF.
Conclusions: Our data suggest that CaMKIIα oxidation may work as a protective mechanism triggered when neurons are exposed to oAβ, but it can have deleterious effects at long term. This work was supported by Spanish Ministry of Science and Innovation and Agencia Estatal de Investigación through grants PID2020-117691RB-I00/AEI/10.13039/501100011033, BIO 2020-113203RB and PID2021-123482OB-I00 plus FEDER Funds. CONICYT-Chile: Fondecyt 12011668 and Millennium Science Initiative Program-ICN09-016/ICN 2021-045.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0071 / #734

Poster Topic: *Theme A: β-Amyloid Diseases / A01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

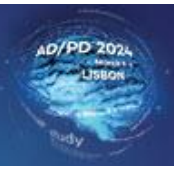
APOE4 IS INSTRUMENTAL IN AUGMENTING RHOA KINASE PHOSPHORYLATION AND CONTRIBUTES THEREBY TO CLASSICAL ALZHEIMER'S DISEASE NEURON PHENOTYPES

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Kristine Freude, Ruixin Tao
University Of Copenhagen, Health Sciences, Frederiksberg, Denmark

Aims: Validation that the APOE4 allele is linked to increased RhoA phosphorylation in neurons. Mechanistic insights into how APOE4 affects the RhoA phosphorylation level in neurons in spradic AD.
Methods: In vitro differentiation of iPSC to glutamatergic neurons, assessment of RhoA activitiy via G-Lisa and western blot. GC-MS and HPLC to measure cholesterol and geranylgeranyl pyrophosphate. Immunocytochemistry, transmission electron microscopy, Multielectrode assays to invesigate synaptic deficits.
Results: Succesful differentiation of glutamatergic neurons from iPSCs carrying various APOE genotypes. The level of normalized RhoA activation level was significantly higher in neurons carrying APOE 4/4 than those carrying APOE 2/2 and APOE 3/3. Even though APOE protein are mainly produced by astrocytes in the brain, it could also be detected in in-vitro differentiated glutamatergic neurons. Moreover, a slight decrease in APOE protein generation in APOE4/4 neurons could be observed. The gene expression level of geranylgeranyl pyrophosphate synthase did not demonstrate significant differences among each cell line. However, the content of geranylgeranyl pyrophosphate was assessed by HPLC and showed an increased trend in APOE4/4 neurons. The increased phosphorylation Tau and secretion of Abeta, as well as dysfunction of synapes observed in neurons carrying the APOE4/4 was reversible via RhoA inhibition.
Conclusions: Our reserach shows that the allelic status of APOE is linked to the phosphorylation of RhoA. An increased level of phosphorylated RhoA was observed in APOE4/4 neurons, leading to AD-specific neuronal pathologies and can be rescued via RhoA inhibition.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0072 / #1148

Poster Topic: *Theme A: β-Amyloid Diseases / A01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

RELATIONSHIPS BETWEEN SIGNAL TRANSDUCTION DISRUPTIONS CAUSED BY MAP KINASES IN ALZHEIMER'S DISEASE

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Stephen Keegan[1], Gregory Cary[1], Jesse Wiley[2], Gregory Carter[1]
[1]The Jackson Laboratory, The Jackson Laboratory, Bar Harbor, United States of America, [2]Sage Bionetworks, Sage Bionetworks, Seattle, United States of America

Aims: The TaRget Enablement to Accelerate Therapy Development for Alzheimer's Disease (TREAT-AD) consortium is missioned to provide tools to the Alzheimer's research community for the development of novel therapeutics. Here we bioinformatically establish the cascading effects of therapeutically targeting MAPK-14.
Methods: The grouping of Alzheimer's disease (AD) candidate proteins into distinct biological domains provides the framework for a biologically interpretable bioinformatic analysis. Exploring the interaction networks assembled from AD biological domains using a weighted key driver analysis yields insight into the potential causality of genes annotated to the domains. Genes in the network are weighted by their TREAT-AD Target Risk Score derived from a meta-analysis of genetic and multi-omics studies pertaining to AD, including ADSP and AMP-AD. Local subgraphs of genes surrounding key drivers implicate genes hypothesized to be impacted by a disease-related change in a driver gene.
Results: We found MAPK-14, annotated to the oxidative stress biological domain, to be a top key driver gene. The subgraph comprised of genes that are neighbors to MAPK-14 comprise the genes most likely to be impacted by changes in the mRNA or protein expression of MAPK-14. We found that changes in MAPK-14 expression are predicted to alter signaling pathways corresponding to cellular responses to lipopolysaccharide stimulus. Within the subnetwork driven by MAPK-14 are the EP300 and PRKCE genes which are involved in the regulation of apoptotic signaling pathway and Fc receptor signaling pathway respectively.
Conclusions: Using the biological domain annotations and weighted key driver analysis, the causality of genes in an interaction network can be inferred. We predict that the modulation of MAPK-14 will stabilize other signal transduction changes in AD brains.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0073 / #1241

Poster Topic: *Theme A: β-Amyloid Diseases / A01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

RNF10 IS A NOVEL SYNAPSE-TO-NUCLEUS MESSENGER OF AMYLOID SYNAPTOTOXICITY

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Elena Marcello[1], Laura D'Andrea[1], Stefano Musardo[1], Ramona Stringhi[1], Filippo La Greca[1], Silvia Pelucchi[1], Nicolò Carrano[1], Ana Ribeiro[1], Bahar Aksan[2], Matteo Audano[1], Francesca Genova[1], Daniela Mauceri[2], Nico Mitro[1], Diego Scheggia[1], Fabrizio Gardoni[1], Monica Di Luca[1]
[1]Università degli Studi di Milano, Department Of Pharmacological And Biomolecular Sciences, Milano, Italy, [2]Heidelberg University, Department Of Neurobiology, Heidelberg, Germany

Aims: Synaptonuclear messengers translate synaptic signaling into changes in gene transcription, thus modulating long-term functional modifications of the synapto-dendritic input. Alterations of such proteins lead to synaptic failure, suggesting a contribution to synaptopathies such as Alzheimer's Disease (AD). During AD early stages, the amyloid-β peptide (Aβ) oligomers trigger the disruption of mechanisms of neuronal plasticity, eventually resulting in synapse loss and in cognitive deficits. In this frame, the synaptonuclear messenger RING Finger Protein 10 (RNF10) operates as a mobile hub that docks NMDA receptor-derived signalosomes to nuclear target sites, regulating genes involved in spine morphology and AD pathogenesis. We aimed at investigating potential involvement in AD-synaptic dysfunction.
Methods: We used several imaging and biochemical approaches to investigate RNF10 pathway in AD in vitro and in vivo models.
Results: RNF10 expression and localization are altered in the hippocampus but not in the cortex of AD patients. To investigate the RNF10-triggered neuronal pathways in AD, we exposed primary hippocampal cultures to Aβ oligomers. Aβ triggers a calcium-dependent NMDA receptor-induced RNF10 nuclear translocation. RNASeq data show that RNF10 silencing prevents the Aβ oligomers-driven changes in the expression of genes implicated in mitochondrial function and synaptic plasticity, such as neurogranin. In the hippocampus of APP/PS1 mice we detected an upregulation of RNF10 signaling in the initial stages of the pathology. The RNF10 downregulation in the hippocampus of APP/PS1 mice before the onset of the pathology can upregulate the levels of neurogranin and ATP synthase in mitochondria and, thereby, restores cognitive function.
Conclusions: Our findings suggest that RNF10 can play a key role in translating Aβ-induced signaling into synaptic and mitochondrial dysfunction, thus contributing to AD cognitive deficits.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0074 / #1662

Poster Topic: *Theme A: β-Amyloid Diseases / A01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

AMYLOID BETA-OLIGOMERS INHIBIT THE NUCLEAR CA2+ SIGNALS AND THE NEUROPROTECTIVE GENE EXPRESSION INDUCED BY HIPPOCAMPAL NEURONAL ACTITIVTY

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Andrea Paula-Lima[1,2,3,4], Pedro Lobos[3,5], Ignacio Vega-Vasquez[3], Barbara Bruna[5], Silvia Gleitze[3], Jorge Toledo[6], Steffen Härtel[3,6,7], Cecilia Hidalgo[3,4,8]
[1]Universidad de Chile, Institute For Research In Dental Sciences (icod), Faculty Of Dentistry, Santiago, Chile, [2]Interuniversity Center for Healthy Aging (CIES), Universidad De Chile, Santiago, Chile, [3]Universidad de Chile, Biomedical Neuroscience Institute, Santiago, Chile, [4]Universidad de Chile, Department Of Neuroscience, Santiago, Chile, [5]Universidad de Chile, Advanced Clinical Research Center, Clinical Hospital, Santiago, Chile, [6]Universidad de Chile, Laboratory For Scientific Image Analysis, Center For Medical Informatics And Telemedicine, Faculty Of Medicine., Santiago, Chile, [7]Universidad de Chile, Anatomy And Biology Of Development Program, Institute Of Biomedical Sciences, Faculty Of Medicine, Santiago, Chile, [8]Universidad de Chile, Physiology And Biophysics Program, Institute Of Biomedical Sciences And Center For Exercise, Metabolism And Cancer Studies, Faculty Of Medicine, Santiago, Chile

Aims: Hippocampal neuronal activity generates dendritic and somatic Ca^{2+} signals, which depending on stimulus intensity, rapidly propagate to the nucleus and induce the expression of transcription factors and genes with crucial roles in cognitive functions. Soluble Amyloid-beta Oligomers (AβOs), the main synaptotoxins engaged in the pathogenesis of Alzheimer's disease, generate aberrant Ca^{2+} signals in hippocampal neurons, increase their oxidative tone and disrupt structural plasticity. Here, we explored the effects of sub-lethal AβOs concentrations on activity-generated nuclear Ca^{2+} signals and on the Ca^{2+}-dependent expression of neuroprotective genes.
Methods: To induce neuronal activity, neuron-enriched primary hippocampal cultures were treated with the $GABA_A$ receptor blocker gabazine (GBZ), and and nuclear Ca^{2+} signals were measured in AβOs-treated or control neurons transfected with a genetically encoded nuclear Ca^{2+} sensor. Cytoplasmic Ca^{2+} signals were detected in neurons transfected with the genetically encoded cytoplasmic Ca^{2+} sensor, or loaded with Fluo-4 or FURA-2 indicators. To evaluate whether AβOs interrupt the GBZ-induced increase in CREB phosphorylation, we used immunofluorescece (Ser-133 p-CREB). The mRNA levels of Neuronal Per Arnt Sim domain protein 4 (Npas4), Brain-derived Neurotrophic Factor (Bdnf), Ryanodine Receptor type-2 (RyR2), and the antioxidant enzyme NADPH-Quinone-Oxidoreductase (Nqo1) were determined by qPCR. Statistical analysis was performed with One-way ANOVA followed by Bonferroni test or two-tailed Student's t-test.
Results: Incubation (6 h) with AβOs significantly reduced the nuclear Ca^{2+} signals and the enhanced phosphorylation of CREB induced by GBZ. Likewise, incubation (6 h) with AβOs significantly reduced the GBZ-induced increases in the mRNA Npas4, Bdnf, RyR2 and the antioxidant enzyme Nqo1.
Conclusions: Based on these findings we propose that AβOs, by inhibiting the generation of activity induced nuclear Ca^{2+} signals, disrupt key neuroprotective gene expression pathways required for hippocampal-dependent learning and memory processes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0075 / #2174

Poster Topic: *Theme A: β-Amyloid Diseases / A01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

BETA-AMYLOID:NA,K-ATPASE:SRC KINASE SIGNALING PATHWAY IN ALZHEIMER'S DISEASE

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Maria Strelkova[1], Anna Tolstova[1], Alexei Adzhubei[1,2], Evgeny Barykin[1], Vladimir Mitkevich[1], Alexander Makarov[1], Irina Petrushanko[1]
[1]Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Laboratory Of Protein Conformational Polymorphism In Health And Disease, Moscow, Russian Federation, [2]Washington University School of Medicine and Health Sciences, Department Of Microbiology, Immunology, And Tropical Medicine, Washington, United States of America

Aims: Src-kinase plays an important role in neurogenesis, metabolism and receptor sensitivity. This work is aimed at investigation of the putative role of beta-amyloid in Src-kinase hyperactivation in Alzheimer's disease and characterisation of their interaction with Na,K-ATPase that mediates this process.
Methods: Src-kinase autophosphorylation was performed *in vitro*. The autophosphorylated Src-kinase levels were measured as phospho-Y416 Src/Src Western blot signals ratio. The dissociation constants were measured with the Microscale Thermophoresis using His-tag labeling. The full-length Src-kinase conformations were obtained with REHTMD using GROMACS software. Open source servers were used for global docking. The results were analyzed with QASDOM server.
Results: We have shown for the first time that beta-amyloid acts as a specific ligand of Na,K-ATPase, triggering the activating autophosphorylation of Src-kinase bound to Na,K-ATPase.

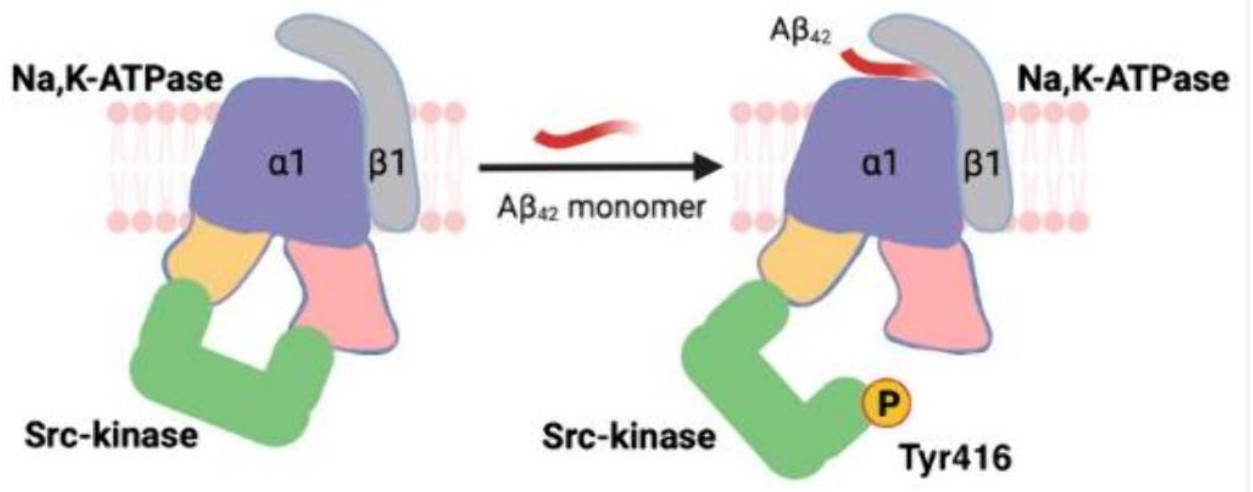


Fig.1. The presumptive scheme of Src-kinase activation by beta-amyloid (Petrushanko et al., *Cells*, 2022). By now we have looked further into Src:Na,K-ATPase interaction. The similarity of dissociation constants obtained for dephosphorylated Src:Na,K-ATPase complex and for autophosphorylated Src:Na,K-ATPase revealed that interaction between Src SH2-domain and Na,K-ATPase is essential for the whole complex stability. Semi-stable conformations of full-length Src-kinase including N-terminal domain were obtained and consequently used in global docking with Na,K-ATPase structure. The comparison between predicted interaction interfaces of Na,K-ATPase with full-length Src-kinase structures and structures of crystalline Src-kinase without N-terminal domain demonstrates the crucial

role of Src-kinase N-terminus in its interaction to Na,K-ATPase.

Conclusions: The neurotoxic effects of beta-amyloid in Alzheimer's disease may be associated with the long-term activation of Src-kinase through Na,K-ATPase:beta-amyloid interaction, thus making the complex the potential therapeutic target. To impair its stability, the competitive inhibitors to the SH2- or N-terminal domain of Src-kinase can be developed. This research was funded by Russian Science Foundation (Grant#19-74-30007).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0076 / #2476

Poster Topic: *Theme A: β-Amyloid Diseases / A01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

ASTROCYTE CA2+ SIGNAL UNCOUPLING TO CEREBROVASCULAR FUNCTION IN 5XFAD MODEL OF AMYLOID BURDEN

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Blaine Weiss[1], Chris Gant[1], Pradoldej Sompol[2], Olivier Thibault[3], Susan Kraner[1], Christopher Norris[2]
[1]University of Kentucky, Sanders Brown Center On Aging, Lexington, United States of America, [2]University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America, [3]University of Kentucky, Pharmacology, Lexington, United States of America

Aims: In this study, we investigated the impact of amyloid burden on astrocyte calcium signaling and stimulation-evoked vasoactivity in fully awake mice to characterize direct associations between stimulation-evoked neurovascular coupling and endfoot calcium signals.
Methods: 5XFAD and littermate control mice were aged to 6 months before they were injected with AAV2/5-Gfa104-jGCaMP8f into barrel cortex followed by cranial window installation. Fully awake mice were imaged 3 weeks later using two-photon microscopy. Cerebral architecture in barrel cortex was illuminated using 500kD rhodamine dextran. Functional hyperemia was assessed during timed air puff stimulation of the contralateral whiskers. Calcium signals were recorded from reactive astrocytes before, during, and after whisker stimulation. Transients were analyzed by change in fluorescence ΔF/F over different cellular compartments by custom Matlab algorithms. Using a modeling algorithm, vascular tone in response to stimulation was measured, along with attached endfoot calcium levels.
Results: Astrocytes from 5XFAD mice showed a significant reduction in endfoot calcium signaling amplitudes and delayed rise time compared to wild type controls. Signaling properties such as amplitude, kinetics, and connectivity within networks were also characterized between the 5XFAD and control mice. Astrocyte calcium signaling was initiated after the onset of neurovascular coupling, and 5XFAD mice exhibited a significant increase in latency between neurovascular tone changes, and peak endfoot calcium transience.
Conclusions: Astrocytes from 5XFAD mice showed a significant reduction in endfoot calcium signaling amplitudes and rise time compared to wild type controls. Signaling properties such as amplitude, kinetics, and connectivity within networks were also characterized between the 5XFAD and control mice. Astrocyte calcium signaling was initiated after the onset of neurovascular coupling, and 5XFAD mice exhibited a significant increase in latency between neurovascular tone changes, and peak endfoot calcium transience.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0077 / #1561

Poster Topic: *Theme A: β-Amyloid Diseases / A01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress, chaperones*

THE ROLE OF THE "UNFOLDED PROTEIN RESPONSE" AND THE PERK PATHWAY IN PARKINSON'S DISEASE: STUDY OF GENETIC POLYMORPHISMS

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

Marika Alborghetti[1], Nicole Piera Palomba[2], Edoardo Bianchini[1], Domiziana Rinaldi[1], Claudia Strafella[3], Valerio Caputo[3], Emiliano Giardina[3], Ferdinando Nicoletti[2], Teresa Esposito[4], Francesco Pontieri[1]
[1]Sapienza, University of Rome, Department Of Neuroscience, Mental Health And Sensory Organs (nesmos), Rome, Italy, [2]IRCSS Neuromed, Pozzilli, Is, Isernia, Italy, [3]IRCCS Fondazione Santa Lucia, Rome, Rome, Italy, [4]Institute of Genetics and Biophysics CNR, Biomedicine, Napoli, Italy

Aims: Background: The accumulation of α-synuclein in Parkinson's disease (PD) leads to the stress of endoplasmic reticulum (ER). The resulting cellular response is called "Unfolded Protein Responce" (UPR), and is activated with the aim of reducing protein synthesis and stimulating the expression of chaperone proteins to prevent protein aggregation and the degradation of already aggregated proteins. UPR is controlled by several sensor proteins, including PERK (PKR-like ER kinase). Aim of the study: To study a possible association between the development of PD and the presence of polymorphisms of the genes coding for proteins involved in the UPR and in particular in the PERK pathway.
Methods: This analysis focused on the study and analysis of 180 genetic variants (SNV) in a cohort of 800 PD patients and 600 healthy controls. Of these, 27 concern genes coding for proteins involved in the UPR (EIF2AK3, LRRK2, ATF4, ATF6, XBP1, BCL2, EIF2A, ERN1). The DNA
was extracted from the blood samples and the Open Array ™ technology allowed a massive and simultaneous genotyping of all the samples under examination.
Results: The analysis made it possible to find 51 SNVs with a statistically significant association with susceptibility to PD. Some of these concern EIF2AK3 coding for PERK. One missense genetic variant of EIF2AK3 resulted protective towards PD development.
Conclusions: Our study confirms the involvement of UPR and in particular of the PERK pathway in the development of PD. Further analyzes will be necessary to correlate these polymorphisms not only with the pathophysiological mechanisms, but also with the clinical course of PD. The PERK pathway represents a potential target for the development of new therapeutic strategies for both neuroprotective and symptomatological purposes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0078 / #1799

Poster Topic: *Theme A: β-Amyloid Diseases / A01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress, chaperones*

PROTEOMIC CHARACTERIZATION OF SPPL2B-DEFICIENT MICE REVEALS UP-REGULATION OF THE SYNAPTIC TRANSPORTER KINESIN-LIKE PROTEIN KIF1A ACCOMPANIED BY INCREASED LOCOMOTOR ACTIVITY

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

Cristina Contini[1], Greca Lai[1], Alessandra Schirru[1], Jack Badman[2], Per Nilsson[2], Tiziana Cabras[1], Simone Tambaro[2]
[1]University of Cagliari, Dep. Life And Environmental Sciences Biomedical Section, Proteomics Unit University Of Cagliari, Monserrato, Italy, [2]Karolinska Institute, Department Of Neurobiology, Care Sciences And Society, stockholm, Sweden

Aims: Signal Peptide-Peptidase like 2b (SPPL2b) is an intramembrane brain-specific peptidase, part of the GxGD-type aspartyl proteases family, similar to the enzymatically related presenilin proteins. SPPL2b is involved in the cleavage of several Alzhimer´s disease (AD)-related type II substrates, such as BRI2, TNF-alpha, Clec7a, and Neuregulin-1. The SPPL2b cleavage releases intracellular fragments, which are either degraded or act as signaling molecules. The physiophatological role of SPPL2b remains elusive. This study aims to investigate the effect of SPPL2b genetic deletion to identify alterations in the brain proteome and their impact on mice behavior.
Methods: We evaluated cortex and hippocampus proteome in SPPL2b-deficient and wild-type mice at 3 and 12 months of age. The brain tissues were analyzed using a shot-gun proteomic approach based on high-resolution mass spectrometry. The observed up-regulation of the Kinesin-like protein KIF1A was investigated through Western Blot and Immunofluorescence analysis. Furthermore, SPPL2b mouse behavior was characterized using open field and Elevated plus maze tests.
Results: The proteomics from SPPL2b mice showed qualitative and quantitative differences between WT and KO mice and in relation to the age, as well as different protein interaction networks, were identified. Notably, the Kinesin-like protein KIF1A was consistently up-regulated in both cortex and hippocampus in 3 and 12-month-old mice. Further Western blot and immunofluorescence validation confirmed a significant up-regulation of KIF1A. Behavioral analysis showed significantly higher motility and a higher frequency in open arms in SPPL2b-deficeint mice.
Conclusions: These studies identified several proteins that may underlie distinct aspects of the physiological and pathological roles of SPPL2b, such as KIF1A, which mutagenesis or downregulation has been shown to be involved in neurodegeneration and AD. Furthermore, these data could hepl to identify candidate proteins for further development as biomarkers.

P0079 / #835

Poster Topic: *Theme A: β-Amyloid Diseases / A01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress, chaperones*

CHIP-SEQ DATA ANALYSIS REVEALED T CELL INVOLVED AUTOIMMUNITY IN THREE BRAIN REGIONS OF AD PATIENTS

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

Kun Han, Lin Wang, Zheng Yin, Stephen Wong
Houston Methodist Research Institute, Systems Medicine And Bioengineering, Houston, United States of America

Aims: Alzheimer disease (AD) is biologically characterized by the formation of pathologic β-amyloid-containing plaques and tau-containing neurofibrillary tangles. However, the causes have not been completely elucidated. In this study, our hypothesis is that autoinflammation might accumulate within the central nervous system, contributing to the pathogenesis of AD. The objective thus was to analyze publicly available Chip-seq datasets on the frontal cortex, hippocampus, and temporal cortex of healthy volunteers and AD patients to validate the hypothesis.
Methods: Chip-seq data analysis was performed on brain tissue samples from both healthy individuals and AD patients across a wide age range from 20 to over 100 years old.
Results: We identified age-irrelevant genes in all the three brain regions that significantly up- or down-regulated in AD patients compared to healthy individuals. Note that proinflammatory genes were overexpressed in AD patients, while anti-inflammatory genes were downregulated compared to healthy population. There are multiple human leukocyte antigen (HLA) members among the differentially expressed genes, suggesting a potential autoimmune response involving T cells targeting the central nervous system. Meanwhile, in the AD frontal cortexes, we identified age-relevant features that exhibited opposite expression patterns compared to healthy counterparts. Through pathway analysis, they can be classified into four major categories, with one category related to Neddylation, which is involved in proteasomal protein degradation to maintain homeostasis and has implications for antigen presentation, T cells activation, and AD.
Conclusions: In summary, we identified both age-irrelevant and relevant genes in three different brain regions of AD patients, suggesting a significant involvement of proinflammatory genes and potential T-cell mediated autoimmunity against the central nervous system in AD patients. We also highlighted the role of HLA genes and Neddylation-related pathways in AD pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0080 / #2386

Poster Topic: *Theme A: β-Amyloid Diseases / A01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress, chaperones*

CATHEPSIN B GENE DELETION IMPROVES BEHAVIORAL DEFICITS AND REDUCES PATHOLOGY IN MODELS OF ALZHEIMER'S DISEASE AND NEUROLOGICAL DISORDERS

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

Vivian Hook[1], Thomas Reinheckel[2], Junjun Ni[3], Zhou Wu[4], Mark Kindy[5], Christoph Peters[2], Gregory Hook[6]
[1]University of California, San Diego, Pharmaceutical Sciences, And Neurosciences, La Jolla, United States of America, [2]Albert Ludwigs University, Molecular Medicine, Freiburg, Germany, [3]Beijing Institute of Technology, Molecular Medicine, Beijing, China, [4]Kyushu University, Pharmacology, Fukuoka, Japan, [5]University of South Florida, Pharmaceutical Sciences, Tampa, United States of America, [6]American Life Science Pharmaceuticals, Neuroscience, La Jolla, United States of America

Aims: Cathepsin B is a powerful lysosomal protease. The goal of this research was to evaluate cathepsin B gene knockout outcomes for amelioration of brain behavioral dysfunctions and neuropathology in neurological disease animal models of Alzheimer's disease, traumatic brain injury, and related.
Methods: Several neurological disease mouse models of Alzheimer's disease (AD), traumatic brain injury (TBI), and others were subjected to cathepsin B gene knockout and evaluated for improvements in behavioral dysfunctions including memory deficit and compromised motor function. Brain neuropathology in AD models was assessed for Abeta peptides and amyloid load, and a TBI model was assessed for brain lesions and neuronal loss. These efforts assessed cathepsin B mediation of neurodegenerative disease conditions.
Results: Deletion of the cathepsin B gene resulted in significant improvements in behavioral deficits and provided amelioration of neuropathology of Alzheimer's disease (AD), traumatic brain injury (TBI), and related models of brain disorders. In AD models expressing amyloid precursor protein (APP) mimicking common sporadic AD, cathepsin B knockout improved memory deficit, ameliorated neuropathology, and reversed Abeta peptide biomarkers.
Conclusions: Overall, the extensive data provides strong evidence that deletion of the cathepsin B gene improves behavioral dysfunction and reduces brain neuropathology in Alzheimer's disease, traumatic brain injury, and related neurological disease models. These findings support cathepsin B as a drug target for inhibitors to block its upregulation and thereby ameliorate cognitive deficit in Alzheimer's disease and improve behavioral dysfunctions in TBI-related brain injuiry and related neurological diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0081 / #357

Poster Topic: *Theme A: β-Amyloid Diseases / A01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress, chaperones*

APOE4 ALTERS EARLY ENDOSOMAL DYNAMICS IN PRIMARY NEURONS

POSTERS: A01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES

Emma Nyberg[1], Sabine Konings[1], Nils Lindblom[1], Oxana Klementieva[1], Isak Martinsson[2], Gunnar Gouras[1]
[1]Faculty of Medicine, Lund University, Experimental Medical Science, Lund, Sweden, [2]Norwegian University of Science and Technology, Kavli Insitute For Systems Neuroscience And Center For Neural Computation, Trondheim, Norway

Aims: APOE4 genotype is the most important genetic risk factor for developing AD. Accumulating evidence suggests that ApoE4 affects the endosomal system; however, our understanding how ApoE4 affects the endolysosomal pathway in neurons is incomplete. We aim to explore how ApoE isoforms affect the endolysosomal system in primary mouse neurons and if it changes with time in culture (modelling ageing) and prolonged neuronal activity.
Methods: To study cellular changes in neurons, we use primary hippocampal/cortical brain cultures, harvested from ApoE KO mice and ApoE3 or ApoE4 targeted replacement mice. We analyse the neurons after 18 and 25 days in vitro (DIV18 and DIV25). To explore how ApoE isoforms adapt to elevated activity DIV18 primary cultures are treated for 48 h with bicuculline.
Results: We found that mature (DIV18) ApoE4 neurons present less prominent early endosomes in distal dendrites compared to ApoE3. With time in culture early endosomes seem to accumulate in distal dendrites of both ApoE4 and ApoE KO neurons. Regions with high default network activity are vulnerable to AD pathology. By treating the culture with bicuculline for 48 h we increase neuronal excitability, and we hypothesized that the endosomal system is affected differently between the ApoE isoforms. Preliminary data show that 48 h of bicuculline reduces the number of early endosomes in the cell soma in ApoE4 neurons compared to its baseline (untreated control). In contrast, ApoE3 and ApoE KO neurons have either increased, or similar numbers of early endosomes as their baseline.
Conclusions: The endolysosomal pathway is a highly dynamic and important system for neurons, and is increasingly linked to AD. Our preliminary findings point toward ApoE4 initially altering early endosomal dynamics in neurons. These alterations change depending on the cellular context.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0082 / #2323

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

TO INVESTIGATE THE THERAPEUTIC EFFECT OF HYPERICIN ON PARKINSON'S DISEASE AND ITS BIOLOGICAL MECHANISM BASED ON NRF2-ERK1/2 PATHWAY

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Li Shan Fan[1], Hui-Jie Fan[2], Qi Xiao[2], Si Xiang Niu[2], Lei Xu[2], Bao Guo Xiao[3], Cun Gen Ma[1], Zhi Chai[1]
[1]Shanxi University of Chinese Medicine, Shanxi University Of Chinese Medicine, jinzhong, China, [2]Shanxi University of Chinese Medicine, Shanxi University Of Traditional Chinese Medicine Multiple Sclerosis Key Research Laboratory, Jinzhong, China, [3]Fudan University, Institute Of Neurology, Huashan Hospital, Institutes Of Brain Science And State Key Laboratory Of Medical Neurobiology, Fudan University, shanghai, China

Aims: This study aims to regulate Nrf2-ERK1/2 signaling pathway through hypericin, inhibit oxidative stress, and finally achieve the purpose of treating PD.
Methods: Male C57BL/6 mice were divided into normal group, MPTP group, hypericin low, medium and high dose groups. In addition to the normal group, the remaining mice were intraperitoneally injected MPTP to establish Parkinson's disease model, once a day for 7 days. Since the first day of MPTP injection, hypericin low, medium and high dose groups were intragastricated with hypericin solution of 25 mg/kg, 50mg/kg and 100mg/kg, 0.2ml each, for 2 consecutive weeks. The expressions of tyrosine hydroxylase (TH), Nrf2 and p-ERK1/2 proteins in brain tissues of rats in each group were detected by Western Blot. The number of TH positive neurons in the substantia nigra was detected by immunofluorescence technique.
Results: Compared with the normal group, the gait frequency of each paw in MPTP group increased ((P<0.001); Compared with MPTP group, hypericin low-dose, medium-dose and high-dose groups reduced the footfrequency of each paw ((P<0.01). Western Blot results showed that compared with the normal group, the expressions of TH, Nrf2 and p-ERK1/2 proteins in MPTP group decreased ((P<0.01); Compared with MPTP group, TH, Nrf2 and p-ERK1/2 protein levels were increased in hypericin low, medium and high dose groups. Immunofluorescence results showed that the number of TH positive cells in MPTP group decreased compared with normal group, and the number of TH positive cells in hypericin low, medium and high dose groups increased compared with MPTP group.
Conclusions: Hypericin can effectively improve the motor dysfunction of PD mice, and has a protective effect on Daergic neurons of PD mice, which may be related to inhibiting oxidative stress.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0083 / #2026

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

BNIP3L/NIX-MEDIATED MITOPHAGY IMPAIRMENT IN GLUCOCORTICOID-ENRICHED ALZHEIMER'S DISEASED BRAINS

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Khanh Do[1,2], Minh Tran[1,2,3], You Jung Kang[2,3], Chaeyeon Been[2,4], Hansang Cho[1,2,3]
[1]Sungkyunkwan University, Department Of Intelligent Precision Healthcare Convergence, Suwon, Korea, Republic of, [2]Sungkyunkwan University, Institute Of Biophysics, Sungkyunkwan University, Suwon, Korea, Republic of, [3]Sungkyunkwan University, Department Of Biophysics, Suwon, Korea, Republic of, [4]Sungkyunkwan University, Department Of Biological Sciences, Sungkyunkwan University, Suwon, South Korea., Institute Of Biophysics, Sungkyunkwan University, Suwon, Korea, Republic of

Aims: Exposure to chronic stress or elevated glucocorticoid hormone levels has been associated with cognitive deficits and increased risk for Alzheimer's disease (AD), potentially due to negative impacts on mitophagy processes. However, the full extent of its impact on mitochondrial function balance in the AD brain cell system has not fully been understood. Here, we investigate the intracellular mechanisms of how elevated glucocorticoids induce BNIP3L/NIX-mediated mitophagy impairment in neurons and glial cells, contributing to AD.
Methods: This study uses a 9-week-long human mini-brain on a chip to delve into how glucocorticoids heighten AD markers by altering mitophagy activities, considering cortisol hypersecretion common in AD patients. Focusing on AD specifics and broader aging brain responses, we scrutinized the dysfunction of NIX-mediated mitophagy and the consequential aggregation of damaged mitochondria, fostering brain degradation.
Results: Our primary findings demonstrate that glucocorticoids induce the accumulation of damaged mitochondria in neurons by inhibiting NIX-driven mitophagy, subsequently causing a decrease in ATP production and synaptic density, along with the onset of tau pathology. Secondly, Prolonged co-culturing of astrocytes and neurons with high glucocorticoids leads to a dip in NIX-regulated mitophagy and a drop in mitochondrial genesis, likely influenced by the enhanced neuroinflammation evident with GFAP and MAO-B's activity. Finally, Glucocorticoids inflict mitochondrial damage in microglia but curtail proinflammatory markers (CD86, iNOS), weakening phagocytic action and resulting in Aβ accumulation.
Conclusions: In summary, sustained elevated levels of glucocorticoids obstruct mitophagy in neuronal and glial cells by inhibiting NIX, culminating in tau accumulation. This research highlights the critical need for research on developing therapies targeting mitochondrial efficacy in healthy aging.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0084 / #1868

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

STUDY OF MITOCHONDRIAL TRANSFER IN APP(NL-G-F) MICE PRIMARY NEURONAL CELLS

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Romain Giraud[1], Luana Naia[1], Liesbeth Voorbraeck[2], Shubin Guo[3], Maria Ankarcrona[2]
[1]Karolinska Institutet, Neurobiology, Care Sciences And Society, STOCKHOLM, Sweden, [2]Karolinska Institutet, Neurobiology, Care Sciences And Society, Stockholm, Sweden, [3]Westlake University, Westlake University, Hangzhou, China

Aims: Mitochondrial function and degradation (mitophagy) show early impairments in Alzheimer´s disease (AD), which can contribute to neurodegeneration. In neurodegenerative models, recent evidence showed bilateral mitochondrial transfer between astrocytes and neurons. Astrocytic mitochondria are transferred to neurons, thus restoring mitochondrial function and neuronal viability, while neuronal mitochondria are transferred to astrocytes to undergo mitophagy. The first objective is to study for the first time this mitochondrial transfer in clinically relevant AD models. Mitochondrial transfer involves extracellular vesicles (EVs) containing mitochondrial fragments, named mitovesicles. However, this EVs subtype is still poorly studied. Therefore, the second objective is to isolate and characterize mitovesicles in an AD mouse model.
Methods: The studies are performed using primary cultures from the APP^{NL-G-F} mouse, a clinically relevant AD model. The study of mitochondrial transfer is done using micro-fluidic and Boyden culture chambers, which allow co-culturing of astrocytes and neurons in which mitochondria are differentially fluorescently labeled. The isolation of mitovesicles is done using Tangential Flow Filtration and ultracentrifugation, and the characterization of their protein content is done by Western Blot and proteomics.
Results: Mitochondrial transfer has been successfully observed. While WT neuron-derived mitovesicles mainly integrate the host astrocytic mitochondrial network, APP^{NL-G-F}-derived mitovesicles show reduced engulfment and integration and induce higher number of mitophagy events in APP^{NL-G-F} astrocytes. EVs are enriched in both membrane (e.g., Atp5a) and matrix proteins (e.g., pyruvate dehydrogenase), however, mitovesicles were not fractioned from the global EVs pool. Therefore, protocol optimization is required to get better purity prior to proteomic analysis.
Conclusions: Mitochondria transfer have been observed in APP^{NL-G-F} neuronal cells. Further optimization of protocols is required to quantify this transfer and purify mitovesicles from general EVs pool.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0085 / #1776

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

NARINGENIN ALLEVIATES PARAQUAT-INDUCED OXIDATIVE DAMAGE, MITOCHONDRIAL DYSFUNCTION, NEUROINFLAMMATION AND NEURODEGENERATION IN A RAT MODEL OF PARKINSON'S DISEASE.

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Mir Hilal Ahmad[1], Manas Sahu[1], Moshahid Rizvi[2], Amal Mondal[3]
[1]Jawaharlal Nehru University, School Of Life Sciences (sls), New-Delhi, India, [2]Jamia Millia Islamia University, Department Of Biosciences, New-Delhi, India, [3]Jawaharlal Nehru University, School Of Life Sciences, New Delhi, India

Aims: The present study explored the potential neuroprotective role of NAR in PQ-induced Parkinsonism in Wistar rats. This aimed to study the effect of Naringenin against paraquat-induced oxidative, mitochondrial dysfunction, neuroinflammation and neurodegeneration in a rat model of PD.
Methods: Oxidative damage, mitochondrial dysfunction, neuroinflammation and neurodegeneration were determined by performing western blot analysis and Immunohistochemistry.
Results: Naringenin treatment significantly reduced paraquat-induced oxidative stress by modulating the paraquat-induced aberrant levels of antioxidant enzymes, mitochondrial dysfunction by increasing the mitochondrial complex activities, neuroinflammation by decreasing the protein expressions of GFAP and IBA-1, and neurodegeneration by increasing the protein expressions of MAP2 and NeuN in PQ-intoxicated rats.
Conclusions: Naringenin exhibited promising neuroprotective properties in the current study against paraquat-intoxicated rats, indicating its potential therapeutic properties against Parkinson's pathology. So, NAR shows neuroprotection against PQ-induced neurotoxicity and neurodegeneration, indicating its therapeutic potential against Parkinson's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0086 / #584

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

DETECTION OF MOLECULAR ALTERARIONS IN THE OLFACTORY MUCOSA IN ALZHEIMER'S DISEASE

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Riikka Lampinen[1], Alexey Afonin[1], Veronika Górová[1], Elina Penttilä[2], Heikki Löppönen[2], Anne Koivisto[3,4,5], Katja Kanninen[1]
[1]University of Eastern Finland, A. I. Virtanen Institute For Molecular Sciences, Kuopio, Finland, [2]University of Eastern Finland and Kuopio University Hospital, Department Of Otorhinolaryngology, Kuopio, Finland, [3]Kuopio University Hospital, Department Of Neurology, Neuro Centre, Kuopio, Finland, [4]University of Eastern Finland, Brain Research Unit, Department Of Neurology, School Of Medicine, Kuopio, Finland, [5]University of Helsinki, Department Of Neurology And Geriatrics, Helsinki University Hospital And Neurosciences, Faculty Of Medicine, Helsinki, Finland

Aims: Olfactory dysfunction has been linked to the early phases of Alzheimer's disease (AD). The olfactory mucosa (OM), located in the upper nasal cavity, is accessible from living individuals via biopsy or swab sampling for molecular inspection. Previously, we and others have reported AD-related alterations, including amyloid-beta secretion, in the cells of the OM, and proven the safety of the OM sampling. However, the proteomic alterations occurring in the OM in individuals with AD have not previously been studied.
Methods: We have recruited and collected OM biopsies and swab samples from individuals with AD or mild cognitive impairment (MCI) and cognitively healthy controls for a discovery-phase proteomics study. The OM biopsy and swab samples (N=6 individuals/group) were obtained from different nostrils of the same individual during a single visit in the clinic and further processed for non-targeted proteomics with LC-ESI-MS/MS. All the participants of the study (> 50-year-old; males and females) underwent a careful diagnostic examination.
Results: With the preliminary LC-ESI-MS/MS run a total of 6821 different proteins were initially identified and quantified with a data independent acquisition method in OM biopsy samples, and 6593 proteins in OM swab samples. A total of 5429 of the identified proteins were found in both sample types. A large fraction of the proteins that were found differentially expressed in AD and MCI when compared to controls were mitochondrial. This is in line with our previously reported scRNA-seq experiments with primary cultures of AD OM cells.
Conclusions: The results of this study provide novel information on the utility of OM biopsies and swabs to study the early molecular alterations occurring in AD and suggest mitochondrial impairment as an early pathological feature in these samples.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0087 / #1389

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

MITOCHONDRIAL DEFECTS IN DOWN SYNDROME BRAIN OCCURS EARLY IN LIFE: IMPLICATION FOR NEURODEGENERATION.

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Chiara Lanzillotta[1], Antonella Tramutola[1], Daniel Esteve[2], Fabio Di Domenico[1], Marzia Perluigi[1], Eugenio Barone[1]
[1]Sapienza University of Rome, Department Of Biochemical Sciences, Rome, Italy, [2]University of wisconsin, Department Of Neurology, Wisconsin, United States of America

Aims: The impairment of mitochondrial function and increased levels of oxidative stress are two important factors contributing to the cognitive impairment associated with Down syndrome (DS). One potential source for mitochondrial defect could be an imbalance in mitochondrial proteostasis. In this regard several studies indicate that a specialized mitochondrial Unfolded Protein response (UPRmt) is activated upon aberrant accumulation of damaged or unfolded proteins in the mitochondrial matrix, resulting in the up regulation of key genes involved in the mitochondrial response. Therefore, the main goal of this project is to identify potential links between UPRmt activation and AD-related neurodegeneration in DS.
Methods: We evaluated the levels of specific protein implicated in the UPRmt (ATF5, GRP75, ATF4, CHOP, SIRT3, HSP60) in the hippocampus of Ts2Cje (DS model) and euploid (n=6/group) at different ages (0, 1, 6 months). Furthermore, we analyzed whether changes of the UPRmt were associated with: (i) proteins regulating brain energy metabolism and mitochondrial biogenesis (mitochondrial complexes, AMPK and PGC1A, TFAM, mitofusin and OPA1); (ii) oxidative stress (HNE and 3-NT); (iii) proteins mediating synaptic plasticity (PSD95, Syntaxin and BDNF).
Results: Ts2Cje showed an early activation of the UPRmt at P0 demonstrated by the early significant increase of GRP75. The protective activation of the UPRmt activation is lost at 1 month of age in Ts2Cje mice, during brain maturation, resulting in reduced levels of mitochondrial complexes, energy metabolism as well as increased levels of oxidative stress.
Conclusions: We propose that a close link exists among UPRmt, mitochondrial defects and oxidative stress drives the impairment of energy metabolism early in life before consistent AB deposition and neurofibrillary pathology in DS, thus contributing to early onset AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0088 / #1228

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

KEY SEQUENCE MOTIF IN REDOX CHEMISTRY OF METAL-AMYLOID BETA COMPLEXES STUDIED WITH NATIVE MASS SPECTROMETRY

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Frederik Lermyte, Sarah Brandner, Tanja Habeck
Technical University of Darmstadt, Clemens-schöpf-institute For Organic Chemistry And Biochemistry, Darmstadt, Germany

Aims: High concentrations of transition metals are found within plaques in Alzheimer's disease patients' brains. Chemical reduction of these metals is associated with production of neurotoxic reactive oxygen species (ROS). The underlying mechanism of this reduction is not fully understood. The goal of this study was to use native mass spectrometry to understand which amino acid residues are critical for this chemistry.
Methods: Measurements were carried out using a Synapt XS ion mobility – mass spectrometer (Waters Corporation) equipped with electrospray ionisation. Full-length and truncated amyloid beta sequences were studied, followed by customised sequences for in-depth investigation. Metal-free and metal-bound peptides were activated with varying energies; even-electron and radical fragments were subsequently quantitated.
Results: Activation energy series of different amyloid beta(1-16) variants (which contain the metal-binding domain) showed similar gas-phase behaviour concerning even-electron and radical-directed fragmentation. However, when bound to Cu(II), the human peptide showed threefold higher abundance of certain radical-directed fragmentation pathways. By careful analysis of fragmentation energetics and products, we ruled out both a known non-specific radical-directed mechanism, and secondary even-electron fragmentation. Instead, our results indicate a previously unreported, yet specific radical-directed origin. To identify the key amino acid residues in this mechanism, customized peptides were used, designed to resemble either the human or rodent sequence with one residue being replaced at a time. We were thus able to establish the key sequence motif that is essential for the mechanism, and rationalized our observations based on the known coordination spheres of Cu(II) and Cu(I) in solution.
Conclusions: A unique gas-phase reaction for Cu(II)-bound human amyloid beta was observed. Unravelling this mechanism could lead to a better understanding of ROS-induced damage to neurons and potentially support the development of treatments for Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0089 / #2416

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

APOE4-MEDIATED CHANGES IN MITOCHONDRIAL MORPHOLOGY AND EXPRESSION OF NUCLEAR-ENCODED GENES IN CELL MODELS

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Daniela Marinho, Mariana Pires, Ildete L. Ferreira, A. Cristina Rego
University of Coimbra, Cnc-center For Neuroscience And Cell Biology, Coimbra, Portugal

Aims: ApoE4 is the primary genetic risk factor for sporadic Alzheimer's disease (AD), found in 40-65% of all AD patients. ApoE4 has been associated to several pathological processes linked to cognitive impairment. ApoE4 can interact with mitochondria and translocate to the nucleus, regulating the expression of genes involved in aging, amyloid beta (Abeta) production, inflammation and apoptosis, potentially linked to AD pathogenesis. Thus, in this study we aimed to investigate ApoE4-mediated alterations in mitochondrial morphology, function and nuclear translocation, as well as its impact on nuclear-encoded mitochondrial gene expression.
Methods: Different AD cell models were used, namely Wistar rat primary cortical neurons exposed to Abeta1-42 oligomers (AbetaO), primary cortical neurons from APP/PS1 transgenic versus WT mouse embryos, and mouse Neuro2a (N2a)-APPSwe versus N2a-WT cell lines. Cells were transfected with plasmid-encoded ApoE4-GFP or ApoE3- GFP. Mitochondrial function, morphology and mRNA levels of nuclear-encoded mitochondrial proteins were measured.
Results: Data show that ApoE4 is present in the nucleus and mitochondria in AD and WT cell models. Comparing to ApoE3, both rat and mouse WT neurons presented increased nuclear ApoE4 levels. Increased mitochondrial ApoE4 was also observed in Wistar rat primary neurons. In contrast, N2a-APPSwe cells revealed decreased ApoE4 levels in both organelles. Interestingly, decreased mRNA levels of sirtuin 3 in both N2a-WT and N2a-APPSwe cells, and PGC-1alpha in N2a-WT cells were also associated to ApoE4. ApoE4 expression also induced significant changes in mitochondrial morphology in WT rat neurons, APP/PS1 mouse neurons and N2a-WT cells. However, ApoE4 expression did not affect mitochondrial membrane potential or mitochondrial calcium levels in AD cells.
Conclusions: This study evidence ApoE4-mediated changes in mitochondrial morphology and gene expression in both non-AD and AD cell models.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0090 / #2156

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

MITOCHONDRIAL IMPAIRMENT IN A FAMILIAL AZHEIMERS' DISEASE IN VITRO MODEL

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Zahra Motamed[1,2], Daniel Heutschi[1], Carine Gaiser[1], Laura Suter-Dick[1,3]
[1]University of Applied Sciences Northwestern Switzerland, Institute For Chemistry And Bioanalytics, Muttenz, Switzerland, [2]University of Basel, Department Of Biomedicine, Basel, Switzerland, [3]Swiss Centre for Applied Human Toxicology (SCAHT), Toxicology, Basel, Switzerland

Aims: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of extracellular amyloid beta (Abeta) plaques, intracellular neurofibrillary tangles and neuroinflammation, resulting in neuronal and synaptic loss. Mitochondrial dysfunction has been described as an early feature of AD. However, the precise mechanisms regarding its role in AD progression remain unclear. The goal of this work is to evaluate how mitochondria are affected in differentiated neurons and glial cells carrying familial AD (FAD) genotypes.
Methods: We modified the ReN-VM progenitor cell line to express FAD mutations: human amyloid beta precursor protein alone (ReN-GFP-APP) or in combination with a mutation in human presenilin 1 (ReN-GFP-APP-PSEN). Cells were differentiated in Matrigel for up to 9 weeks. Neuro-astroglia differentiation, expression of Abeta and phospho-Tau (p-Tau) were evaluated using immunofluorescence staining, Abeta production via ELISA. Mitochondrial localization was assessed through confocal microscopy and mitochondrial function by evaluating mitochondrial membrane potential (TMRE-staining).
Results: ReN-GFP-APP and ReN-GFP-APP-PSEN differentiated into neurons and astrocytes that produced Abeta 42. Moreover, FAD cells displayed axonal damage. ReN-GFP-APP-PSEN cells showed increased Abeta deposition and p-Tau after 6 and 9 weeks of differentiation, respectively. Additionally, after 6 weeks, fewer TMRE-positive mitochondria were detected in the axons, they appeared densely packed in the neuronal soma of ReN-GFP-APP and ReN-GFP-APP-PSEN cells.
Conclusions: ReN-GFP-APP-PSEN and ReN-GFP-APP cells displayed increased axonal damage at 6 weeks, accompanied by reduced mitochondrial activity compared to 2-week-old cultures**.** Our results show an association between mitochondrial dysfunction and neurodegeneration in an FAD model. Further investigation is required to elucidate the link between mitochondrial dysfunction and AD progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0091 / #722

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

STUDYING MITOCHONDRIAL DYNAMICS IN THE LOCUS COERULEUS NORADRENERGIC SYSTEM WITH IN VIVO ACOUSTO-OPTIC TWO PHOTON IMAGING IN TAUOPATHIES

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Theresa Niedermeier, Paul Feyen, Katharina Ochs, Lars Paeger, Jochen Herms
German Center for Neurodegenerative Diseases, Translational Brain Research, Munich, Germany

Aims: The Locus coeruleus (LC), a small nucleus in the brainstem, is of special interest in the context of neurodegeneration such as in Alzheimer's disease (AD), where it is one of the first regions to show hyperphosphorylated 'pretangle' tau. Mitochondria have been proposed to be linked to this pathology due to the bioenergetic needs of the tonically active LC neurons with their extensive unmyelinated axonal projections. In this work mice expressing GFP in the outer mitochondrial membrane confined to LC neurons in a Cre-dependent manner are utilized to study the dynamics of these organelles in vivo in a model of tauopathy.
Methods: The study of mitochondria is often restricted to immunohisto- or cytochemical analysis, limiting conclusions about temporal aspects. Here we present a novel *in vivo* two-photon imaging method utilizing acousto-optics to study mitochondrial dynamics. Mice with region specific mitochondrial GFP expression were stereotactically injected with Cre-dependent AAVs carrying either human Tau-P301S-mKate2 or mKate2 and chronically imaged at four, five and six months of age.
Results: Moving mitochondria were successfully imaged and analysed, showing a significant reduction in mitochondrial transport in the tauopathy model. This reduction increased over the three recorded timepoints, while average velocity remained constant in controls. Importantly, decreased mitochondrial velocity correlated with a progressive loss of axonal projections in the cortex.
Conclusions: The presence of a significant number of moving mitochondria in adult mammals has been discussed controversially. Here we show not only the abundance of mitochondrial dynamics post neonatal stages, but also the importance of further *in vivo* studies of mitochondria in tauopathies and other diseases. For the first time, to our knowledge, we correlate mitochondrial dysfunction with the "dying-back" hypothesis in the LC *in vivo*.

P0092 / #1202

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

NEUROPROTECTIVE EFFECT OF XMU-MP-1, A NOVEL HIPPO SIGNALING INHIBITOR, AGAINST STREPTOZOTOCIN-INDUCED CELLULAR MODEL OF ALZHEIMER'S DISEASE: INSIGHTS INTO MITOCHONDRIAL DYSFUNCTION

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Manas Sahu, Amal Mondal
Jawaharlal Nehru University, School Of Life Sciences, New Delhi, India

Aims: Alzheimer's Disease (AD), the most common form of dementia, is a growing global health concern with unmet clinical therapeutics to date. Apoptosis is one of the mainstream mechanisms driving neuronal death. The Hippo signaling pathway has recently emerged as a key pathway influencing cell survival, proliferation, and apoptotic-related pathophysiological conditions. Previous studies have highlighted the contributions of a hyper-activated Hippo signaling pathway in executing cellular death in various neurodegenerative disorders, including AD. However, it remains unknown whether suppressing the Hippo pathway can rescue neuronal death in AD and its possible mechanism. In this study, we investigated the beneficial role of the novel Hippo signaling inhibitor, Xmu-mp-1, in a cellular AD model.
Methods: Human neuroblastoma cell line SH-SY5Y was cultured and differentiated into mature neuronal types. Streptozotocin (STZ) treatment induced AD-like features via cellular metabolic changes. For Hippo signaling inhibition in the cells, a pharmacological antagonist, Xmu-mp-1, was used. Cell viability assay, immunocytochemistry, live/dead assay, DCF-DA assay, JC-1 assay, MitoSOX, and MitoTracker staining were performed to evaluate the potential of Xmu-mp-1 in rescuing the toxic effects of STZ treatment.
Results: Xmu-mp-1 protects the cells from cytotoxicity induced by STZ treatment. As evident in the live/dead assay, pre-treatment of differentiated SH-SY5Y cells with Xmu-mp-1 at a dose of 2μM reduced STZ-induced apoptosis. In addition, pre-treatment with Xmu-mp-1 also reduced oxidative stress, mitochondrial depolarization, and associated mitochondrial dysfunction triggered by STZ administration.
Conclusions: Xmu-mp-1 exhibits a neuroprotective role against AD as it improves the reduction in cell viability induced by STZ. Further mechanistic investigations into the neuroprotective role of Xmu-mp-1 revealed that Xmu-mp-1 exhibits neuronal protection by alleviating mitochondrial dysfunction. Future studies are needed to understand the therapeutic potential of Hippo signaling inhibition against AD in detail.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0093 / #834

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

PROTECTIVE ROLE OF ANTIOXIDANTS AND NRF2 ACTIVATORS FROM OXIDATIVE DAMAGE INDUCED BY SPORADIC AND FAMILIAR FORMS OF AMYLOID BETA

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Maria Luisa Valle, Bitseat Getaneh, Jorge Ghiso, Agueda Rostagno
New York University Grossman School of Medicine, Pathology, New York, United States of America

Aims: Over 90% of Alzheimer patients manifest cerebral amyloid angiopathy (CAA), condition that deeply affects brain function by oxidative stress production, vascular cell death, blood brain barrier disruption and, frequently, cerebral hemorrhage. The extent of vascular compromise is exacerbated by the presence of genetic variants, particularly those located at positions 21-23 of amyloid beta. Among them, the E22Q Dutch mutation is associated with early onset very aggressive CAA, and cerebral hemorrhages. Studies from our and other groups indicated mitochondria-mediated pathways dysregulation as a contributing factor to the pathogenesis of CAA. As key providers of brain energy demands, mitochondria are the major consumers of oxygen and the most important generators of reactive oxygen species (ROS). In the current work, we aimed to provide insight into the amyloid beta compromised molecular pathways in microvascular endothelial cells and identify potential new targets for therapeutic intervention.
Methods: Human brain microvascular endothelial cells were challenged with well-defined oligomeric assemblies of both wild type amyloid beta 1-42 and E22Q variant. Using immunofluorescence microscopy and biochemical assays, we evaluated ROS formation and concomitant production of lipid and protein oxidation derivatives.
Results: Our findings demonstrate the formation of oligomeric assemblies of both amyloid beta peptides and induction of dose-dependent ROS formation that, in turn, causes lipid peroxidation and generation of protein carbonylation derivatives. Treatment with antioxidants and activators of Nrf2, a central regulator of the antioxidative response, significantly attenuated ROS production and concomitant ROS-induced damage.
Conclusions: Our data highlights the detrimental role of amyloid beta oligomeric assemblies for microvascular endothelial cells suggesting that modulation of oxidative stress is a complementary therapeutic strategy with the potential to preserve the neurovascular unit integrity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0094 / #708

Poster Topic: *Theme A: β-Amyloid Diseases / A01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

PINOCEMBRIN REGULATED GSK-3B/WNT/B-CATENIN SIGNALING PATHWAY: A NOVEL MECHANISM FOR AB-MEDIATED NEURONAL APOPTOSIS

POSTERS: A01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Kumju Youn[1,2], Jeong-Hyun Yoon[3], Mira Jun[1,2,3]
[1]Dong-A University, Department Of Food Science And Nutrition, Busan, Korea, Republic of, [2]Dong-A University, Center For Food & Bio Innovation, Busan, Korea, Republic of, [3]The graduate School of Dong-A University, Department Of Health Sciences, Busan, Korea, Republic of

Aims: The deposition of amyloid-β (Aβ) peptides has been implicated as a one of pathological hallmark of Alzheimer's disease (AD). Increasing evidence indicates that Aβ initiates oxidative stress and a vicious cycle of mitochondrial damage, leading to apoptotic neuronal death. Pinocembrin (5,7-dihydroxyflavone), a major flavonoid found in honey and propolis, has shown significant neuroprotective property by suppressing Aβ cleaving enzyme in our previous study. The present study investigated a novel anti-AD effect of pinocembrin on mitochondrial dysfunction and apoptosis against Aβ injury.
Methods: Neurotoxicity and apoptosis by Aβ were assessed and the underlying mechanism by which pinocembrin suppressed cell death, mitochondria dysfunction, caspase cascade and GSK-3β/Wnt/β-catenin signaling pathway related protein markers were evaluated in $A\beta_{1-42}$-mediated PC12 cells.
Results: Pinocembrin significantly reversed Aβ-induced cell death, especially pinocembrin at 50 μM a similar neuroprotective effect to that of resveratrol, a well-known positive control. In addition, the compound counteracted Aβ-induced mitochondrial dysfunction, which was supported by maintaining mitochondrial membrane potential, decreasing BAX protein, and increasing BCL-2 protein within the mitochondria as well as upregulating TrxR1 mitochondrial antioxidant enzyme. Mitochondrial dysfunction by Aβ triggered the caspase cascade, whereas pinocembrin suppressed expression of caspase-9, -8 and -3. Interestingly, pinocembrin exerted neuroprotective effects against Aβ by inhibiting GSK-3β activation, which in turn promoted Wnt signaling via nuclear translocation of β-catenin.
Conclusions: Taken together, the present results demonstrated that pinocembrin prevented the Aβ-stimulated mitochondrial apoptosis via GSK-3β/Wnt/β-catenin signaling pathway, providing a useful approach for potential natural agent for AD prevention.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0095 / #794

Poster Topic: *Theme A: β-Amyloid Diseases / A01.h. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

APOE GENOTYPE AFFECTS ENDOLYSOSOMAL CHOLESTEROL LOCALIZATION IN THE BRAIN

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Sherida De Leeuw, Ilana Samsonov, Tal Nuriel
Columbia University Irvine Medical Center, Taub Institute, New York, United States of America

Aims: Aberrant cholesterol processing may be the missing link in the biology of AD. Major genetic risk factor *APOE4* is a key player in cholesterol metabolism in the brain, and previous research from our group has shown that *APOE4* is related to lysosomal cholesterol accumulation in human iPSC-astrocytes, as well as altered endolysosomal morphology in the entorhinal cortex (EC) of aged *APOE4* mice. Therefore, we aim to elucidate the role of *APOE4* genotype in cholesterol mislocalization within the endolysosomal system of the brain.
Methods: We studied endolysosomal cholesterol accumulation in humanized *APOE2*, *E3*, and *E4* mouse brain sections. Cholesterol was labeled using the novel and highly specific D4H* probe, combined with immunohistochemical labeling of late endosomes/lysosomes, also called endolysosomes (CD63). Fluorescence was quantified and colocalized using Imaris.
Results: Quantification of total D4H*-cholesterol spots showed decreasing levels of cholesterol with genotype (*APOE2>E3>E4*), while cholesterol spots were generally decreased in female compared to male brain tissue. Interestingly, cholesterol spots specifically colocalized with endolysosomes showed opposite genotype dependent levels (*APOE2<E3<E4*), meanwhile small differences were detected in the females compared to males. Similar findings were detected in neuron-specific cholesterol and endolysosomal-cholesterol, indicating that neurons play a role in the *APOE*-dependent cholesterol differences detected.
Conclusions: In conclusion, cholesterol was disproportionately colocalized with endolysosomes in *APOE4* brain sections, compared to *APOE3>E2*. Importantly, we found that biological sex affects cholesterol levels, interacting with *APOE* genotype, which may help us understand the biology of sex-based difference in AD risk. We will further characterize cholesterol in early endosomes and lysosomes, determining the implications of *APOE4*-related endolysosomal-cholesterol buildup. Elucidating the biology of *APOE4* will improve our understanding of cellular mechanisms underlying AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0096 / #1012

Poster Topic: *Theme A: β-Amyloid Diseases / A01.h. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

BEHAVIORAL AND MOLECULAR PHENOTYPING OF TWO APP KNOCK-IN MOUSE MODELS OF ALZHEIMER'S DISEASE WITH CYP46A1 UPREGULATION

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Ljerka Delac[1], Francesca Eroli[1], Maria Latorre Leal[1], Gabriela Da Cruz Meda[1], Ines Da Costa Morreira[1], Per Nilsson[1], Ivan Nalvarte[2], Ingemar Björkhem[3], Silvia Maioli[1]
[1]Karolinska Institutet, Division Of Neurogeriatrics, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden, [2]Karolinska Institutet, Biosciences And Nutrition, Flemingsberg, Sweden, [3]Karolinska Institutet, Department Of Laboratory Medicine, Flemingsberg, Sweden

Aims: To investigate whether the beneficial effects of CYP46A1 upregulation on memory and learning can counteract Alzheimer's disease (AD) pathology in a sex-specific manner, we have developed a novel mouse model of Alzheimer's disease with CYP46A1 overexpression.
Methods: We employed single *App* knock-in mice carrying Swedish and Beyreuther/Iberian (App^{NL-F}), and Arctic mutation (App^{NL-G-F}) crossed with mice overexpressing the human CYP46A1 transgene (Cyp46 Tg). Female and male cohorts were aged to 6, 12, and 18 months of age. A battery of cognitive and anxiety-like behavioral tests was conducted, followed by cholesterol and oxysterol measurements and immunohistochemical stainings for AD pathology markers.
Results: The results of our study demonstrate mild effects of CYP46A1 overexpression in spatial working memory at 12 months. At six months of age, only male App^{NL-G-F} mice exhibit anxiolytic behavior, whereas females do not. Interestingly, in the 6-month-old Cyp46 Tg x App^{NL-G-F} cohort, increased serum levels of 24-hydroxycholesterol (24-OH) and 27-hydroxycholesterol were not reflected in the brain, the main site of 24-OH production, as seen previously in Cyp46 Tg mice. Furthermore, quantification of microglia and amyloid-beta deposits at different age points has been carried out to elucidate impact of CYP46A1 overexpression dependent on the age and sex.
Conclusions: These results suggest alterations in cerebral oxysterol metabolism in the presence of triple *App* knock-in mutation and propose Cyp46 Tg x APP knock-in model as a novel platform to investigate cholesterol perturbations in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0097 / #740

Poster Topic: *Theme A: β-Amyloid Diseases / A01.h. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

ZDHHC7 PROMOTES AD-LIKE PHENOTYPE BY INDUCING HYPERPALMITOYLATION OF PROTEINS REGULATING SYNAPTIC PLASTICITY AND BETA AMYLOID METABOLISM

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Salvatore Fusco[1,2], Francesca Natale[1,2], Matteo Spinelli[1,2], Marco Rinaudo[1,2], Walter Gulisano[3], Ida Nifo Sarrapochiello[2], Daniela Puzzo[3], Claudio Grassi[1,2]
[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Dep. Neuroscience, Rome, Italy, [2]Università Cattolica del Sacro Cuore, Department Of Neuroscience, Roma, Italy, [3]University of Catania, Department Of Biomedical And Biotechnological Sciences, Catania, Italy

Aims: Alzheimer's disease (AD) is a growing problem for aging populations worldwide and it represents one of the most demanding challenges for biomedical and pharmacological research. More importantly, all therapeutic attempts made so far based on current knowledge have proven scarcely effective, probably because the molecular mechanisms underlying the onset and progression of the disease still remain poorly understood. An increasing number of studies has also shown the role of palmitoylated proteins in the regulation of synaptic plasticity and neuronal functions. The aim of our study was to investigate the role of zDHHCs and aberrant protein S-palmitoylation in AD.
Methods: S-palmitoylation is a protein post-translational modification regulated by zinc finger DHHC domain containing (zDHHC) S-acyltransferases that modulates both localization and activity of proteins controlling synaptic plasticity and beta amyloid (Aβ) metabolism. We previously discovered that aberrant protein S-palmitoylation plays a pivotal role in the brain insulin resistance (BIR)-dependent cognitive decline.
Results: Here, we demonstrated that hippocampal insulin resistance induced the FoxO1-mediated epigenetic overexpression of zDHHC7 in 3×Tg-AD mice. We also found increase of both zDHHC7 expression and S-palmitoylation levels of synaptic proteins and Beta-Secretase 1 (BACE1) in hippocampi of both 3×Tg-AD mice and AD patients. Hippocampal knockdown of zDHHC7 reduced the hippocampal Aβ deposition and prevented the onset of cognitive deficits in 3×Tg-AD mice. Accordingly, intranasal administration of protein S-palmitoylation inhibitor 2-bromopalmitate ameliorated the synaptic plasticity and cognitive deficits in mice. Finally, we found a direct correlation between BACE1 S-palmitoylation and Aβ 1-42 levels in human hippocampi.
Conclusions: Our data reveal a key role of zDHHC7-driven aberrant S-palmitoylation in the onset and progression of AD-related cognitive impairment and provide new potential targets for the development of therapeutic tools against AD.

P0098 / #1093

Poster Topic: *Theme A: β-Amyloid Diseases / A01.h. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

UNDERSTANDING AB PLAQUE ASSOCIATED LIPID CO-AGGREGATION USING PULSE-CHASE SPATIAL MULTIOMICS

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Junyue Ge, Jörg Hanrieder
University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden

Aims: The primary goal is therefore to employ stable isotope labelling together with advanced novel mass spectrometry imaging to probe Aβ plaque pathology associated lipid dynamics in AD model systems.
Methods: Here, male APP knock-in mice (APPNL-G-F) carrying humanized Aβ sequence, along with Swedish mutation (KM670/671NL) on exon 16, as well as Arctic (E693G) and the Beyreuther/Iberian mutations (I716F) on exon 17, were used in the study. To study spatiotemporal Aβ plaque metabolism, mice were fed MouseExpress (15N, 98%) mouse feed (PULSE) based on ^{15}N following the labelling scheme: PULSE, 10 weeks (weeks 7 to 17), no CHASE (n = 3). Changes in isotope incorporation in Aβ peptides and lipids can spatially be delineated with mass spectrometry imaging (SILK imaging, iSILK). MALDI-MSI under negative-ion mode lipid analysis and subsequent peptide/protein ion imaging were performed at 10 µm spatial resolution on the same brain section from knock-in mice.
Results: By MALDI-MSI lipid analysis, heterogenous distribution of lipids were revealed in the frontal cortex in knock-in mouse brain. GM2 and GM3 showed aggregation only in the plaque, while GM1 showed enrichment in the plaque compared to the region outside of the plaque. ^{15}N enrichment was observed in PS and gangliosides. It was associated with the progressive increase in abundance of an envelope of high mass isotopologues (M1 to M6). There are mainly Aβ1-42 along with Aβ1-38 in the plaques, and ^{15}N-labeled amino acids were incorporated into Aβ peptides. MALDI-MSI detected solely labelled ^{15}N–Aβ1-42, but no unlabelled ^{14}N–Aβ1-42.
Conclusions: Pulse-chase spatial multiomics sheds light on what, where, when and how neuronal lipid species are involved in pathogenioc plaque formation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0099 / #671

Poster Topic: *Theme A: β-Amyloid Diseases / A01.h. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

ALTERATIONS IN PLASMA AND CEREBROSPINAL FLUID FATTY ACIDS IN ALZHEIMER'S DISEASE

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Ricard Lopez-Ortega[1], Farida Dakterzada[2], Mariona Jove[3], Jose Luis Cantero[4], Reinald Pamplona[3], Gerard Piñol-Ripoll[2]
[1]Hospital Universitari Arnau de Vilanova, Clinical Laboratory, Lleida, Spain, [2]Hospital de Santa Maria - IRBLleida, Cognitive Disorders Unit. Cognition And Behaviour Study Group, Lleida, Spain, [3]University of Lleida-IRBLleida, Department Of Experimental Medicine, Lleida, Spain, [4]University Pablo de Olavide, Department Of Physiology, Anatomy And Cellular Biology, Sevilla, Spain

Aims: Objectives: to assess the association of both cerebrospinal fluid (CSF) and plasma fatty acids (FAs) with Alzheimer's disease (AD) diagnosis and mild cognitive impairment (MCI) to AD progression. In addition, we evaluated the relation of FAs with the rate of MCI to AD progression.
Methods: Methods: FA composition of plasma and CSF samples from 289 participants (103 AD, 92 MCI, and 94 control) was determined by gas chromatography flame ionization detector method (GC-FID). The MCI subjects were followed up for a median of 58 (±12.5) months. We controlled our data for age, sex, MMSE, and APOE ε4.
Results: Results: In CSF, higher levels of anti-inflammatory index were associated with decreased risk of AD diagnosis vs MCI (p = 0.005) and higher levels of docosahexaenoic acid (DHA) were associated with reduced risk of MCI to AD progression (p = 0.021). In plasma, higher levels of oleic acid (OA) were associated with reduced risk of AD (p = 0.013) and MCI (p = 0.001) vs control, while higher levels of vaccenic acid were associated with an increased risk of AD vs control (p <0.001) and AD vs MCI (p = 0.006). Higher plasma levels of OA were also associated with reduced risk of MCI to AD progression (p = 0.016). Finally, higher plasma levels of DHA were associated with a higher rate of MCI to AD progression (p = 0.01).
Conclusions: Conclusions: Our results suggest that FA dysregulations at both central (CSF) and systemic (plasma) levels are involved in pathogenesis and progression of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0100 / #200

Poster Topic: *Theme A: β-Amyloid Diseases / A01.h. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

PERIPHERAL BLOOD BIOMARKERS IN PATIENTS WITH ALZHEIMER'S DISEASE AND THE DEVELOPMENT OF PERSONALISED TREATMENTS.

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Carmela Matrone[1], Alfonso Di Costanzo[2]
[1]University of Naples "Federico II", Neuroscience, Naples, Italy, [2]University of Molise, Medicina E Di Scienze Della Salute, Campobasso, Italy

Aims: Recently, peripheral biomarkers in the plasma of patients with Alzheimer's disease (AD) have gained considerable clinical attention. Several studies have identified potential blood signatures that could aid the development of new diagnostic and therapeutic strategies. We analysed the differences in plasma metabolites, Aβ42, and TNFα levels to identify changes that occur simultaneously in patients with AD.
Methods: We used ELISA to measure Aβ42 and TNFα levels, which are indicators of AD progression and systemic inflammatory processes, respectively. Additionally, we conducted metabolomic analysis to evaluate the changes in the vascular components that contribute to the disease. These factors were interpreted with respect to the Mini-Mental State Examination (MMSE) score, which allows measurement of the extent of cognitive decline.
Results: We evaluated the plasma levels of Aβ42 and TNFα in 38 patients with AD and 34 HE subjects. We observed that C26:1- and C28:1- lyso-PC levels increased in AD patients with lower MMSE scores and decreased in patients with higher Aβ42 levels. Additionally, we found that no plasma metabolites were correlated with MMSE scores or Aβ42 levels in patients with high TNFα levels. However, changes in several metabolites in the triacylglyceride pathway were observed in AD patients with higher TNFα, but not in those with higher Aβ42 or lower MMSE scores, suggesting that changes in TNFα might be independent of cognitive deterioration in AD patients.
Conclusions: This study highlights the potential of using a combination of different plasma signatures to define specific clinical phenotypes of patient subgroups, which could lead to the classification of patients with AD and the development of individualized treatment plans.

P0101 / #1821

Poster Topic: *Theme A: β-Amyloid Diseases / A01.h. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

UNCOVERING THE ROLE OF AN AFRICAN-SPECIFIC ABCA7 FRAMESHIFT DELETION ON LIPID METABOLISM AND ALZHEIMER'S DISEASE

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Younji Nam
University of Miami, Genetics, MIAMI, United States of America

Aims: SA1: Assess the impact of the 44-bp deleted *ABCA7* on lipid metabolism and AD pathology. SA2. Evaluate the effect of neuron-microglia crosstalk on lipid homeostasis.
Methods: A) We studied the impact of an ancestry-specific deletion in *ABCA7* on lipid metabolism using patient-derived isogenic iPSC lines. Since cholesterol plays a critical role in Aβ aggregation in neurons and Aβ phagocytosis in microglia, evaluating defects in the lipid metabolism in these lines will provide insight into the role of *ABCA7* in AD pathology. B) We examined how the ABCA7 variant differentially or synergistically impacts lipid metabolism in neurons and microglia in monoculture and co-culture.
Results: Most ABCA7 non-synonymous coding changes associated with AD do not reach the plasma membrane, but we have discovered that the truncated p.Arg578Alafs ABCA7 protein is stable and in fact does localize in the plasma membrane similar to the wild-type protein. We have also demonstrated that the truncated ABCA7 protein has altered cholesterol distribution in the plasma membrane, suggesting a dysfunctional ABCA7 in spite of its membrane localization.
Conclusions: Genetic ancestry plays an important role in AD pathology with AAs having double the incidence of AD compared to non-Hispanic whites (NHW). However, the impact of AA-specific genetic variants on AD development has been understudied. ABCA7 is one of the leading genetic risk factors for African Americans and has a similar risk for African Americans as ApoE4 does in this population. This study will generate valuable phenotypic data in patient-derived neurons and microglia relating to both pathologic and cellular hallmarks of AD, including valuable insights into the role of ABCA7, a gene that has been implicated across populations, in lipid metabolism and AD development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0102 / #784

Poster Topic: *Theme A: β-Amyloid Diseases / A01.h. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

EXTRACELLULAR VESICLES BIOGENESIS AND RELEASE ARE AFFECTED BY ABETA PEPTIDE

POSTERS: A01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Margarida Vaz, Tânia Martins, Odete Da Cruz E Silva, Ana Gabriela Henriques
University of Aveiro, Departement Of Medical Sciences, Aveiro, Portugal

Aims: Alzheimer's disease (AD) represents an important healthcare challenge due to its intricate etiology and increasing prevalence. A main hallmark of AD is the presence of senile plaques, mainly composed of Aβ peptide aggregates. This peptide is extremely toxic, triggering several pathological events, that ultimately lead to neuronal death. Extracellular vesicles (EVs) are nanovesicles secreted by all cell types and recognized as key intercellular communication mediators. In AD, it has been reported that these EVs can carry Aβ, among other proteins relevant in disease pathogenesis as APP or tau, hence contributing to the seeding potential of the toxic proteins. However, Aβ effects in EVs biogenesis and release are not completely understood. Therefore, this work aimed to evaluate the effect of Aβ in this process.
Methods: N2a neuroblastoma cells were treated with Aβ peptide and EVs were then isolated from cells conditioned medium by ultracentrifugation. EVs were characterized by TEM and WB analysis was employed to evaluate the levels of proteins involved in EVs biogenesis and secretion. Additional proteomic studies were also carried out.
Results: A significant increase was observed in the levels of Flotilin, involved in EVs biogenesis, and in two Rab proteins, implicated in EVs secretion. The proteomic analysis also revealed alterations in proteins related to EVs.
Conclusions: These results support that Aβ peptide can alter EVs biogenesis and release. As EVs can be involved in cell communication and signaling events, data suggest that Aβ may have an impact at this level, potentially contributing to the abnormal mechanisms underlying AD pathogenesis. This work was funded by iBiMED under Grant UIDB/04501/2020 and UIDP/04501/2020; MV is supported by the individual PhD grant UI/BD/151354/2021 and TMS by the individual PhD grant SFRH/BD/145979/2019.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0103 / #412

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

BLOOD SERUM FROM ALZHEIMER'S PATIENTS ALTERS MICROGLIAL PHAGOCYTOSIS IN VITRO

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Barbara Altendorfer[1], Iris Leister[2], Sophie Lefèvre-Arbogast[3], Claudine Manach[4], Dorrain Low[4], Mireia Urpi-Sarda[5], Cristina Andres-Lacueva[5], Raúl González-Domínguez[5], Thomas Felder[6], Julia Tevini[6], Andreas Koller[7], Diana Marisa Bessa De Sousa[1], Reinhold Schmidt[8], Paul Lucassen[9], Silvie Ruigrok[9], Chiara De Lucia[10], Andrea Du Preez[10], Catherine Helmer[3], Jeanne Neuffer[11], Mercè Pallàs[12], Cécile Proust-Lima[11], Aniko Korosi[9], Cécilia Samieri[11], Sandrine Thuret[10], Ludwig Aigner[1]
[1]Paracelsus Medical University Salzburg, Institute Of Molecular Regenerative Medicine, Salzburg, Austria, [2]BG Trauma Center Murnau, Spinal Cord Injury Center, Clinical Research Unit, Murnau, Germany, [3]INSERM, Bordeaux Population Health Research Center, Université Bordeaux Segalen, Bordeaux, France, [4]Université Clermont Auvergne, Inrae, Umr1019, Human Nutrition Unit, Clermont Ferrand, France, [5]CIBER Fragilidad y Envejecimiento Saludable (CIBERFES), Instituto de Salud Carlos III, University of Barcelona, Nutrition, Food Science And Gastronomy Department, Faculty Of Pharmacy And Food Science, Barcelona, Spain, [6]Paracelsus Medical University, Department Of Laboratory Medicine, Salzburg, Austria, [7]University Hospital of the Paracelsus Medical University, Research Program For Experimental Ophthalmology And Glaucoma Research, Department Of Ophthalmology And Optometry, Salzburg, Austria, [8]University Hospital of Neurology, Clinical Department Of General Neurology, Graz, Austria, [9]University of Amsterdam, Brain Plasticity Group, Swammerdam Institute For Life Sciences, Amsterdam, Netherlands, [10]King's College London, Department Of Basic And Clinical Neuroscience, Maurice Wohl Clinical Neuroscience Institute, Institute Of Psychiatry, Psychology And Neuroscience, London, United Kingdom, [11]University of Bordeaux, Inserm, Bordeaux Population Health Research Center, Umr 1219, Bordeaux, France, [12]University of Barcelona, Pharmacology Section, Department Of Pharmacology, Toxicology And Medicinal Chemistry, Faculty Of Pharmacy And Food Sciences, And Institute Of Neurociencies, Barcelona, Spain

Aims: Recent studies demonstrated that factors circulating in the blood can have profound effects on synaptic plasticity and neurogenesis thereby shaping brain aging and neurodegenerative diseases. Here, we investigated the effect of blood serum of Alzheimer's disease (AD) patients and individuals experiencing later cognitive decline on microglia function *in vitro*.
Methods: The University Hospital Graz provided us with serum samples from AD patients and age-matched controls (n=30/group). We also obtained baseline blood serum from elderly participants of the Three-City (3C) cohort (n=418), who were cognitively healthy at baseline and divided into controls and cognitively declining over 12 years of follow-up. To assess phagocytosis, the uptake of fluorescent particles was measured by flow cytometry in a human microglia cell line after exposure to human serum.
Results: AD serum-treated microglia showed higher particle uptake compared to controls, which was associated with cognitive impairment in AD patients. Gene expression analysis of serum-treated microglia revealed that AD serum downregulated the transcription factor EB (*Tfeb*), a master regulator of lysosomal biogenesis. Testing the prognostic value of the phagocytosis assay in the 3C cohort, we found no difference between controls and cognitive declined individuals. However, correlations with their serum metabolome revealed an inverse correlation between particle uptake and the omega-3 fatty acid eicosapentaenoic acid (EPA). A similar correlation with EPA was found in the previously analysed AD cohort. *In vitro* EPA treatment reduced phagocytosis in microglia and upregulated levels of *beclin1*, a gene under *Tfeb* control that is important for autophagosome formation.
Conclusions: AD blood increased microglial phagocytic uptake, which inversely correlated with serum EPA levels, while causing lysosomal deficiency. *In vitro* experiments confirmed the EPA-dependent reduction in particle uptake and suggested increased autophagosome formation upon EPA exposure.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0104 / #549

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

FOCAL POINT MICROGLIA RESPONSE: SPATIAL PROFILING OF THE INNATE IMMUNE SYSTEM IN DEMENTIAS WITH PURE AND MIXED PROTEIN PATHOLOGIES

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Tim Bathe[1], Gabriela Hery[2], Jonathan Villareal[1], Eric Cohen[3], Jennifer Phillips[1], Rohan Sharma[1], Wangchen Tsering[1], Stefan Prokop[1]
[1]University of Florida, Pathology, Gainesville, United States of America, [2]University of Florida, Small Animal Clinical Sciences, Gainesville, United States of America, [3]University of Florida, Biomedical Engineering, Gainesville, United States of America

Aims: Despite the identification of a multitude of genetic risk factors for neurodegenerative diseases (ND) in immune associated genes, the precise role of immune processes in disease pathogenesis and progression is far from understood. To better understand the complex interplay between different extracellular and intracellular protein pathologies and the brain's intrinsic immune system in neurodegenerative diseases, the aim of this study is to investigate the role of the immune system, more specifically microglia, in human postmortem brain tissue. Cases without significant pathological changes (Control), pure AD and LBD cases, and cases with mixed protein pathology will be examined and compared. The focus is on changes in the phenotype of microglia in disease-relevant brain regions (hippocampus, frontal cortex, occipital cortex and midbrain).
Methods: To better understand the complex interplay between different extracellular and intracellular protein pathologies and the brain's intrinsic immune system in neurodegenerative diseases, we set out to comprehensively profile immune response profiles in postmortem brain samples of patients with "pure" Alzheimer's disease neuropathological changes (ADNC) (AD), "pure" alpha-Synuclein pathology in Lewy body disease (LBD) and Dementias with "mixed" pathology (MIX). We are combining immunohistochemical profiling of microglia and digital image analysis with deep immunophenotyping using gene expression profiling on the Nanostring nCounter platform and digital spatial profiling on the Nanostring GeoMx platform.
Results: We identified a robust immune activation signature around ADNC. This signature is maintained in MIX patients, irrespective of co-existence of AD pathology and Lewy body (LB) pathology, while LBD patient samples with "pure" LB pathology exhibit a distinct immune signature.
Conclusions: Our studies highlight disease and brain region specific immune response profiles in response to intracellular and extracellular protein pathologies and further underscore the complexity of neuroimmune interactions in neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0105 / #1968

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

DETERMINE THE ROLE OF CLEC7A+ MGND-MICROGLIA IN NEURODEGENERATIVE DISEASES

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Wesley Brandao, Ana Carolina Durao, Jen-Li Barry, Gabryell Thiengo, Zhuoran Yin, Oleg Butovsky
Brigham and Women's Hospital - Harvard Medical School, Neurology, Boston, United States of America

Aims: Microglia play a pivotal role in maintaining brain homeostasis but lose key functions during the course of neurodegenerative diseases. Recently, our group has characterized two major microglia phenotypes: homeostatic microglia (M0) and microglia associated with neurodegenerative disease (MGnD), also known as disease-associated microglia (DAM). The pivotal question in neuroinflammation-targeted therapeutic approaches is whether the MGnD phenotype is beneficial or detrimental in neurodegenerative disease. Aim**:** Define the contribution of Clec7a^{+} MGnD microglia to the progression of neurodegenerative diseases using our novel mouse model, which allows specific targeting of the MGnD-microglia subset.
Methods: Methods: We generated Clec7a-Cre^{ERT2} transgenic mice, which were crossed with ROSA26^{TdTomato} and DTR^{Flox} mice to map MGnD microglia fate and role. In a disease context, these mice were crossed with APP/PS1 and 5xFAD mice or subjected to MOG immunization to induce experimental autoimmune encephalomyelitis (EAE).
Results: Results: We found that MGnD (Clec7a^{+}/ TdTomato^{+}) microglia are present at sites of demyelination, and their numbers correlate with EAE disease scores. Additionally, we demonstrated the specific ablation of MGnD-microglia during EAE development in ROSA26^{DTR} mice. In AD mouse models, Clec7a^{+} microglia were exclusively associated with amyloid beta (Ab) plaques, exhibiting elevated expression levels of MHC-II, GMCSF, and TNFα, while LAP expression was suppressed. Interestingly, we observed decreased expression of Clec7a MGnD microglia in 4-month-old male mice compared to females, which correlated with reduced Ab-plaque load and dystrophic neurons. Fate-mapping analysis indicated a turnover of approximately three months post-activation for Clec7a-TdTomato^{+} microglia, and its deletion leads to an increase in the dystrophic neurons.
Conclusions: Conclusion: Our Clec7a-Cre^{ERT2} mouse model provides a novel platform for studying the MGnD microglia subset in neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0106 / #600

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

DIFFERENTIAL EFFECT OF HEXOKINASE 2 GENE DOSAGE ON MICROGLIAL ACTIVATION AND ALZHEIMER'S DISEASE PROGRESSION.

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Juan Codocedo, Claudia Mera Reina, Peter Lin, Shweta Puntambekar, Brad Casali, Nur Jury Garfe, Pablo Martinez, Israel Coronel, Paul Fallen, Cristian Lasagna-Reeves, Gary Landreth
Stark Neurosciences Research Institute, Indiana University, School of Medicine, Anatomy, Cell Biology And Physiology, Indianapolis, United States of America

Aims: Hexokinase 2 (HK2) is a mitochondrial protein that performs the first step in glycolysis through the phosphorylation of glucose. Previous studies have proposed HK2 as a critical determinant of microglial response in various pathological processes. However, these studies reported conflicting data with respect to the effect of the complete deletion of HK2 on microglial metabolism and disease progression. Thus, the role of microglial HK2 in neuroinflammation remains poorly understood. **Objectives: 1.** Investigate the effect of HK2 gene dosage in the regulation of microglial phenotypes and Alzheimer's progression in the 5xFAD mice. **2.** Explore the molecular mechanisms associated to the inflammatory role of HK2 antagonism in AD.
Methods: Methods: We generated mice with a conditional deletion of one or two copies of HK2 in microglia of the 5xFAD mice. HK2 deletion was induced at 2 months of age and AD pathogenesis was evaluated at 5 months**.** We also investigated the effects of its inhibitor Lonidamine. *In vitro*, we investigated the mechanisms by which HK2 regulates microglial responses to Aβ.
Results: Results: The complete loss of HK2 exacerbates inflammation, by inducing mitochondrial activation of the inflammasome. Conversely, the partial antagonism of HK2, displays reduced pathology in the 5XFAD mice. Decreased activity of HK2 increase the levels of its cytosolic target IKBα, an NFKβ inhibitor, that prevents expression of inflammatory genes including several elements of the inflammasome.
Conclusions: Conclusions: HK2 partial antagonism prevents inflammation through a non-metabolic mechanism associated to the modulation of NFKβ signaling. The complete loss of HK2 affects an alternative inflammatory pathway, associated to mitochondrial dysfunction and activation of the inflammasome, demonstrating that HK2 regulates inflammation through different mechanisms and the result of its therapeutic targeting will depend of it molecular context.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0107 / #1186

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

STUDYING THE IMPACT OF ALZHEIMER'S DISEASE POLYGENIC RISK SCORES ON MICROGLIAL FUNCTION IN VITRO

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Wannes Dejonckheere[1], Sofie Carmans[1], Annerieke Sierksma[2], An Snellinx[2], Sarah Borrie[2], Yasmina Abakkouy[3], Isabelle Cleynen[3], Stephanie Humblet-Baron[4], Bart De Strooper[5], Rik Vandenberghe[6], Tom Cornelissen[1]
[1]reMYND, Cro, Leuven, Belgium, [2]VIB-KU Leuven, Neuroscience, Leuven, Belgium, [3]KU Leuven, Human Genetics, Leuven, Belgium, [4]KU Leuven, Microbiology, Immunology And Transplantation, Leuven, Belgium, [5]Flanders Institute for Biotechnology (VIB), Centre For Brain And Disease Research, Leuven, Belgium, [6]KU Leuven, Experimentele Neurologie, Leuven, Belgium

Aims: The risk of developing Alzheimer's disease (AD) is strongly affected by an individual's genetic make-up, even for non-familial AD cases. This genetic predisposition can be quantified by determining the presence of an individual's genetic risk loci. The combined weight of these risk loci can then be displayed as the polygenic risk score (PRS). Currently a prediction accuracy of up to 84% between AD cases and healthy controls is achieved. Interestingly, the majority of these risk genes are highly, if not only, expressed in microglia rather than in other brain cells. Therefore we set out to investigate how this PRS contributes to microglial function in vitro.
Methods: iPSC's from APOE3/E3 positive subjects with a high, low and intermediate PRS for developing AD and 4 APOE4/E4 carriers (high PRS, mainly driven by the presence of APOE4) were differentiated into microglia. Microglial morphology and motility were assessed after LPS stimulation while microglial phagocytosis was studied by detecting the uptake of bioparticles or Abeta42 oligomers/fibrils.
Results: iPSC's successfully differentiated into microglia as indicated by the presence of high levels of microglial mRNA markers. After LPS stimulation, microglia tend to adapt a rod like morphology while treatment with bioparticles or Abeta42 oligomers/fibrils leads to a more swollen spherical shape. Bioparticles and Abeta42 oligomers and sonicated fibrils were also rapidly phagocytosed while fibrillar Abeta42 was taken up slower. The contribution of the PRS on microglial function is currently being investigated.
Conclusions: How PRS affects microglial function and microglial contribution to AD development is currently unknown. Here we try to resolve this gap by studying microglial function in iPSC derived microglia from subjects with divergent PRS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0108 / #1936

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

RG5942 A MIR-155 PHARMACOLOGICAL BLOCKER, MODULATES MICROGLIA RESPONSE AND MITIGATES COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Ana Carolina Durao[1], Wesley Brandao[1], Zhuoran Yin[1], Madison Carpenter[1], Morgan Carlson[2], Oleg Butovsky[1]
[1]Brigham and Women's Hospital - Harvard Medical School, Neurology, Boston, United States of America, [2]Regulus Therapeutics Inc., Biology, San Diego, United States of America

Aims: Background: Microglia, the brain's resident immune cells, play a crucial role in maintaining brain homeostasis and influencing the progression of Alzheimer's disease (AD). In neurodegenerative conditions, microglia transform into a neurodegenerative phenotype known as MGnD, the functional mechanisms of which remain poorly understood. MicroRNA-155 (miR-155), previously linked to pro-inflammatory activation in microglia and monocytes through TREM2-APOE signaling, has shown increased expression in various neurodegenerative diseases, including AD, amyotrophic lateral sclerosis and multiple sclerosis. **Objectives:** To investigate the role of miR-155 in AD mouse models.
Methods: Methods: We generated miR-155$^{fl/fl}$ mice crossed with Cx3cr1Cre^{ERT2} mice on an APP/PS1 background. We employed RNAseq and immunohistochemistry to analyze gene expression profiles and AD pathology, while cognitive function was assessed through spontaneous alternation and forced alternation tests. Additionally, in collaboration with Regulus Therapeutics, we developed novel compounds capable of suppressing miR-155 in microglia, both in vitro and in an acute neurodegenerative mouse model.
Results: Results: Our findings reveal that microglial deletion of miR-155 induces a pre-MGnD activation state via interferon-g (IFN-γ) signaling, leading to enhanced compaction of amyloid plaques, reduced dystrophic neurites, alleviated synaptic degradation associated with plaques, and improved cognitive performance. Furthermore, preliminary tests have demonstrated the efficacy of the RG5942 compound in suppressing miR-155 expression in the N9 microglial cell line after LPS stimulation and in an acute neurodegenerative mouse model.
Conclusions: Conclusion: Our study unveils a novel miR-155-mediated regulatory mechanism in MGnD microglia and suggests that targeting miR-155 could be a promising therapeutic strategy for AD. Blocking miR-155 holds the potential to limit neurodegenerative pathology and preserve cognitive function in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0109 / #1863

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

EFFECT OF AGING, AMYLOID PATHOLOGY AND APOE ISOFORM ON MICROGLIA PHENOTYPE AND GENE EXPRESSION.

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Nicholas Fitz, Iliya Lefterov, Radosveta Koldamova
University of Pittsburgh, Eoh, Pittsburgh, United States of America

Aims: Alzheimer's disease (AD) is a multifactorial disease with aging as the major risk factor and APOE representing the major genetic risk factor for late-onset AD. Microglia play an essential role in response to amyloid pathology and AD associated neuroinflammation. Less is known about the impact of major AD risk factors on normal microglial response. The current study aim is to profile the age-dependent microglial transcriptomic and proteomics changes in response to amyloid pathology and expressed APOE isoforms in an Alzheimer's disease mouse model.
Methods: Brain samples from Alzheimer's disease model mice expressing human APOE isoforms at different ages were used to isolate microglia and perform transcriptomic and proteomic analysis.
Results: To gain further insight in the correlation between amyloid pathology, APOE isoform and aging in the microglial transcriptome, we performed RNA-seq using isolated microglia. We identified phenotype-correlated networks using Weighted Gene Co-Expression Network Analysis (WGCNA) and identified that aging is the strongest factor that affects microglial transcriptome in both WT and APP mice. We also defined that APOE isoform-specific effect on microglial transcriptome significantly correlated to amyloid pathology and genes affected by both amyloid pathology and aging. The identified targets were validated using FISH. Finally, we performed proteomics analysis on the microglia isolated from the same groups of mice.
Conclusions: These findings demonstrate the importance of microglia in the pathogenesis of AD. APOE genotype and aging, the main risk factors for AD, affect microglial responses which may further aggravate neurodegeneration. Targeting microglia may be a preventive intervention to delay the progression of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0110 / #2767

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

INFLAMMATORY MICROENVIRONMENT IN A BETA-AMYLOID MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Robin Guay-Lord, Laurent Potvin-Trottier, Lionel Breuillaud, Elodie Brison, Barry Bedell
Biospective Inc, Technology, Montreal, Canada

Aims: Beta-amyloid (Aβ) accumulation in Alzheimer's disease (AD) activates microglia and astrocytes. It is vital to improve our understanding of the spatial relationships between Aβ pathology and neuroinflammation. As such, the objective of this work is to provide quantitative measures of activated microglial and reactive astrocytes in the microenvironment of Aβ pathology in an APP/PS1 mouse model of AD.
Methods: We have developed a fully-automated method to identify, count, spatially localize, and characterize microglia, astrocytes, and Aβ plaques in multiplex immunofluorescent sections in APP/PS1 (ARTE10) transgenic mice [1]. We used a novel machine learning-based morphometric analysis to identify activated microglia. We quantified the microgliosis and astrogliosis both in the local microenvironment of the plaques (Fig. 1A) and distant to the plaques as a function of disease progression.
Results: We found that microglia identified as activated (Fig. 1B) by our machine learning model are denser, have more highly branched processes, and have less circular soma compared to non-activated microglia (Fig. 1C). ARTE10 mice demonstrated an age-dependent increase in Aβ plaques, microgliosis, and astrogliosis (Fig. 2). Analysis of the Aβ plaque microenvironment showed microgliosis primarily located less than 10 µm away from the plaques, with higher Iba-1 stain density (Fig. 3A), microglia density (Fig. 3B), and activated microglia density (Fig. 3C) compared to wild-type (WT) mice (dashed line). Interestingly, the astrogliosis also showed an increase with proximity to the plaques, but was also increased outside of the local plaque microenvironment (Fig. 3D). **Figure**

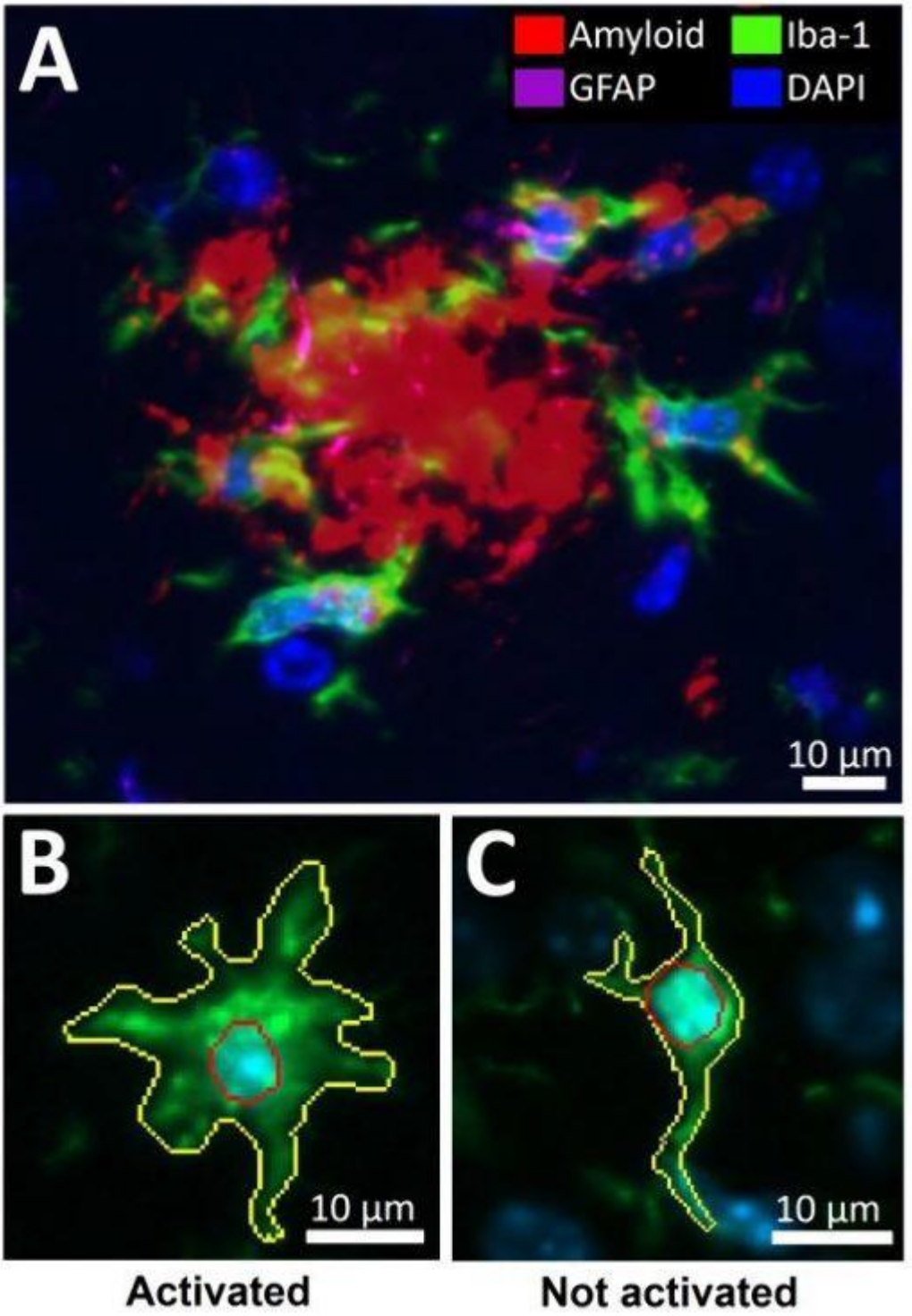

A
Amyloid
Iba-1
GFAP
DAPI
10 µm
B
10 µm
C
10 µm
Activated
Not activated

Figure 1:

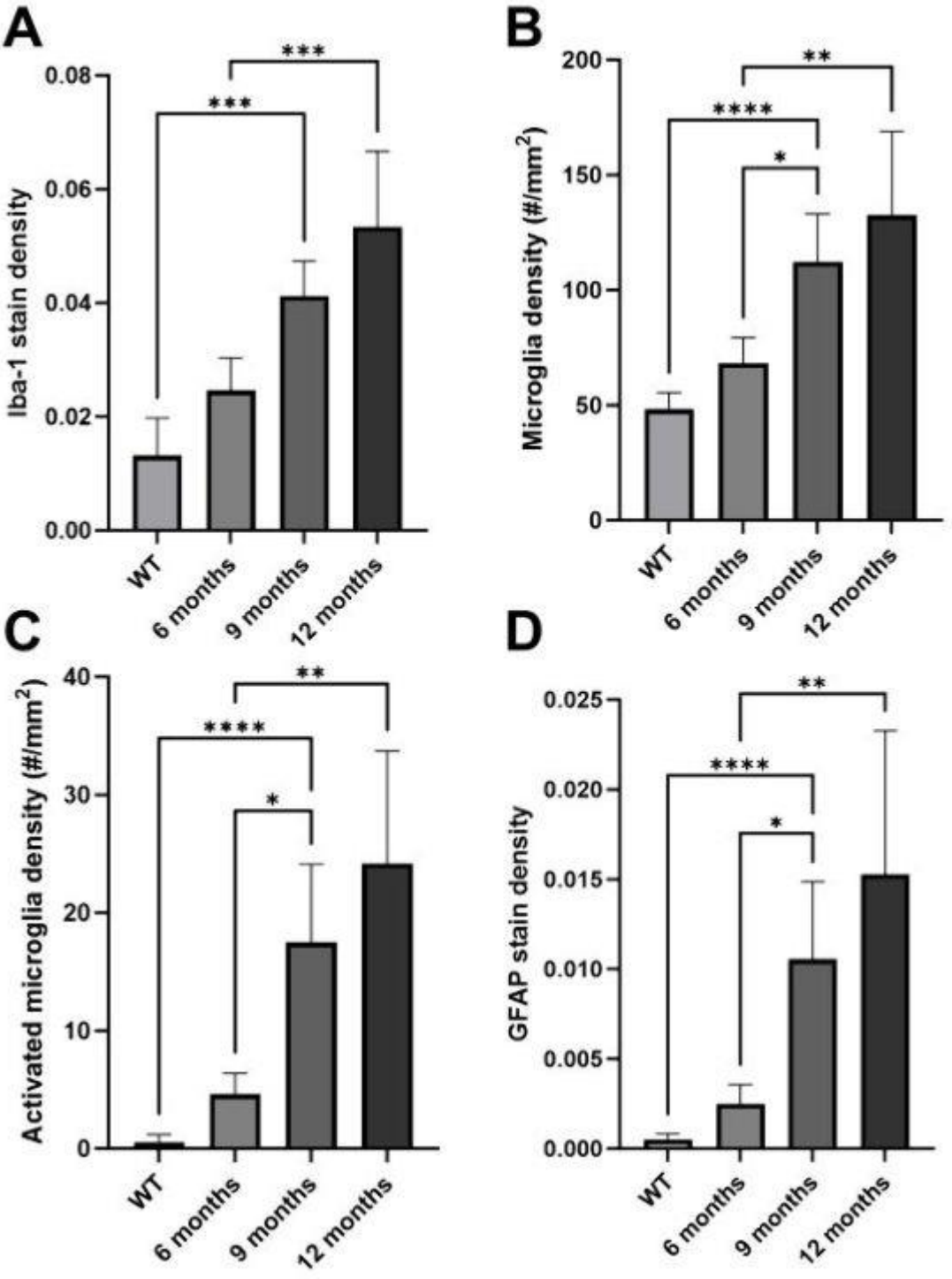
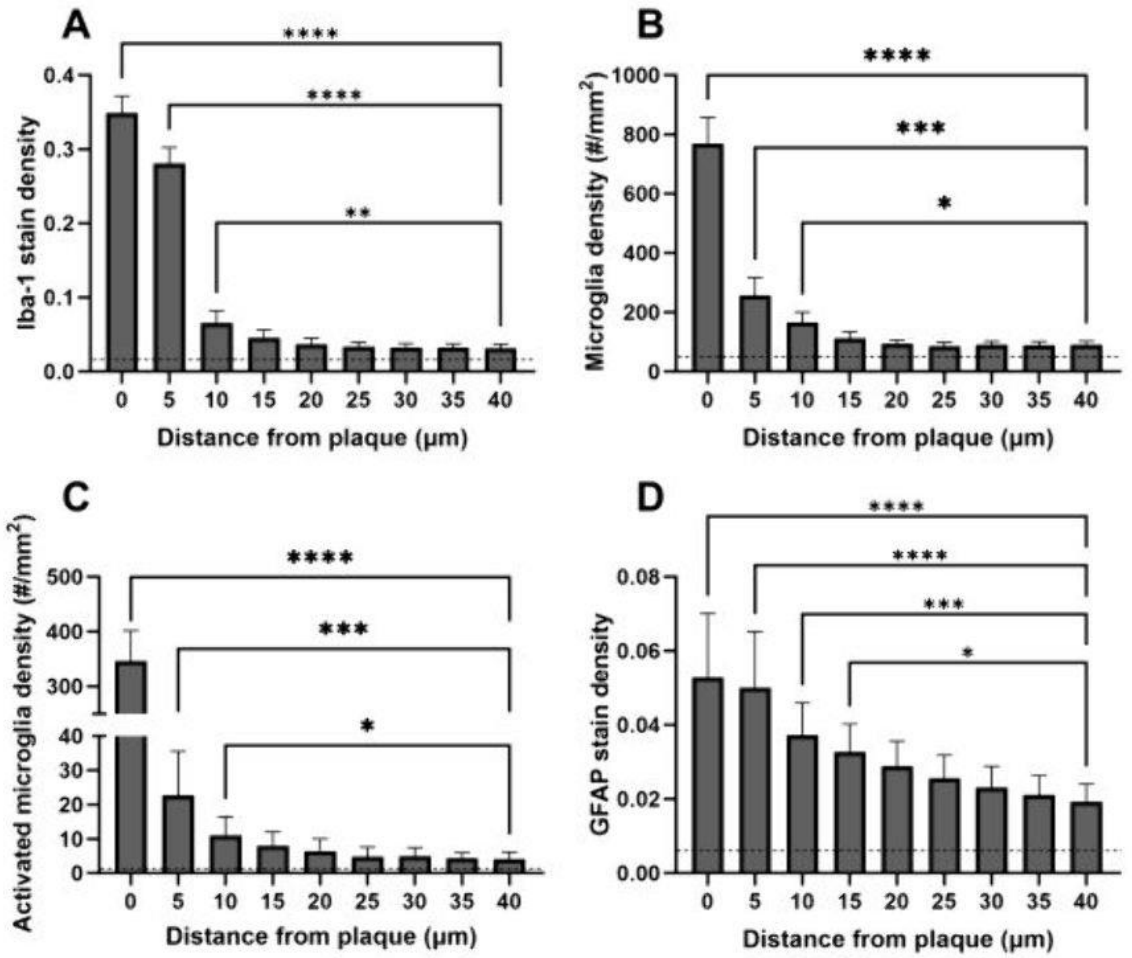

A
Iba-1 stain density
0.08
0.06
0.04
0.02
0.00
***
***
WT
6 months
9 months
12 months
B
Microglia density (#/mm²)
200
150
100
50
0
**
****
*
C
Activated microglia density (#/mm²)
40
30
20
10
0
D
GFAP stain density
0.025
0.020
0.015
0.010
0.005
0.000

Figure 3:



Conclusions: Characterizing the neuroinflammatory microenvironment around Aβ plaques can potentially provide sensitive measures for the evaluation of putative disease-modifying therapeutic agents for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0111 / #1704

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

UNRAVELING THE RELATIONSHIP BETWEEN MICROGLIA AND NEUROFILAMENT LIGHT CHAIN

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Christina Heiss[1], Stefanie Fruhwürth[1], Lana Grötschel[2], Maria Olsson[3], Henrik Zetterberg[2,3,4]
[1]Sahlgrenska Academy, Institute of Neuroscience and Physiology, Department Of Psychiatry And Neurochemistry, Göteborg, Sweden, [2]Department of Psychiatry and Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden, [3]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: Alzheimer's disease (AD) is a neurodegenerative disease leading to elevated levels of neurofilament light chain in both cerebrospinal fluid and blood. Microglial activation plays a pivotal role in the progression of AD and various hallmark pathologies have been associated with microglial activation. However, it remains unknown how increased NfL levels affect microglia and how microglia in different states respond to NfL. Here we aim to elucidate the relationship between microglia and elevated levels of NfL as observed in AD.
Methods: We use human induced-pluripotent stem cell (hiPSC) derived microglia and neurons to study the mode of uptake of NfL. Labelled NfL is added to hiPSC-derived microglial cultures and uptake is assessed by fluorescence. Additionally, NfL, released by neurons, is measured in media of neuronal cultures and neurons co-cultured with microglia.
Results: Utilizing two different labeling methods, our results show a clear uptake of labelled NfL-proteins into microglia. The use of a pH-dependent dye indicates that the observed uptake happens via phagocytosis or endocytosis pathways. We further show a reduction in NfL levels in cultures of neurons when microglia are added.
Conclusions: In summary, our data convincingly illustrates the active uptake of NfL by microglia in response to neuronal degeneration. To strengthen its clinical and Alzheimer's disease (AD) research implications, further investigations are needed to elucidate the precise mechanism of this uptake.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0112 / #1978

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

INHALED XENON MODULATES MICROGLIA AND AMELIORATES DISEASE IN MOUSE MODELS OF AMYLOIDOSIS AND TAUOPATHY

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Ilya Ilin[1], Wesley Brandao[2], Nimansha Jain[3], Zhuoran Yin[2], Kilian Kleemann[2], Madison Carpenter[2], Mathew Blurton-Jones[4], Howard Weiner[5], David Holtzman[6], Oleg Butovsky[2]
[1]General Biophysics LLC, Neurology, Wayland, United States of America, [2]Brigham and Women's Hospital, Harvard Medical School, Neurology, Boston, United States of America, [3]Washington University School of Medicine, Neurology, St. Louis, United States of America, [4]University of California Irvine, Department Of Neurobiology And Behavior, Irvine, United States of America, [5]BWH, Neurology, Brookline, United States of America, [6]Washington University in St. Louis, Neurology, St. Louis, United States of America

Aims: Background: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder. Currently, anti-amyloid antibody treatments modestly slow disease progression in mild dementia due to AD. Emerging evidence shows that homeostatic dysregulation of the brain immune system, especially that orchestrated by microglia, plays a significant role in the onset and progression of the disease, including an increase in neuroinflammation and oxidative stress. Thus, a major question is how to modulate the phenotype and function of microglia to treat AD. Xenon gas (Xe) is a noble gas used in human patients as an anesthetic and neuroprotectant in treating brain injuries. Xe penetrates the blood-brain barrier, which can make it an effective therapeutic. **Objectives:** evaluate if Xe-gas treatment has a protective immunomodulatory role to ameliorate AD.
Methods: Methods: APP/PS1, humanized 5xFAD and P301S (tau) mice were treated with Xe 50% once a week for 2-3 months. After this period microglia and peripheral immune cells were evaluated by Immunohistochemistry, flow cytometry and scRNA-seq.
Results: Results: we identified that Xe inhalation polarizes mouse and human microglia towards an intermediate state of activation that we have termed as 'pre-MGnD' in an acute neurodegeneration model and mouse models with AD-like pathology, i.e., 5xFAD (amyloid) and P301S (tau). This microglial phenotypic transition enhanced amyloid plaque compaction and reduced dystrophic neurites. Moreover, Xe inhalation reduced brain atrophy, and neuroinflammation and improved nest-building behavior in APOE4:P301S mice. Mechanistically, Xe inhalation polarizes homeostatic microglia toward a pre-MGnD state via IFNg signaling that maintains the microglial phagocytic response while suppressing its pro-inflammatory properties.
Conclusions: Conclusion: these results support the translation of Xe inhalation as a novel approach to treating AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0113 / #2762

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

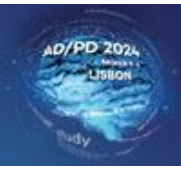
INNATE IMMUNITY PROTEIN IFITM3 REGULATES ALZHEIMER'S DISEASE-ASSOCIATED MICROGLIAL RESPONSE

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Tanya Jain[1], Georgia Frost[1], Yue-Ming Li[2]
[1]Weill Cornell Medicine, Neuroscience, New York, United States of America, [2]Memorial Sloan Kettering, Chemical Biology Program, New York City, United States of America

Aims: Amyloid plaques consist Aβ peptides, which are sequentially cleaved by α or β-secretase and then γ-secretase (GS) from amyloid precursor protein (APP). Our lab has previously identified interferon response protein IFITM3 as a γ-secretase (GS) modulatory protein that is upregulated in the human AD brain as well as in the 5xFAD mouse brain, particularly in glia. We have shown that IFITM3 regulates GS activity in neurons, and a deficit in IFITM3 results in decreased GS cleavage of APP, leading to reduced amyloid plaque deposition in the 5xFAD mouse. With our new studies, we want to: 1. Investigate the consequence of IFITM3 deficit on cognitive decline and neuronal loss in AD 2. Investigate whether IFITM3 plays a role in amyloid clearance by microglia
Methods: We have generated 5xFAD;IFITM3$^{-/-}$;TREM2$^{-/-}$ mice and have established human stem cell-derived IFITM3-/- microglial cells. We have used a panel of mouse behavioural, immunohistochemical and transcriptomic studies and *in vitro* microglial assays to investigate the function of IFITM3 in the phagocytic clearance of Aβ by microglia, its interplay with TREM2 and downstream signaling in the context of neuroinflammation.
Results: We have found that IFITM3 is highly expressed and inducible in microglial cells. We have shown that 5xFAD;IFITM3$^{-/-}$ mice have rescued cognition and neuronal loss compared to 5xFAD mice, and have an upregulation of several microglial DAM genes. In our *in vitro* microglial model, we have found that IFITM3$^{-/-}$ microglia display enhanced uptake of Aβ peptide, enhanced lysosomal degradation, and enhanced TREM2 expression and signaling.
Conclusions: With these studies, we have determined a novel role of IFITM3 in microglia. We have also found evidence of an interplay of IFITM3 with TREM2. These studies confirm IFITM3 is a viable therapeutic target AD treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0114 / #1924

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

THE ROLE OF PURINERGIC RECEPTOR P2Y12 FOR MICROGLIA FUNCTION IN THE ALZHEIMER BRAIN: FROM ZEBRAFISH TO HUMANS

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Sofia Wüstenhagen[1], Kazi Tanzina Rahman[1], Sarra Zenagui[1], Yasmin Abdul Jabbar[1], Anders Wallin[1,2], Francesco Locatelli[1,2], Petronella Kettunen[1,2]
[1]University of Gothenburg, Neuroscience And Physiology, Gothenburg, Sweden, [2]Sahlgrenska University Hospital, Psychiatry, Cognition And Old-age Psychiatry, Mölndal, Sweden

Aims: The purinergic receptor P2Y12 is expressed by microglia and has been proposed to be involved in neuroinflammation related to neurodegenerative disorders, including Alzheimer's disease (AD). In this study, we used a newly developed p2y12 CRISPR zebrafish line in combination with human biofluid samples to better understand the role of P2Y12 in AD.
Methods: To explore the role of P2y12 in microglia function, we crossed the p2y12 mutants with transgenic ApoE:GFP fish marking microglia. We investigated microglia phagocytosis and lysosomal function in detail in vivo using confocal microscopy. Moreover, we measured the levels of P2Y12 in CSF samples from AD patients and controls from the Gothenburg Mild Cognitive Impairment study.
Results: Our experiments show that lack of P2y12 impairs microglia function, including microglia morphology, phagocytosis, as well as lysosomal function. Moreover, P2Y12 was measured in human CSF and data were correlated to other patient variables, such as the core AD CSF biomarkers indicating disease progression.
Conclusions: Taken together, our findings suggest that P2y12 is critical for cellular functions of microglia, which could underlie the pathological process in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0115 / #611

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

REPRODUCIBLE AND CONTROLLABLE HUMAN IPSC-DERIVED CORTICAL TISSUE MODELS TO INVESTIGATE ALZHEIMER'S DISEASE.

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Julien Klimmt[1], Carolina Cardoso Gonçalves[1], Stephan Müller[2], Caterina Carraro[3], Severin Filser[1], Lars Paeger[4], Jochen Herms[4], Stefan Lichtenthaler[2], Joachim Schultze[3], Christian Haass[5], Dominik Paquet[1]
[1]University Hospital, LMU Munich, Institute For Stroke And Dementia Research, Munich, Germany, [2]German Center for Neurodegenerative Diseases, Neuroproteomics, Munich, Germany, [3]German Center for Neurodegenerative Diseases, Systems Medicine/single Cell Genomics, Bonn, Germany, [4]German Center for Neurodegenerative Diseases, Translational Brain Research, Munich, Germany, [5]Ludwig-Maximilians-University Munich & German Center for Neurodegenerative Diseases, Biochemistry, Munich, Germany

Aims: Human iPSC-based Alzheimer's Disease (AD) models have great potential for mechanistic and translational studies, as they enable investigation of pathomechanisms in human brain cells. However, current iPSC-AD models show low reproducibility and cell type diversity, lack physiological cell-cell interactions, or show only earliest disease phenotypes. Therefore, we aim to develop more reproducible and controllable iPSC-AD models that combine multiple brain cell types and enable analysis of pathomechanisms in a human, 3D cortical tissue-like environment.
Methods: We optimized protocols to differentiate iPSCs into cortical neurons, astrocytes, and microglia. We combined these differentiated cells into 3D co-cultures and characterized them using stainings, mass spectrometry analysis and functional assays. Using CRISPR/Cas9, we introduced AD-causing mutations to study AD pathogenesis in an isogenic system.
Results: By 3D co-culturing all cell types we established modular, human cortical tissue models that display dense networks of neuritic processes that are stable for >6 months without formation of a necrotic core. Added microglia migrate into and tile the cultures, surveil the environment and react to tissue damage. We further confirmed maturation of the cultures, e.g., by formation of synapses and deposition of a brain-like extracellular matrix. In AD cultures, we observed typical phenotypes such as increased Aβ secretion and age-dependent accumulation of extracellular and insoluble Aβ, increased levels of phospho-tau and microglial activation. Upon addition of exogenous Aβ42, we found aggregation into plaque-like structures with surrounding axonal dystrophies.
Conclusions: We developed a reproducible and controllable, human cortical tissue model to study cell states, crosstalk, and functionality in health and disease. Currently, we expand the model by including additional cell types such as oligodendrocytes and test approaches to elicit endogenous formation of plaque pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0116 / #1237

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

TARGETING HEXOKINASE 2 TO MODULATE INFLAMMATORY RESPONSE OF MICROGLIAL CELLS AFTER TRAUMATIC BRAIN INJURY AND ITS IMPACT ON AD-LIKE DEMENTIA

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Claudia Mera Reina, Juan Codocedo, Peter Lin, Anushay Ansari, Paul Fallen, Cristian Lasagna-Reeves, Gary Landreth
Stark Neurosciences Research Institute, Indiana University, School of Medicine, Anatomy, Cell Biology And Physiology, Indianapolis, United States of America

Aims: Traumatic brain injury (TBI) and Alzheimer's disease (AD) are devastating neurological disorders, whose complex relationship is not completely understood. Persistent activation of microglia represents a mechanistic link between the development of a secondary injury after TBI, Aβ deposition and dementia. Activated microglia undergo a shift to aerobic glycolysis, to power the various energy intensive activities that subserve the change in microglia phenotype. Hexokinase 2 (HK2), an enzyme that catalyzes the first step in glycolysis, it is an important driver of microglial activation in various pathological processes. **Objective:** We propose that targeting HK2 could be of therapeutic utility for limiting inflammation-induced secondary injury and acceleration of AD pathogenesis in an amyloid mouse model subjected to mild TBI (mTBI).
Methods: To determine the role of HK2-driven microglial activation in the mTBI-induced AD pathology acceleration, we performed controlled cortical impact (CCI) in 5xFAD mice with inducible inactivation of microglial HK2. Additionally, we tested the therapeutic potential of HK2 antagonism using its pharmacological inhibitor, Lonidamine, inmediatly after CCI. Microglial gene expression was evaluated by qPCR. Cortical cytokine levels were measured by Elisa and Aβ species were evaluated by western blot. Cognitive dysfunction was tested in a Y-maze.
Results: HK2 expression was significantly up regulated at 7 days post CCI and its levels remained high after 30 days post injury. In 5xFAD mice, mTBI increased the expression of inflammatory cytokynes as well as the abundance of Aβ oligomeric forms. Importantly, HK2 antagonism attenuated these effects. Additionally, there was a reduction in the expression of several genes associated with microglial activation.
Conclusions: The antagonism of HK2 during the recovery phase post-TBI, had a potent anti-inflammatory effect, limiting the secondary injury associated with microglial dysfunction and progression to AD-like pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0117 / #1197

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

TOTAL PLCG2 DEPLETION IMPAIRS MICROGLIAL RESPONSES AND CONFERS DIVERSE TRANSCRIPTIONAL ALTERATIONS IN A MURINE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Evan Messenger[1], Andy Tsai[2], Peter Lin[1], Adrian Oblak[1,3], Miguel Moutinho[1,4], Guixiang Xu[1], Anushay Ansari[1], Bruce Lamb[1,4], Gary Landreth[1,4], Stephanie Bissel[1,4]
[1]Indiana University School of Medicine, Stark Neuroscience, Indianapolis, United States of America, [2]Stanford University School of Medicine, Wu Tsai Neurosciences Institute, Stanford, United States of America, [3]Stark Neurosciences Research Institute, Indiana University, School of Medicine, Department Of Radiology & Imaging Sciences, Indianapolis, United States of America, [4]Indiana University School of Medicine, Anatomy, Cell Biology And Physiology, Indianapolis, United States of America

Aims: Many of the genes associated with altered risk for Alzheimer's disease (AD) are predominantly expressed in microglia and affect innate immune responses. Among these genes is PLCG2, a mediator of transmembrane signaling that acts downstream of many immune receptors on microglia, including TREM2. Recent RNA-Seq studies suggest a vital role for PLCG2 in many aspects of AD pathology, including the immune response. Reduction in PLCG2 activity is associated with exacerbated AD pathology, but the mechanisms underlying these effects remain unclear.
Methods: We explored the impact of *Plcg2* ablation or haploinsufficiency in the amyloidogenic 5xFAD murine model of AD and compared this to 5xFAD mice deficient in *Trem2.*
Results: While *Plcg2* haploinsufficiency increased X34+ and 6E10+ amyloid plaque pathology, loss of *Plcg2* exhibited similar pathology as wildtype and *Trem2*-deficient mice. Additionally, *Plcg2* deficiency significantly impaired microglial interactions with plaques and showed reduced immunoreactivity of microglia activation marker CD68 when compared to *Plcg2*$^{+/-}$ mice. Gene expression analysis of bulk RNA-Seq data revealed several biological processes altered by loss of *Plcg2*, including pathways associated with the microglial response, metabolism, synapses, and cell signaling. WGCNA produced many significant modules of co-expressed genes such as those associated with immunity, metabolism, and neuronal processes. Importantly, one module was differentially expressed between each genotype and contained predominantly immune-related genes, including DAM genes.
Conclusions: PLCG2 depletion impairs the ability of microglia to effectively transduce surface receptor signals in response to amyloid plaques, leading to a stunted immune response. Additionally, the WGCNA reveals a role for PLCG2 in metabolism, neuronal functioning, and mitochondrial health in AD. Overall, this study highlights the importance of PLCG2 in the innate immune response to amyloid pathology and reveals several novel pathways which may be regulated by PLCG2.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0118 / #2846

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

PHENOTYPIC CHARACTERIZATION OF A NOVEL SPI1*RS1377416 MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Giedre Milinkeviciute[1], Celia Da Cunha[1], Katelynn Tran[1], Adrian Mendoza-Arvilla[1], Shimako Kawauchi[1], Jonathan Neumann[2], Amber Walker[2], Andrea Tenner[1,3,4], Frank Laferla[1,5], Grant Macgregor[2,6], Kim Green[1,4]
[1]University of California Irvine, Institute For Memory Impairments And Neurological Disorders, Irvine, United States of America, [2]University of California Irvine, Transgenic Mouse Facility, Irvine, United States of America, [3]University of California Irvine, Molecular Biology And Biochemistry, Irvine, United States of America, [4]University of California Irvine, Neurobiology And Behavior, Irvine, United States of America, [5]University of California, Irvine, Neurobiology And Behavior, Irvine, United States of America, [6]University of California Irvine, Developmental And Cell Biology, Irvine, United States of America

Aims: Genome-Wide Association Studies (GWAS) implicate SPI1 as a risk factor for late-onset Alzheimer's Disease (LOAD). Within the brain, *SPI1* encodes a microglia-specific transcription factor, PU.1, necessary for microglial proliferation and activation. *SPI1* rs1377416 has been identified as a non-coding GWAS risk variant for AD. Here, we introduced the *Spi1* rs1377416 variant into the mouse genome to explore its impacts on AD pathogenesis.
Methods: By using CRISPR/Cas9, we generated *Spi1*rs1377416* mice that carry a non-coding mutation corresponding to the rs1377416 SNP found in human *SPI1*. We crossed the *Spi1* mice with the 5xFAD mouse model of amyloidosis and aged them to 4 and 12 months of age. Coronal brain sections were then obtained and immunolabeled with several markers to visualize amyloid plaques, glial cells and assess axonal and neuritic damage. Confocal images were then obtained and quantified in subiculum and cortex.
Results: We found an age-related increase in dense core plaque number and size in the subiculum of 5xFAD;*Spi1* mice. Despite this, microglial volume as well as astrocytic activation were reduced in 5xFAD;*Spi1* compared to 5xFAD mice at 12 months. Correspondingly, neuritic dystrophy and axonal damage were diminished. Notably, significant sex differences were observed in different analyses with males being affected less than females (with the exception of plaque deposition).
Conclusions: Our results indicate that the rs1377416 variant of *Spi1* induces an age-dependent increase in amyloid deposition in the 5xFAD model of amyloidosis. Moreover, this *Spi1* variant exerts a protective effect by suppressing astrocytic response and preventing neuritic and axonal damage. There is a strong sex difference observed between males and females when the variant is present and requires further investigation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0119 / #177

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

MICROGLIA: SENSORS AND MODULATORS OF ALZHEIMER'S DISEASE-RELATED NETWORK HYPEREXCITABILITY

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Lennart Mucke[1,2], Kaitlyn Ho[1], Gui-Qiu Yu[1], Cathrine Petersen[1,2], Victor Huang[1,2], Sara Knowles[1,2], Melanie Das[1,2]
[1]Gladstone Institute of Neurological Disease, Gladstone Institutes, San Francisco, United States of America, [2]Department of Neurology and Weill Institute for Neurosciences, University Of California San Francisco, San Francisco, United States of America

Aims: Neural network and immune dysfunctions may engage in a vicious circle promoting cognitive decline in Alzheimer's disease (AD) [*iScience* 24: 103245 (2021), *Neurobiol. Dis.* 186: 106263 (2023)]. To further test this hypothesis, we modulated the expression or amino acid sequence of the triggering receptor expressed on myeloid cells 2 (TREM2) or its adapter protein TYROBP and examined how these manipulations affect network hyperexcitability in AD-relevant models.
Methods: Mice lacking one or both *Trem2* or *Tyrobp* alleles and knockin mice expressing the common variant (CV) or R47H variant of human TREM2 were challenged with an excitotoxin or crossed with knockin mice bearing amyloidogenic variants of the amyloid precursor protein. Epileptiform activity ("hyperexcitability") was measured by video-EEG recording. Learning and memory were assessed by behavioral assays, neuropathological alterations by immunohistochemistry and confocal microscopy, and gene expression changes by RT-qPCR or RNA-seq.
Results: Reduced expression of TREM2 or TYROBP exacerbated hyperexcitability in excitotoxin-challenged mice. Expression of human TREM2-R47H, but not TREM2-CV, had similar effects. TREM2-R47H also worsened the age-dependent development of spontaneous hyperexcitability in mice with amyloid plaques. Reducing mouse TREM2 or expressing human TREM2-R47H, but not TREM2-CV, caused aberrant increases in the density of excitatory synapses in some but not other brain regions, compared to controls, potentially increasing excitation/inhibition ratios. Preliminary quantifications of synapses and behaviors suggest that expression of human TREM2-R47H may cause more marked effects than ablation of one mouse *Trem2* allele.
Conclusions: These results suggest that microglia/macrophages can suppress hyperexcitability of different causes and that this function depends on both TREM2 and TYROBP. Variants of these proteins may increase the risk of AD or other dementias, at least in part, by promoting network hyperexcitability.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0120 / #1036

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

INTRAVENTRICULAR INJECTION OF NOX2 BLOCKATOR PREVENTS THE APPEARANCE OF PATHOLOGICAL FEATURES IN MICE MODEL OF THE EARLY STAGES ALZHEIMER'S DISEASE

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Kristina Mukhina[1], Alexander Makarov[1], Irina Popova[1,2]
[1]Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Laboratory Of Protein Conformational Polymorphism In Health And Disease, Moscow, Russian Federation, [2]Institute of Theoretical and Experimental Biophysics Russian Academy of Sciences, Laboratory Of Systemic Organization Of Neurons Named After O. S. Vinogradova, Pushchino, Russian Federation

Aims: Alzheimer's disease (AD) is the most common neurodegenerative pathology with a poorly understood etiology. Recent data point out that ROSs may play a principal role in the initiation of AD. The main source of ROS in the brain is NADPH oxidase 2 (NOX2), located on the membrane of microglial cells. The study examined the effect of NOX2 blockade using the selective inhibitor GSK2795039 (GSK) on the manifestation of early markers of AD in mice with beta amyloid (Ab)-induced pathology.
Methods: To create an acute model of AD BALB/c mice were neurosurgically operated by injecting Abeta into the brain ventricle. GSK was administered i.c.v. within 3 days after surgery. Animal behavior was evaluated in Open Field and Social Interaction tests on days 7 and 14 after Abeta injection. Immunohistochemistry was performed on slices stained with antibodies to Iba-1 and the area and the number of microglial cells in areas CA1 and DG were counted. Brain homogenate was separated into fractions and analyzed for biochemical markers of oxidative stress.
Results: It was found that NOX2 blockade reduces aggression and enhances pro-social interaction in animals without worsening the general condition; prevents activation of microglia in the hippocampus, reducing cell area and number of processes; significantly reduces the level of the markers of oxidative stress - ROS and lipid peroxides and increases the level of reduced glutathione in the membrane, cytoplasmic and mitochondrial fractions of the brain homogenate.
Conclusions: GSK prevents the development of pathological changes associated with the initial stage of Abeta pathology at the behavioral, cellular and subcellular levels. Supported by the Russian Science Foundation (grant #19-74-30007)

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0121 / #1359

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

HUMAN CORTICAL ORGANOIDS AS A POTENTIAL MODEL FOR MICROGLIA-NEURON INTERACTION

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Nataliia Novosolova[1], Polina Abushik[1], Mireia Gomez Budia[1], Sohvi Ohtonen[1], Minna-Mari Tervo[1], Susanne Michels[1], Raisa Giniatullina[1], Nelli-Noora Välimäki[1], Sarka Lehtonen[1,2], Jari Eerik Koistinaho[3,4], Antonios Dougalis[1], Paula Korhonen[1], Tarja Malm[1]
[1]University of Eastern Finland, A.i. Virtanen Institute For Molecular Sciences, Kuopio, Finland, [2]University of Helsinki, Neuroscience Center, Helsinki, Finland, [3]University of Helsinki, Helsinki Institute Of Life Science, Helsinki, Finland, [4]University of Helsinki, Drug Research Program, Division Of Pharmacology And Pharmacotherapy, Helsinki, Finland

Aims: Majority of the models of human neuronal disorders are presented by rodents, yet human neuronal functions have been reported to be significantly different from their rodent counterparts. Human induced pluripotent stem cell (hiPSC) -derived brain organoids offer an ample opportunity to investigate neuronal operational properties in a human context. Here we describe the electrophysiological properties of hiPSC-derived cortical-like brain organoids grown in air-liquid interphase.
Methods: By using the whole-cell patch clamp technique in current and voltage clamp modes, we recorded the basic neuronal operational properties in organoids matured with or without microglia for 4,5,6 and 7 months *in vitro*.
Results: Our data show that the presence of microglia significantly enhanced the frequency of spontaneous excitatory postsynaptic currents in the recorded neurons. Moreover, electrical stimulation of the slice during a positive current pulse led to a cessation of action potential firing suggesting inhibitory synaptic GABA release. Reconstruction of patch-clamped, biocytin-filled neurons revealed the presence of apical dendrite, axon, and different types of spines in the recorded neurons.
Conclusions: Our data suggest that the air-liquid interphase culture of human cortical-like organoids has the characteristics of functional neuronal network with excitatory and inhibitory system and could be used as a potential model for microglia-neuron interaction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0122 / #2321

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

FUNCTIONAL ANALYSIS OF BIOMARKER CANDIDATES FOR MICROGLIAL ACTIVATION

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Ida Pesämaa, Stefanie Fruhwürth, Henrik Zetterberg
Institute of Neuroscience and Physiology, Gothenburg University, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden

Aims: With the emergence of anti-amyloid therapies and microglia-modulating therapies, biomarkers for microglial activation are urgently needed. Recently, we identified six proteins (FABP3, MDH1, GDI1, CAPG, CD44, GPNMB) in models of microglial activation, with increased levels in the CSF of individuals with neurodegeneration and/or amyloid abnormalities. The levels of these proteins increase in a microglial activation-dependent manner, with FABP3, MDH1, and GDI1 as the most promising of the six candidates. Here, we aim to link the current biomarker candidates with functional information, such as biological pathways and characteristics crucial for microglial activation.
Methods: To identify functions related to the reported biomarker candidates, we revised our data, as well as additional proteomics datasets as published by others. We investigated correlations within these proteomic datasets, with a special focus on correlations between the levels of proteins related to microglial activation and neuroinflammation. Furthermore, we made use of in vitro models (iPSC-derived microglia) to study the functions of FABP3, MDH1, and GDI1 in the context of microglial activation.
Results: Our preliminary results confirm the previously reported positive and statistically significant correlation between CSF levels of FABP3, MDH1, GDI1, and CHI3L1. Furthermore, we have identified additional proteins that show a correlation with these four proteins, including LDHB and MPI. Finally, pathway analysis suggests that the majority of these proteins are involved in metabolic pathways including glycan degradation and pyruvate metabolism.
Conclusions: Taken together, our results further support the involvement of the reported biomarker candidates in the process of microglial activation. Moreover, our findings emphasize the importance of metabolic pathways in the context of microglial activation. Information regarding the biological function of a biomarker is likely to improve its application and it may even contribute to a more personalized treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0123 / #673

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

ABCA7 DEFICIENCY IMPAIRS THE RESPONSE OF MICROGLIA TO AMYLOID PATHOLOGY IN A HUMANIZED MODEL OF AD

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Jessie Premereur[1,2], Paula Miquel[1,2], Bob Asselbergh[2], Alma Mohebiany[1,2], Lena Duchateau[2,3], Kristel Sleegers[2,3], Renzo Mancuso[1,2]
[1]VIB Center for Molecular Neurology, Microglia And Inflammation In Neurological Disorders (mind) Lab, Antwerpen, Belgium, [2]University of Antwerp, Biomedical Sciences, Antwerpen, Belgium, [3]VIB Center for Molecular Neurology, Complex Genetics Of Alzheimer's Disease Group, Antwerpen, Belgium

Aims: The ATP-binding cassette transporter, subfamily A member 7 (ABCA7) is one of the most important AD risk genes identified, wherein loss of function (LOF) variants are linked to several microglial pathways, including lipid metabolism and endocytosis. However, the contribution of ABCA7 to microglial biology and AD remains largely unknown. Our main objective is to define the role of ABCA7 dysfunction in microglial homeostasis and AD pathology.
Methods: We generated two ABCA7-KO ESC lines and one patient-derived iPSC line (E709fs), together with their isogenic controls, and differentiated all lines into ESC/iPSC-derived microglia (ESC/iPSC-MG) using our MIGRATE protocol. To understand the effect of microglial ABCA7 dysfunction on AD pathology *in vivo*, we transplanted them into the brains of AD (AppNL-G-F) and control mice. At 6 months, we investigated the differences in the microglia transcriptome and cellular surface proteins using CITE-sequencing (Cellular Indexing of Transcriptomes and Epitopes), and their response to amyloid pathology with histopathology.
Results: ABCA7 LOF microglia display an altered internalization of amyloid β particles *in vitro*, indicating either enhanced phagocytic capacity or diminished degradation. Grafted ABCA7-KO cells displayed a reduced activation in response to amyloid pathology, both at the level of transcriptomic and histopathology. In contrast to TREM2 variants, ABCA7-KO microglia do cluster around plaques similarly to controls but do not engage into a disease associated program, suggesting correct recognition of the AD protein aggregates but failure to engage their endo-lysosomal system and process phagocytic material appropriately.
Conclusions: Our data suggests that distinct molecular mechanisms operate in microglia to contribute to the risk of AD, where ABCA7 LOF microglia fail to engage in an activated response profile.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0124 / #1344

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

DISTINCT GLYCOSYLATION CHANGES IN ALZHEIMER'S AB OLIGOMER- AND LIPOPOLYSACCHARIDE-ACTIVATED HUMAN MICROGLIA

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Xinyu Tang[1], Ryan Schindler[2], Jacopo Lucente[3], Armin Oloumi[2], Danielle Harvey[4], Carlito Lebrilla[2], Angela Zivkovic[1], Lee-Way Jin[3], Izumi Maezawa[3]
[1]University of California Davis, Nutrition, Davis, United States of America, [2]University of California Davis, Chemistry, Davis, United States of America, [3]University of California Davis, Pathology And Laboratory Medicine And M.i.n.d. Institute, Sacramento, United States of America, [4]University of California Davis, Public Health, Davis, United States of America

Aims: Glycosylation and complex carbohydrates have been reported to play critical roles in the early pathogenesis and progression of Alzheimer's disease (AD). However, the potential of these molecules to serve as biomarkers and targets for disease intervention remains largely unexplored. Microglia, the brain-resident immune cells, are key players in AD pathogenesis; however, their glycosylation changes in AD-relevant conditions are poorly understood.
Methods: We examined glycosylation and gene expression changes following the activation of human-induced pluripotent stem cell-derived microglia (hiMG) by amyloid-β oligomers (AβO). For comparison, we also examined responses to lipopolysaccharides (LPS). The glycosylation and glycosphingolipid profile of hiMG were measured using a mass spectrometry (MS)-based glycomic and glycosphingolipidomic approach. The changes in glycosyltransferase gene expression were measured using RNA-seq.
Results: AβO and LPS induced highly distinct glycosylation changes. AβO induced a decrease in bisecting GlcNAc N-glycans, aligning with downregulation of the MGAT3 (N-acetylglucosaminyltransferase 3) gene, and an increase in sialylation, with congruent upregulation of ST3GAL (α2,3-sialyltransferase 2, 4, and 6) genes. These changes were not induced by LPS; instead, LPS induced a decrease in complex N-glycans, aligning with the downregulation of mannosidase genes (MAN1A1, MAN2A2, MAN1C1), and an increase in terminal fucosylation, accompanied by upregulation of the fucosyltransferase 4 (FUT4) gene and downregulation of the α-L-fucosidase 1 (FUCA1) gene. However, glycosphingolipids did not reveal significant changes induced by AβO or LPS.
Conclusions: Distinct glycosylation pathways induced by AβO may contribute to microglial impairments in the early stages of AD. Further investigations of players within these pathways may uncover therapeutic targets for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0125 / #789

Poster Topic: *Theme A: β-Amyloid Diseases / A01.i. Disease Mechanisms, Pathophysiology: Microglia*

XBD173 ALTERS MICROGLIAL SYNAPTIC ENGULFMENT VIA 18 KDA TRANSLOCATOR PROTEIN (TSPO)

POSTERS: A01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Zhishen Zhang[1,2], Mochen Cui[1,2,3], Juan Zu[1,2,3], Yuan Shi[1,2,4], Jochen Herms[1,2,4]
[1]Center for Neuropathology, Ludwig-maximilians-universität München, münchen, Germany, [2]German Center for Neurodegenerative Diseases, (dzne), München, Germany, [3]München Medical Research School, Ludwig-maximilians-universität München, Munich, Germany, [4]Ludwig-Maximilians-Universität München, Munich Cluster For Systems Neurology (synergy), Munich, Germany

Aims: 18 kDa translocator protein (TSPO) is an ancestral protein with multifaceted functions in the central nervous system (CNS). Previous studies have demonstrated distinct effects of selected TSPO ligands on cognition but with elusive mechanisms. In the CNS, microglia substantially impact cognition by constantly regulating synapses. Recently, we observed that modulating TSPO altered microglial morphology and their phagocytic activity towards synaptic materials. Here, we aim to investigate further the TSPO-mediated microglia-synapse interactions and microglial synaptic engulfment using a widely applied TSPO ligand.
Methods: We chose XBD173, a selected TSPO ligand of the phenylpurine class. We employed long-term *in vivo* 2-photon microscopy to monitor the interactions between eGFP-labelled microglia and eYFP-labelled dendritic spines in transgenic mice. We also employed multiplex immunostaining, coupled with super-resolution confocal microscopy and post hoc 3D reconstruction to evaluate the microglial phagocytic activity of synaptic materials and their TSPO expression in XBD173/vehicle-fed wild-type (WT) mice.
Results: After 21 days of XBD173/vehicle administration, we observed significant morphological alterations of cortical microglia in XBD173-fed WT mice with lowered TSPO expression. Furthermore, we observed that the microglia of XBD173-fed mice contained reduced lysosomes (CD68) containing less synaptic materials (PSD95). In addition, in XBD173-fed mice, we observed an altered pattern of microglia-synapse interactions compared to the vehicle-fed ones. Both effects were suppressed upon genetic depletion of TSPO, supporting the dependency of these microglial alterations on TSPO.
Conclusions: We report microglial engulfment of synaptic materials can be modulated by XBD173 via TSPO in mice. Our findings fill the gap by yielding evidence on how XBD173 affects microglial functionality and synaptic plasticity in the CNS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0126 / #1037

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

THE POTENTIAL UTILITY OF LONGITUDINAL CHANGES OF PLASMA GFAP AS A SECONDARY ENDPOINT TO MONITOR AD CLINICAL TRIALS.

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Sarah Abbas[1], Pamela Lukasewicz Ferreira[1], Bruna Bellaver[1], Guilherme Povala[1], Douglas Teixeira Leffa[1], Firoza Lussier[1], Francieli Rohden[1], Cristiano Schaffer Aguzzoli[1], Hussein Zalzale[1], Carolina Soares[1], Marina Scop-Meidros[1], Guilherme Negrini[1], Markley Silva Oliveira Junior[1], Nesrine Rahmouni[2], Jenna Stevenson[2], Cécile Tissot[2], Stijn Servaes[2], Joseph Therriault[2], Thomas Karikari[3], Nicholas Ashton[4], Andréa L. Benedet[4], Henrik Zetterberg[5], Kaj Blennow[5], Pedro Rosa-Neto[2], Tharick A Pascoal[6]
[1]University of Pittsburgh, Psychiatry, PITTSBURGH, United States of America, [2]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [3]University of Gothenburg, Psychiatry And Neurochemistry, Göteborg, Sweden, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [5]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [6]Department of Neurology and Psychiatry, University Of Pittsburgh School Of Medicine, Pittsburgh, United States of America

Aims: To evaluate the association between longitudinal changes in plasma GFAP levels and AD pathophysiology and test its utility to monitor drug effects on AD clinical trials.
Methods: We assessed 107 individuals across the AD spectrum[Cognitively unimpaired(CU) n=71, mean age (SD) = 71.5(6.48); CU Aβ+,n=26, mean age (SD) =73.3(5.29); CI Aβ+,n=28, mean age (SD) =70.44(7.01)] from TRIAD cohort. All individuals had Aβ PET measurements at baseline.Sample size estimation was for a hypothesized 25% drug effect on plasma GFAP reduction. Linear regressions were used to test associations between plasma GFAP with cognition (MMSE),and plasma p-tau217, adjusted for age, sex, and education.
Results: We found a significant increase in the percentage of change of plasma GFAP in all groups, with the highest annual rate of progression in CU Aβ+ individuals(Fig.1A).The effect size was relatively similar across all groups, with CU Aβ+ individuals presenting the highest numerical value (0.48) (Fig.1B).When including only CU Aβ+ individuals, the sample size required for a trial would be 1067 individuals per arm(a reduction of 12% when compared to the entire CU population)(Fig 1C).A significant correlation was found between the rate of change of plasma GFAP and baseline plasma GFAP in the CU population(Fig 2A).In CI Aβ+,rate of change of plasma GFAP negatively correlated with rate of change of MMSE(Fig 2B) and positively correlated with baseline and longitudinal plasma p-tau217(Fig 2C & 2D).

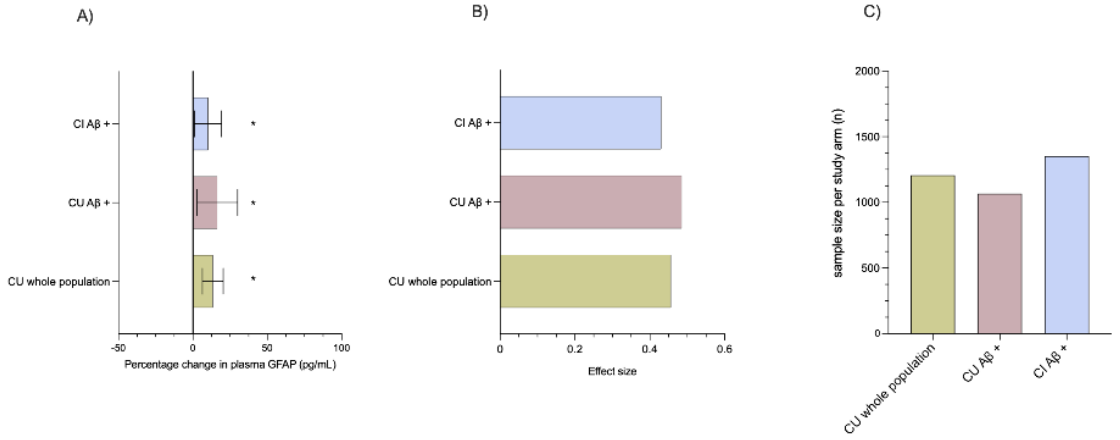


***Figure1*. Percentage of change and effect size of plasma GFAP levels in individuals across the AD continuum; sample sizes required for AD clinical trials powered to use changes in plasma GFAP as a surrogate.** A) Horizontal bars show the mean percentage change with a 95% confidence interval in individuals stratified by amyloid-β status and clinical diagnosis. [CU (mean =13.4% , SD= 29.38), CU Aβ + (mean=16.39%, SD=33.78), and CI Aβ + (mean=10.16%, SD= 23.58)], * indicates that the 95% confidence interval did not cross the zero line. B) The bars represent the effect sizes, calculated as the ratio between the mean and SD of the percentage of change over time points. [CU=0.45, CU Aβ += 0.48, CI Aβ + =0.43]. C) Vertical bars show sample size per arm required for hypothesized clinical trials in [CU (n=1206), CU Aβ + (n=1067), CI Aβ + (n=1353)].

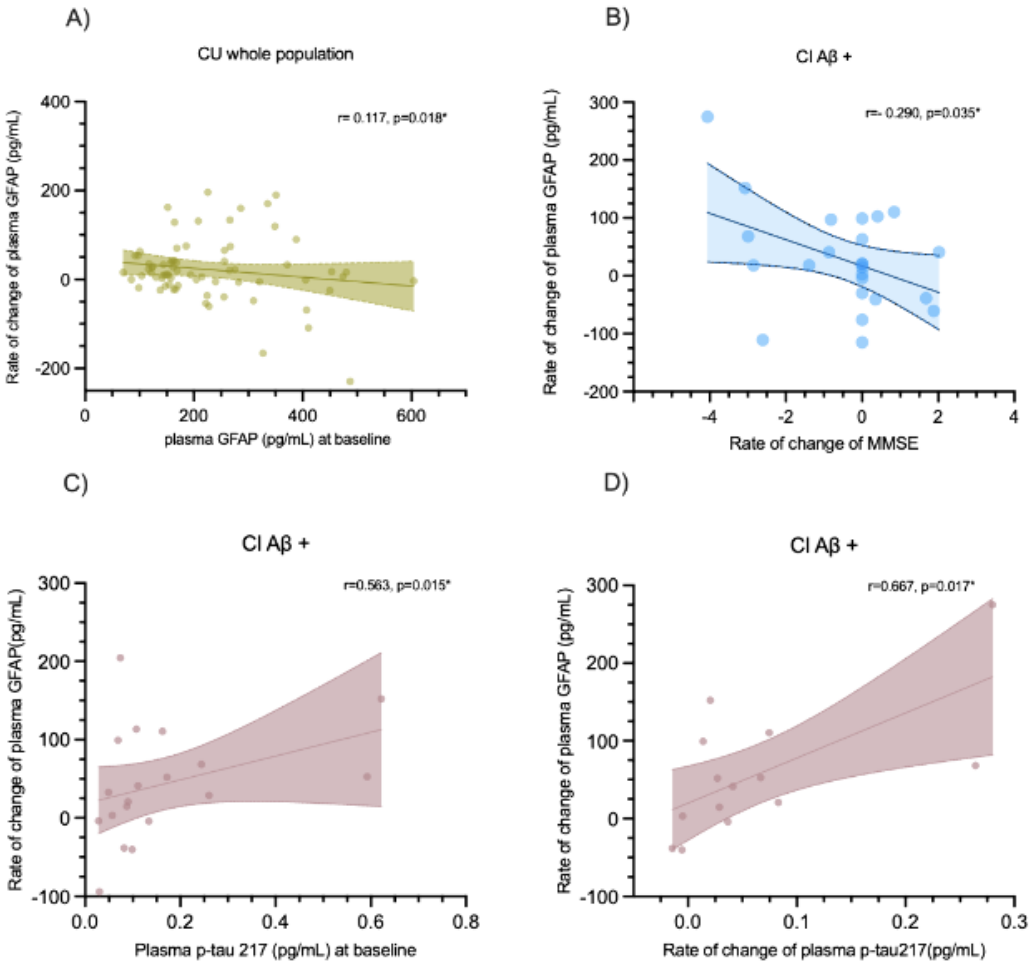


Figure2. **Association among rate of change of plasma GFAP in CU whole population, and MMSE and plasma p-tau217 in CI Aβ+ individuals.** Linear regressions showing the associations between the rate of change of plasma GFAP levels and A) Baseline plasma GFAP in CU whole population, B) Rate of change of MMSE in CI Aβ+ individuals, (C and D) Baseline and rate of change of plasma p-tau217 in CI Aβ + individuals.

Conclusions: Changes in GFAP in CU depended on baseline CU levels whereas changes in GFAP in CI Aβ+ associated with parallel cognitive decline and tau phosphorylation.Our findings suggest Plasma GFAP is a robust biomarker for tracking AD progression and may potentially be used as a secondary endpoint in AD clinical trials with CU Aβ+ individuals requiring a relatively smaller sample size.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0127 / #1217

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

IPSC-DERIVED HUMAN BRAIN TISSUE MODELS TO INVESTIGATE GLIAL CROSSTALK IN AD

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Carolina Cardoso Gonçalves[1,2], Julien Klimmt[1], Sophie Robinson[1,3], Christian Haass[3,4], Dominik Paquet[1,4]
[1]University Hospital, LMU Munich, Institute For Stroke And Dementia Research, Munich, Germany, [2]LMU Munich, Graduate School For Systemic Neurosciences, Planegg-Martinsried, Germany, [3]Ludwig-Maximilians-Universität München & Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Biochemistry, Munich, Germany, [4]Munich Cluster for Systems Neurology, Synergy, Munich, Germany

Aims: Astrocytes, microglia and oligodendrocytes are critical players in the maintenance of nervous system homeostasis and response to injury. Dysfunction of these cell types and their crosstalk can therefore enhance neuroinflammation and is thought to play an important role in neurodegenerative diseases such as Alzheimer's Disease (AD). However, the components and mechanisms that mediate neuron-glia and glia-glia crosstalk and how this becomes dysfunctional in AD is poorly understood. A major challenge of studying glial crosstalk in AD in a human context comes from the current lack of experimental human models recapitulating late-stage AD phenotype and containing major glial cell types in a physiological 3D environment.
Methods: We generated a reproducible and modular human induced pluripotent stem cell (hiPSC-) based 3D tissue model containing neurons, astrocytes, microglia and oligodendrocytes to study the interactions between the different cell types in physiological and disease contexts. Using CRISPR/Cas9, we introduced AD-causing mutations as well as alterations in AD risk factors such as ApoE and Clusterin to promote AD phenotypes. Our modular co-culture approach allows us to assess the effect of cell-type-specific genotypes in an AD environment, providing a unique asset to investigate glial crosstalk.
Results: We are incorporating astrocytes and microglia with ApoE-, Clusterin- or double-knockout genotypes to our 3D-AD model and evaluate the role of these AD-related proteins in Aβ accumulation, p-Tau and disease progression. By incorporating oligodendrocytes, we achieved myelination which allow us to study alterations in myelin production and maintenance as well as oligodendrocyte effect in an AD context.
Conclusions: Our cultures enable new research opportunities not only in the AD field to study the effect of different mutations on a specific cell type, but also in the future to investigate other diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0128 / #1008

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

3.5D QUANTITATIVE IFISH FOR INVESTIGATING THE SPATIAL DISTRIBUTION OF ASTROCYTIC MRNA AND PROTEIN IN ALZHEIMER'S DISEASE

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Mochen Cui[1,2,3], Juan Zu[1,2,3], Qiang Huang[1,2], Yuan Shi[1,2,4], Jochen Herms[1,2,4]
[1]Ludwig-Maximilians-Universität München, Center For Neuropathology, Munich, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Department Of Translational Brain Research, Munich, Germany, [3]Ludwig-Maximilians-Universität München, Munich Medical Research School, Munich, Germany, [4]Ludwig-Maximilians-Universität München, Munich Cluster For Systems Neurology (synergy), Munich, Germany

Aims: Considerable efforts have been dedicated to elucidating the involvement of astrocytes in Alzheimer's disease (AD). While conventional techniques such as *in situ* hybridization and immunostaining have enabled the examination of astrocytic mRNA and proteins, they prove insufficient in capturing the subcellular heterogeneity of these components within astrocytes due to their intricate morphology and the occurrence of local translation in distant processes. Consequently, we aim to devise a method that permits simultaneous investigation of astrocytic mRNA and proteins at subcellular precision in AD.
Methods: We introduce a methodology referred to as "3.5D iFISH," a fusion of multiplex immunofluorescent staining (i) and modified mRNA *in situ* hybridization (FISH). It facilitates the simultaneous detection of protein and mRNA targets within astrocytes, making use of commercially available probes on free-floating murine brain sections. Additionally, our methodology is optimized for subsequent super-resolution confocal scanning and analysis via Imaris, enabling spatial examination of specific protein and mRNA within 3D reconstructed astrocytes (3.5D).
Results: We employed the *APPPS1dE9* mice and selected mRNAs encoding diazepam binding inhibitor (DBI), an astrocytic protein elevated in AD, as a proof of concept. We visualized the DBI protein, mRNA, and the intricate astrocytic architecture. Notably, we observed a significant upregulation of DBI protein and mRNA in processes of plaque-surrounding astrocytes. While in astrocytes distant from plaques, DBI protein and mRNA exhibit majorly somatic expression.
Conclusions: The 3.5D iFISH method offers a practical way to simultaneously characterize the expression of protein and mRNA in astrocytes in the AD context. It also facilitates the subsequent quantification of their subcellular distribution. Importantly, our approach is adaptable for various targets and can be extended to other cell types, e.g., microglia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0129 / #1449

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

ASTROCYTIC INSULIN RECEPTOR ABLATION PRECIPITATES ALZHEIMER'S DISEASE ONSET

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Amaia Ezkurdia[1,2], María Javier Ramírez[1,2], Maite Solas[1,2]
[1]IdISNA, Navarra Institute For Health Research, Pamplona, Spain, [2]University of Navarra, Pharmacology And Toxicology, Pamplona, Spain

Aims: Insulin is an important regulator of glucose homeostasis and metabolism. However, its role in the central nervous system is not yet fully understood. The role of insulin and its receptor (i.e. the insulin receptor, IR) in neurons has been widely studied. However, the role of insulin action in astrocytes remains unknown. Astrocytes provide structural, energetic and metabolic support to neurons, and also form the blood-brain barrier, being indispensable for adequate brain homeostasis. Interruption of astrocytic insulin signalling could change those astrocytic functions and thus, alter neuronal activity leading to cognitive deficiencies. In this line, this study aims to evaluate the impact of astrocytic IR deletion on Alzheimer's disease (AD).
Methods: In vitro, cellular metabolism was examined using an extracellular flux analyzer (Seahorse). In vivo, astrocyte-specific gene ablation was performed using tamoxifen-inducible Cre/LoxP approaches. Once IR deletion is obtained those mice were crossed with APP/PS1 AD mouse model. Brain glucose metabolism was evaluated by 18F-FDG PET. Peripheral metabolic characterization was performed by glucose tolerance and insulin tolerance tests. Memory was assessed using the Fear conditioning and Morris Water Maze tasks. Beta-amyloid accumulation was assessed by immunohistochemistry and ELISA.
Results: IR-ablated astrocytes featured reduced glucose uptake and glycolysis, upon amyloid-beta treatment. In our hands astrocytic IR deletion precipitates AD pathology in APP/PS1 mice inducing cognitive deficiencies. This cognitive perturbances are accompanied by lower brain glucose uptake. Interestingly, IR deletion in astrocytes induced an increase in amyloid-beta burden in AD mice.
Conclusions: Astrocytic IR ablation drives brain and systemic metabolism towards a less efficient glucose-handling phenotype and accelerates AD features inducing cognitive deficiencies and elevated amyloid burden.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0130 / #832

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

SPATIAL TRANSCRIPTOMICS ANALYSIS IDENTIFIES GLIAL STATES ASSOCIATED WITH HUMAN AMYLOID PLAQUE MICROENVIRONMENT

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Berke Karaahmet, Laurine Duquesne, Ya Zhang, Alina Sigalov, Christina Yung, Alexandra Kroshilina, Mariko Taga, Hans-Ulrich Klein
Columbia University Irving Medical Center, Neurology, New York, United States of America

Aims: Advances in transcriptomics have led to the identification of many molecular regulators involved in Alzheimer's disease (AD) pathology. While sophisticated single-cell based methods have revealed heterogeneous glial states in the AD brain, the histological localization of these signatures in relation to AD pathology has not been fully characterized due to the loss of spatial information. In this study, we aim to elucidate the glial states identified within the vicinity of amyloid-beta (Aβ) plaques.
Methods: For spatial transcriptomics, we optimized 10X Genomics' Visium pipeline (55-um spots) for immunohistochemistry on fresh frozen dorsolateral prefrontal cortex tissue of 17 donors acquired from Religious Orders Study/Memory and Aging Project (ROSMAP). We performed immunostaining for astrocytes using anti-GFAP and Aβ using Thioflavin S (ThioS) prior to following manufacturer's instructions for library preparation. We deconvolved our spatial dataset to identify localization of cellular states using Cell2location. To construct single nucleus reference transcription profiles containing cell state annotation, we used an unpublished dataset that consists of over 450 samples from ROSMAP. We then performed correlation analyses on the distance from plaque and deconvolution estimates within the 350-um radius around ThioS$^+$ plaques.
Results: We found a cluster of *SERPINA3* expressing astrocytes to be correlated with ThioS$^+$ plaque. This astrocyte state resembles previously discovered Disease-Associated Astrocytes in mouse models of AD. In contrast, we found several microglial states, thought to be involved in redox homeostasis, that were significantly underrepresented at the plaque niche.
Conclusions: Here, we demonstrate the heterogeneity in glial communities within the AB microenvironment. We show evidence that Serpina3$^+$ astrocytes seem to be more strongly associated with plaques, whereas several microglial clusters are found away from plaques. The role of these glial states in pathophysiology remains to be elucidated.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0131 / #1727

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

DETERMINING A TIME COURSE OF GLIAL CHANGES ASSOCIATED WITH CEREBRAL AMYLOID ANGIOPATHY

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Katelynn Krick[1], Sherika Johnson[1], Colin Rogers[2], Tiffany Sudduth[2], Erica Weekman[1], Donna Wilcock[1]
[1]Indiana University School of Medicine, Stark Neurosciences Research Institute, INDIANAPOLIS, United States of America, [2]University of Kentucky, Sanders Brown Center On Aging, Lexington, United States of America

Aims: Cerebral Amyloid Angiopathy (CAA) is a condition found at the intersection of Alzheimer's disease and vascular contributions to cognitive impairment and dementia (VCID). In the human brain it is observed when amyloid beta (Ab) accumulates in small/medium-sized cerebral blood vessels, altering vascular function and contributing to hypoperfusion and cognitive decline. The current study seeks to track the progression of CAA and associated neuroinflammation and glial cell changes in Tg2576 mice.
Methods: Mice were aged to 8-, 14-, 20-, and 27-months and assessed for CAA pathology via histology. Gene expression was evaluated in hippocampal tissue by qPCR, comparing 8- and 20-month APP and wildtype groups. Protein expression was evaluated via digital spatial profiling in the same APP mice, grouped by age or CAA presence compared to wildtype controls. CAA presence was defined as Ab surrounding lectin-positive vessels. Regions of interest were categorized as either positive or negative for CAA based on this criterion.
Results: Congophillic plaque deposition along the vasculature increased in width, length, and area in a time dependent manner in both the frontal cortex and hippocampus. Astrocyte marker GFAP and proinflammatory receptor TNFR1 gene expression both increased at 20 months compared to 8 months in the APP group. Of the protein profile assessed (Mouse Neural Cell Profiling and Mouse Glial Cell Subtyping), the most consistent changes were found in astrocyte markers. Both Aldh1l1 and S100B were increased at 20 months compared to 8 months of age in both APP and WT mice. GFAP protein expression was found to increase with both age and CAA.
Conclusions: This study showed increased vascular amyloid deposition and astrocyte gene and protein expression over time, further supporting a role for astrocytes in etiology and/or reaction to CAA.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0132 / #234

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

PTDP-43 INCLUSIONS IN ASTROCYTIC ENDFEET: A POTENTIAL MECHANISM FOR BBB AND GLYMPHATIC SYSTEM DYSFUNCTION IN ALZHEIMER'S DISEASE

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Jessica Santiago[1], Dovile Poceviciute[2], Shorena Janelidze[3], Oskar Hansson[4], Malin Wennström[5]
[1]Lund University, Clinical Sciences, Malmö, Sweden, [2]Lund University, Department Of Clinical Sciences, Malmö, Malmö, Sweden, [3]Lund University, Department Of Clinical Sciences, Lund, Sweden, [4]Skåne University Hospital, Clinical Sciences, Malmo, Sweden, [5]Lund University, Department Of Clinical Sciences, Malmö, Sweden

Aims: Since functional astrocytic endfeet are crucial for the maintenance of the blood-brain barrier (BBB) and the glymphatic system and play an important role in Amyloid beta (Aβ) clearance, we hypothesize that the accumulation of toxic phosphorylated TDP-43 (pTDP43) can accelerate Alzheimer's Disease (AD) pathology by damaging these astrocytic structures. The main objectives of this study were to investigate the presence of pTDP-43 inside astrocytic endfeet, and its potential association with signs of BBB and glymphatic system dysfunction, as well as its connection to Alzheimer's Disease, specifically regarding the accumulation of Aβ in AD brains.
Methods: Using immunostaining against pTDP-43 and markers for astrocytes (GFAP), astrocytic endfeet (AQP4), and BBB leakage (CD146), we investigated the presence of astrocytic pTDP-43 in hippocampi of AD cases and non-demented-controls, as well as in cultured astrocytes exposed to Aβ40. Localization was determined by confocal microscopy and the stained area fraction was analyzed using Image J.
Results: We found pTDP-43 inclusions within astrocytic endfeet. These perivascular inclusions were more prominent in AD than in controls and correlated with the disease severity and loss of CD146 and AQP4. Exposure to Aβ40 led to the translocation of astrocytic pTDP-43 from the nuclei to the cytoplasm, a known sign of TDP-43 pathology.
Conclusions: The findings support our hypothesis that pTDP-43 in astrocytic endfeet contributes to AD pathology by impairing brain clearance mechanisms and highlight pTDP-43 potential as a therapeutic target in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0133 / #849

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

PLASMA GFAP IS ASSOCIATED WITH WHITE MATTER ABNORMALITIES IN THE ALZHEIMER'S DISEASE CONTINUUM

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Markley Silva Oliveira Junior[1], Bruna Bellaver[2], Firoza Lussier[3], Pamela Lukasewicz Ferreira[2], Guilherme Povala[2], Douglas Teixeira Leffa[2], Guilherme Bauer-Negrini[3], Hussein Zalzale[2], Francieli Rohden[2], Carolina Soares[3], Andréa L. Benedet[4], Nicholas Ashton[4], Cécile Tissot[5], Joseph Therriault[5], Stijn Servaes[6], Jenna Stevenson[6], Nesrine Rahmouni[6], Chang Hyung Hong[7], Hyun Rho[7], Eduardo R Zimmer[8], Kaj Blennow[9], Henrik Zetterberg[9], Thomas Karikari[10], Pedro Rosa-Neto[5], Sang Son[7], Tharick A Pascoal[11]
[1]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America, [2]University of Pittsburgh, Psychiatry, PITTSBURGH, United States of America, [3]University of Pittsburgh, Psychiatry, Pittsburgh, United States of America, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [5]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [6]McGill University, Neurology And Neurosurgery, Montreal, Canada, [7]Ajou University School of Medicine, Psychiatry, Suwon, Korea, Republic of, [8]Department of Pharmacology, Graduate Program in Biological Sciences: Biochemistry (PPGBioq) and Phamarcology and Therapeutics (PPGFT), Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil, [9]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [10]University of Gothenburg, Psychiatry And Neurochemistry, Göteborg, Sweden, [11]Department of Neurology and Psychiatry, University Of Pittsburgh School Of Medicine, Pittsburgh, United States of America

Aims: Investigate the association of plasma glial fibrillary acidic protein (GFAP) with white matter hyperintensity (WMH) in the Alzheimer's disease (AD) continuum.
Methods: We assessed 941 individuals from a research (TRIAD, n = 150) and a clinical cohort (BICWALZ, n = 791). Linear regressions accounting for age and sex were used to estimate the associations. In the BICWALZ cohort, levels of plasma GFAP were compared between individuals across the Fazekas scale (a clinical scale used to quantify the amount of white matter hyperintense lesions). Between-group differences were verified using ANCOVA followed by the Tukey Test.
Results: In TRIAD, an increase in GFAP levels was associated with WMH levels. When we stratified these individuals by diagnosis and corrected the model for Aβ burden, we observed that this association is independent of Aβ (β =0.000008299, Z score= 0.22062, p=0.00382; **Fig.1A**). GFAP levels present significant interaction within the Fazekas stage (F1, F2, F3) in the BICWALZ cohort. GFAP levels are higher in individuals in F2 and F3 compared to F1 (**Fig.1B**). Among these individuals, females present higher levels of GFAP in F1 [mean (F=174.31|M=139.04); p< 0.0001] and F2 (p< 0.0001; **Fig.1C**). No sex differences in the association between GFAP and WMH were observed in the TRIAD cohort.

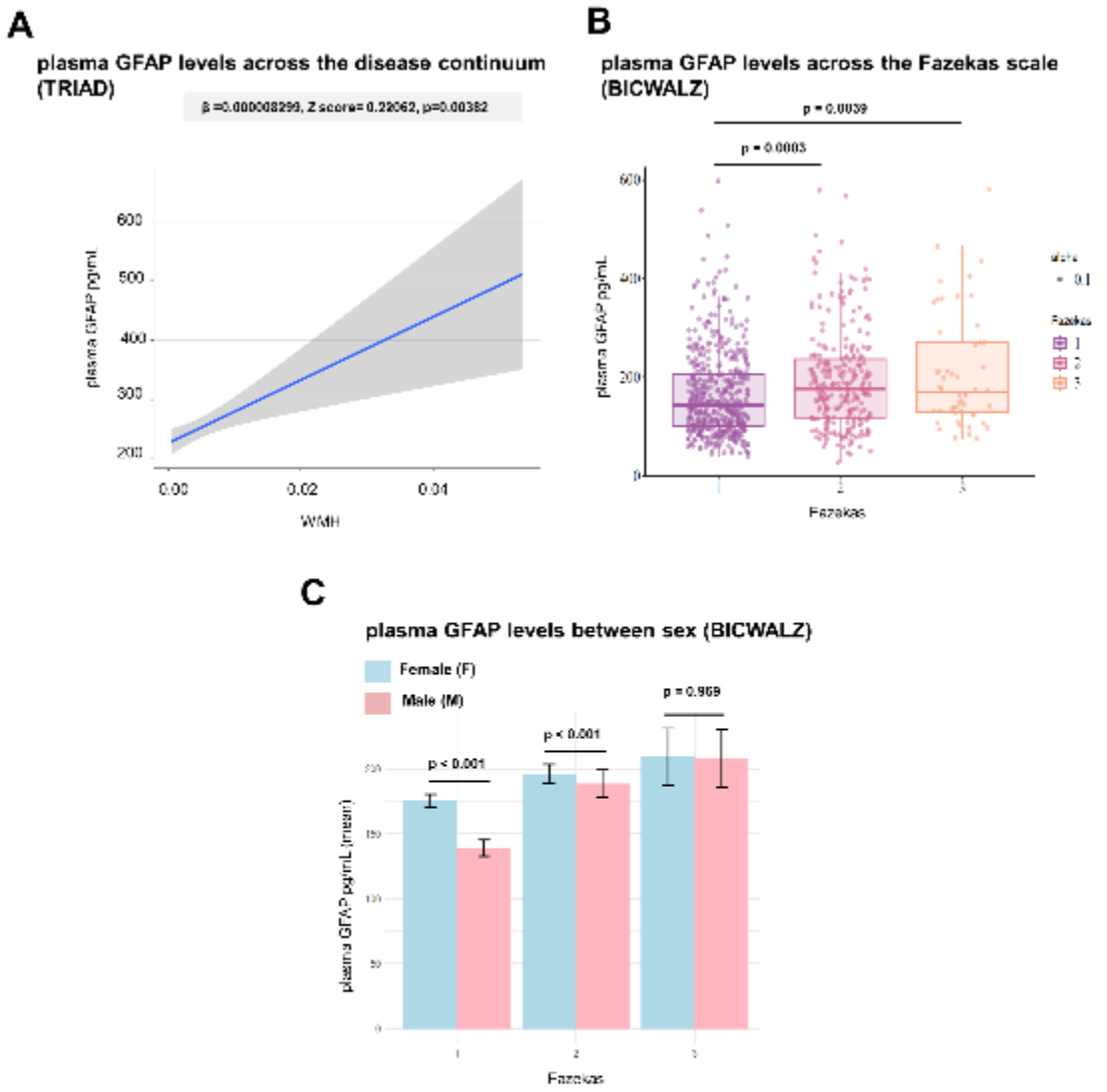


Figure 1. Plasma GFAP levels are associated with WMH in the disease continuum. (A) Linear regression shows the association between plasma GFAP levels as independent of Aβ burden. (B) Plasma GFAP levels increase within the Fazekas scale, and (C) females show greater plasma GFAP levels than males in F1 and F2 stages.

Conclusions: These findings highlight that GFAP levels are linked to cerebrovascular disease stages independent of AD pathology. The studies testing the association between GFAP levels and AD pathophysiology should consider the burden of cerebrovascular disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0134 / #1003

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

CHEMOGENICALLY ACTIVATED ASTROCYTES IN THE HIPPOCAMPUS REVEAL ASTROCYTE DYSFUNCTION IN ALZHEIMER'S DISEASE.

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Benjamin Tournier[1], Kelly Ceyzériat[1], Aurélien Badina[1], Yesica Gloria[1], Aida Fall[1], Quentin Amossé[2], Stergios Tsartsalis[2], Philippe Millet[2]
[1]University of Geneva, Psychiatry, Geneva, Switzerland, [2]University Hospitals of Geneva, Psychiatry, Geneva, Switzerland

Aims: The major goal of this study is to determine whether astrocytic control of hippocampal cellular functions is modified in Alzheimer's disease. *In vivo* measurements of connectivity between the hippocampus and the striatum, behavioral and *postmortem* measurements of neuroinflammation and pathological markers were performed after acute or chronic stimulation of astrocytes to reveal pathological alterations in astrocytic function.
Methods: We injected astrocyte-specific designer receptors exclusively activated by designer drugs (DREADD) delivered by adeno-associated virus (AAV) vectors or AAV controls in the hippocampus of 6 month-old WT or TgF344-AD rats. Simultaneous SPECT imaging for striatal dopamine release, brain activity and locomotor recordings were then performed after acute (3mg/kg, single i.p. injection) or chronic treatment (0.015mg/ml in drinking water, 3weeks) with clozapine N-oxide to activate astrocytes. After euthanasia, dopamine receptor D2 (D2R) and different aggregated forms of beta-amyloid (Aβ) were measured by ELISA. Double immunofluorescence made it possible to measure the activation of glial cells.
Results: In WT animals, acute and chronic activation of hippocampal astrocytes induce alteration of brain activity in dopaminergic areas and dopamine release in the striatum. This release results in a greater locomotor activity after acute but not chronic activation, which could originate from the downregulation of the D2R in the striatum that we observed. All these effects (dopamine release, brain activity and locomotor stimulation) are absent in TgF344-AD animals following astrocytes stimulation. However, chronic astrocyte stimulation induced a decreased in the highly aggregated forms of Aβ-40 and Aβ-42, which may be explained by the greater microglial phagocytic activity towards Aβ that we observed.
Conclusions: This study clearly shows an early astrocytic control deficit of hippocampal cellular functions and of Aβ accumulation in Alzheimer's disease. [supported by the SNSF grant: 310030_212322]

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0135 / #2919

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

AMYLOID-BETA-DEPENDENT ASTROCYTE MICRODOMAIN HYPERACTIVATION IS MEDIATED BY GLUTAMATE ACCUMULATION

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Felix Unger[1,2], Benedikt Zott[1,2]
[1]Technical University of Munich, Institute Of Neuroscience, Munich, Germany, [2]Technical University of Munich, Department Of Neuroradiology, Munich, Germany

Aims: Accumulating evidence from mouse models of Alzheimer's Disease (AD) reports aberrant astrocytic calcium signaling at early disease stages. However, the mechanisms are still unclear. In neurons, the main driver of neuronal hyperactivity is an amyloid β (Aβ)-dependent disruption of the reuptake of synaptically released glutamate. Because Aβ blocks glutamate reuptake transporters mainly on astrocytic membranes and astrocytes possess functional glutamate receptors mediating intracellular calcium transients, we ask whether glutamate accumulation may cause Aβ-dependent astrocytic hyperactivity.
Methods: In our study, we combine two-photon calcium and glutamate imaging in astrocytes and neurons to decipher the mechanisms of the increased synaptically evoked calcium signals in vivo and in acute brain slices in the hippocampus. We model early AD by the acute application of synthetic and human brain-derived soluble Aβ oligomers and investigate their mechanisms of action using pharmacology.
Results: We found that the acute application of Aβ dimers increases the number and amplitude of calcium signals in astrocytes in the hippocampal CA1 region of wildtype mice in vivo via a metabotropic glutamate receptor (mGluR)-dependent mechanism. Second, in acute hippocampal slices, we established that synaptically released glutamate binds to astrocytic mGluRs and induces calcium signals in the microdomains of astrocytes. The application of oligomers leads to increased levels of glutamate at astrocytic membranes and potentiation of microdomain calcium signals. These effects can be mimicked by applying the glutamate reuptake blocker DHK and depend on mGluR activation.
Conclusions: Together, our data demonstrate that Aβ-dependent glutamate accumulation is a critical mechanism of astrocytic hyperactivity. This provides a mechanistic link between astrocytic and neuronal hyperactivity in early AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0136 / #1894

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

CHARACTERIZATION OF ASTROCYTIC EXTRACELLULAR VESICLES IN A MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Liesbeth Voorbraeck[1], Romain Giraud[1], Maria Ankarcrona[1], Luana Naia[2]
[1]Karolinska Institutet, Neurobiology, Care Sciences And Society, Stockholm, Sweden, [2]Karolinska Institutet, Neurobiology Care Science And Society, Stockholm, Sweden

Aims: Mitochondrial dysfunction is an early feature in Alzheimer's disease (AD) as both amyloid beta peptide and hyperphosphorylated tau interfere with proper mitochondrial function and clearance of damaged mitochondria, which is especially detrimental at the level of the synapses, as it may impede neuronal transmission and contribute to neurodegeneration. We hypothesize that mitochondrial transfer is triggered by stress conditions and propose a feedback-loop in which healthy mitochondria are transferred from astrocytes to neurons, while neurons can transfer their damaged mitochondria to surrounding astrocytes to aid in mitophagy through extracellular vesicles (EVs). Furthermore, we believe this process is affected in AD, therefore, we set out to characterize astrocytic EVs in a disease relevant context.
Methods: EVs were isolated from conditioned media of primary cortico-hippocampal astrocytes derived from *App*$^{NL-G-F}$ and wildtype (WT) mice with a C57BL/6-J background through tangential flow filtration (TFF) followed by size-exclusion chromatography (SEC). After separation, the different fractions were kept separately for characterization, using nanoparticle tracking analysis (NTA), immunoblotting and proteomic analysis.
Results: We found that astrocytic EVs have an average size of 165 nm, which was constant across all fractions. The number of EVs produced per million astrocytes ranges between 10^9 and 10^{10} and no significant difference in EV number or size was found between WT and *App*$^{NL-G-F}$ cultures. Immunoblot and proteomics confirmed the presence of classic EV markers, including ALIX and Flotilin-1, as well as a variety of mitochondrial markers including proteins found in the mitochondrial matrix (PDH), mitochondrial membrane (VDAC1 and TOM20), and proteins involved in fission and fusion processes (OPA1).
Conclusions: Through characterization of astrocytic EVs, we hope to gain a better understanding of the transfer mechanism of mitochondria and its implications in neuronal health and future therapeutic applications.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0137 / #2996

Poster Topic: *Theme A: β-Amyloid Diseases / A01.j. Disease Mechanisms, Pathophysiology: Astroglia*

ASTROCYTIC HEMOGLOBIN IS A H2O2-DECOMPOSING PEROXIDASE AND THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE

POSTERS: A01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Woojin Won[1], Elijah Lee[2], Ki Duk Park[3,4], C. Justin Lee[1]
[1]Institute for Basic Science (IBS), Center For Cognition And Sociality, Daejeon, Korea, Republic of, [2]Korea Institute of Science and Technology (KIST), 2center For Brain Disorders, Brain Science Institute, Seoul, Korea, Republic of, [3]Korea Institute of Science and Technology, Center For Brain Disorders, Seoul, Korea, Republic of, [4]University of Science and Technology, Daejeon,, Division Of Bio-medical Science & Technology, Daejeon, Korea, Republic of

Aims: Urgent need for innovative treatments for Alzheimer's disease (AD). Astrocytic hydrogen peroxide produced by reactive astrocytes is highlighted as a cause of AD pathogenesis. However, effective antioxidant drugs either lack or require high doses for a significant effect. Our goal is to evaluate "KDS12025," a catalyst targeting astrocytic H2O2, to enhance memory and astrocyte function in Alzheimer's disease.
Methods: In vitro H2O2 Assay, Chemical Libraries Synthesis, Binding Affinity and Computational Modeling, Off-Target Selectivity Assay, PAMPA for BBB Permeability, Cultured Primary Astrocyte Preparation, Intracellular H2O2 Detection, Cell Viability, and Electrophysiology Methods, with a focus on Hbb shRNA Vector and RT-PCR for Gene Silencing.
Results: we have developed and tested a recently synthesized potent, blood-brain barrier permeable H_2O_2-decomposing catalyst, KDS12025 (IC50 = 60 nM; 1,666-fold selectivity over sodium pyruvate) in cultured astrocytes and animal models of AD. Unlike conventional H_2O_2 scavengers, we found that KDS12025 acts as a catalyst for peroxidase enzymes, such as brain hemoglobin (Hb), which have a potent function of decomposing H_2O_2 into harmless water. Computational modeling and binding assay elucidate the mechanistic interaction of KDS12025 with Hb, highlighting its pivotal role. KDS12025 effectively aided in the decomposition of excessive H_2O_2 in amyloid beta 42-incubated cultured astrocytes. Moreover, devastating memory impairment in AD model was rescued by KDS12025. Interestingly, regardless of whether administered through intraperitoneal injection or ad libitum consumption, a consistent positive effect was observed. Finally, Hbβ-small hairpin RNA experiments *in vitro* and *in vivo* validated the requirement Hbβ in the action of KDS12025.
Conclusions: KDS12025 is a novel, blood-brain barrier permeable catalyst that promotes the decomposition of neurotoxic hydrogen peroxide in Alzheimer's disease by enhancing the peroxidase activity of brain hemoglobin, showing significant therapeutic potential in both cellular and animal models.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0138 / #1193

Poster Topic: *Theme A: β-Amyloid Diseases / A01.k. Disease Mechanisms, Pathophysiology: Neurogenesis*

NEURAL STEM CELLS-DERIVED EXOSOMES PROMOTE SYNAPTIC RESISTANCE TO AMYLOID OLIGOMERS BY MODULATING THE NEUROINFLAMMATORY TONE IN THE HIPPOCAMPUS

POSTERS: A01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEUROGENESIS

Giulio Taglialatela[1], Pietro Scaduto[1], Salvatore Saieva[1], Jutatip Guptarak[1], Kathia Johnson[2], Wen Ru Zhang[1], Maria-Adelaide Micci[2]
[1]University of Texas Medical Branch, Neurology, Galveston, United States of America, [2]University of Texas Medical Branch, Anesthesiology, Galveston, United States of America

Aims: Alzheimer's disease (AD) is the most common and severe age-associated neurodegenerative dementia. While aging is the most significant risk factor for AD, disruption of synapses by oligomers of both amyloid beta (Aβ) and tau, via converging synergistic mechanisms, is one of the earliest events leading to memory dysfunctions. We previously found that exosomes secreted by hippocampal neural stem cells (NSCexo) act via specific miRNAs to provide synaptic protection against amyloid oligomers. Here we aimed to investigate how NSCexo, in comparison to mature neurons-derived exosomes (MNexo), modulate microglia in the hippocampus by performing immunofluorescence and transcriptomic analyses.
Methods: Male and female adult wild-type mice were injected ICV with PKH-26-labelled NSCexo or MNexo and the mice were euthanized 24h later. For the analysis of microglia activation, the brains were post-fixed in 4% PF and processed for immunofluorescence analysis using specific antibodies against Iba1 and CD68 (a marker of activation). For transcriptomic analysis, the hippocampus was dissected, snap frozen and processed for single nuclei RNA sequencing (snRNA seq) and for bulk RNA sequencing (RNA seq) on total homogenates and synaptosome fractions.
Results: Both NSCexo and MN-exo were taken up by microglia in the hippocampus. However, only NSCexo treatment led to elevated levels of microglial activation, as evidenced by increased CD68 immunostaining. RNA-seq and snRNA seq data further showed that immune response pathways were selectively activated by NSCexo in the hippocampus.
Conclusions: Our findings indicate that NSCexo have a significant impact on microglial activation, which could underlie their protective mechanism against AD pathology. These interactions result in specific gene expression changes in the hippocampal microglia, reinforcing the idea that increased levels of hippocampal stem cells could contribute to synaptic resilience against AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0139 / #2127

Poster Topic: *Theme A: β-Amyloid Diseases / A01.k. Disease Mechanisms, Pathophysiology: Neurogenesis*

IN VIVO TARGETING OF INTRACELLULAR ABETA_OLIGOMERS RESCUES HIPPOCAMPAL NEUROGENESIS AND MEMORY DEFICITS OF TG2576 MICE

POSTERS: A01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEUROGENESIS

Raffaella Scardigli[1,2], Laura Coppola[2], Sofia Mancini[2], Elena Fiori[2], Silvia Middei[3], Federico La Regina[2], Giovanni Meli[2], Antonino Cattaneo[2,4]
[1]Institute of Translational Pharmacology- CNR, Dept. Of Biomedical Sciences, Rome, Italy, [2]European Brain Research Institute (EBRI), Dept. Of Neurosciences, Rome, Italy, [3]IBBC-CNR, Dept. Of Biomedical Sciences, Monterotondo-Rome, Italy, [4]Scuola Normale Superiore, Dept. Of Physiology, Pisa, Italy

Aims: Decrease in adult neurogenesis has been described to correlate with Alzheimer's disease (AD) progression, but defects in this process at early stage of AD have not been explored yet. We have previously demonstrated that SVZ neurogenesis is reduced in Tg2576 mice at a presymptomatic stage due to intracellular Amyloid-beta oligomers (AβOs) accumulation in adult neural stem cells (aNSCs). We investigated if AβOs targeting in the dentate gyrus of young Tg2576 can rescue adult hippocampal neurogenesis (AHN) and recover AD-related memory deficits.
Methods: We analyzed the proliferative and differentiative features of resident and hippocampal-derived aNSCs of Tg2576 at a presymptomatic age, in relationship with the amount of Aβ and AβOs, measured by Western blot and Dot blot approaches. Upon intrabody conformational targeting of intracellular AβOs in vivo, based on viral-mediated delivery of the anti-AßOs scFvA13-KDEL intrabody, ER retained, we performed behavioural tests to evaluate cognitive improvement linked to AHN rescue.
Results: We observed proliferation and differentiation deficit of AD hippocampal progenitors, which are due to AβOs accumulation, as both defects can be rescued by the expression of scFvA13-KDEL intrabody, that interferes with the intracellular formation of AβOs in hippocampal aNSCs. Lentiviral delivery of scFvA13-KDEL in the dentate gyrus of young Tg2576 mice increased AHN and rescued Fear Conditioning, Pattern Separation and Social Novelty deficits. Moreover, intrabody treatment at symptomatic stage also ameliorated memory dysfunction in older mice.
Conclusions: We demonstrated a causal link between AβOs accumulation and reduced AHN in AD at presymptomatic stage. We also provided an innovative disease modifying gene-therapy approach to neutralize intracellular natural-occurring AβOs in the dentate gyrus, able to rescue hippocampal-dependent memory deficits, exploitable as an early therapeutic intervention to counteract disease onset and progression (funded by NGEU-MUR, PNRR-Mnesys-PE0000006).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0140 / #816

Poster Topic: *Theme A: β-Amyloid Diseases / A01.l. Disease Mechanisms, Pathophysiology: Vasculature, microbleeds, hypertension, angiogenesis*

FITNESS LEVEL MODIFIES THE RELATIONSHIP BETWEEN AORTIC STIFFNESS AND CEREBRAL HEMODYNAMICS

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

Brianne Breidenbach[1,2,3], Matt Glittenberg[1,2,3], Tarun Naren[4], Grant Roberts[4], Talia Brach[1,2,3], Mackenzie Jarchow[1,2,3], Sarah Lose[1,2,3], Leonardo Rivera-Rivera[4], Ira Driscoll[1,2,3], Sterling Johnson[2,3,5], Sanjay Asthana[2,3,5], Yue Ma[3], Bradley Christian[4], Dane Cook[6,7], Oliver Wieben[4,8], Ozioma Okonkwo[1,2,3]
[1]University of Wisconsin-Madison, Department Of Medicine, Madison, United States of America, [2]University of Wisconsin-Madison, Wisconsin Alzheimer's Institute, Madison, United States of America, [3]University of Wisconsin-Madison, Wisconsin Alzheimer's Disease Research Center, Madison, United States of America, [4]University of Wisconsin Madison, Department Of Medical Physics, Madison, United States of America, [5]William S. Middleton VA Hospital, Geriatric Research Education And Clinical Center, Madison, United States of America, [6]University of Wisconsin Madison, Department Of Kinesiology, Madison, United States of America, [7]William S. Middleton Memorial Veterans Hospital, School Of Medicine And Public Health, Madison, United States of America, [8]University of Wisconsin Madison, Department Of Radiology, Madison, United States of America

Aims: To investigate the moderating effects of fitness on the relationship between arterial [aortic] stiffness and cerebral hemodynamics indexed by blood flow (Q), pulsatility index (PI) and resistive index (RI).
Methods: Cognitively unimpaired adults (n=77; Mean age=63.7) from the Wisconsin Registry for Alzheimer's Prevention and the Wisconsin Alzheimer's Disease Research Center participated in this study. Fitness was measured via VO_{2MAX} and participants were subsequently classified into fitness percentiles based on reference standards for age and sex established through normative data. Extremes of high and low fitness groups were defined as falling above or below the 75th or 25th fitness percentile, respectively. Aortic stiffness (aoPWV) and cerebral hemodynamics were measured by 2D phase contrast MRI in the ascending and abdominal aorta and 4D Flow cerebrovascular MRI, respectively. Covariate-adjusted (age, waist-to-hip ratio, and history of hypertension and cardiovascular disease) multivariable regression examined relationships between aoPWV and cerebral hemodynamics (Q, PI, and RI), as a function of fitness, for total blood flow (Q_{Total}) and for the left$_{(L)}$, right$_{(R)}$ and average$_{(avg)}$ internal carotid artery (ICA), middle cerebral artery (MCA) and anterior cerebral artery (ACA). Analyses focused on the extremes of high and low fitness (N=52, Mean age = 64.4).
Results: There were significant interactions between fitness and aoPWV on **cerebral Q** (ICA_R: p=0.028), **PI** (ICA_R: p=0.005; MCA_L: p=0.039; MCA_R: p=0.022; MCA_{AVG}: p=0.010) and **RI** (ICA_R: p=0.04; MCA_R: p=0.013; MCA_{AVG}: p=0.012; ACA_{AVG}: p=0.044), indicating that those with extremely high fitness demonstrated improved hemodynamics compared to the low fitness group even within the context of increasing aoPWV (Figs 1-3).

Figure 1. Blood Flow (Q)

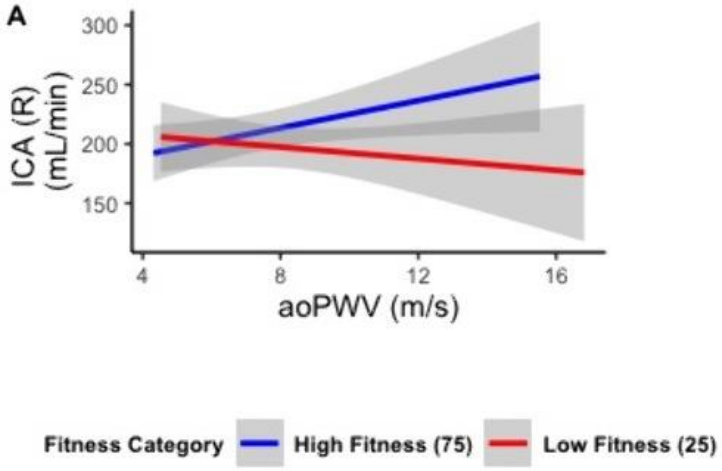


Figure 2. Pulsatility Index (PI)

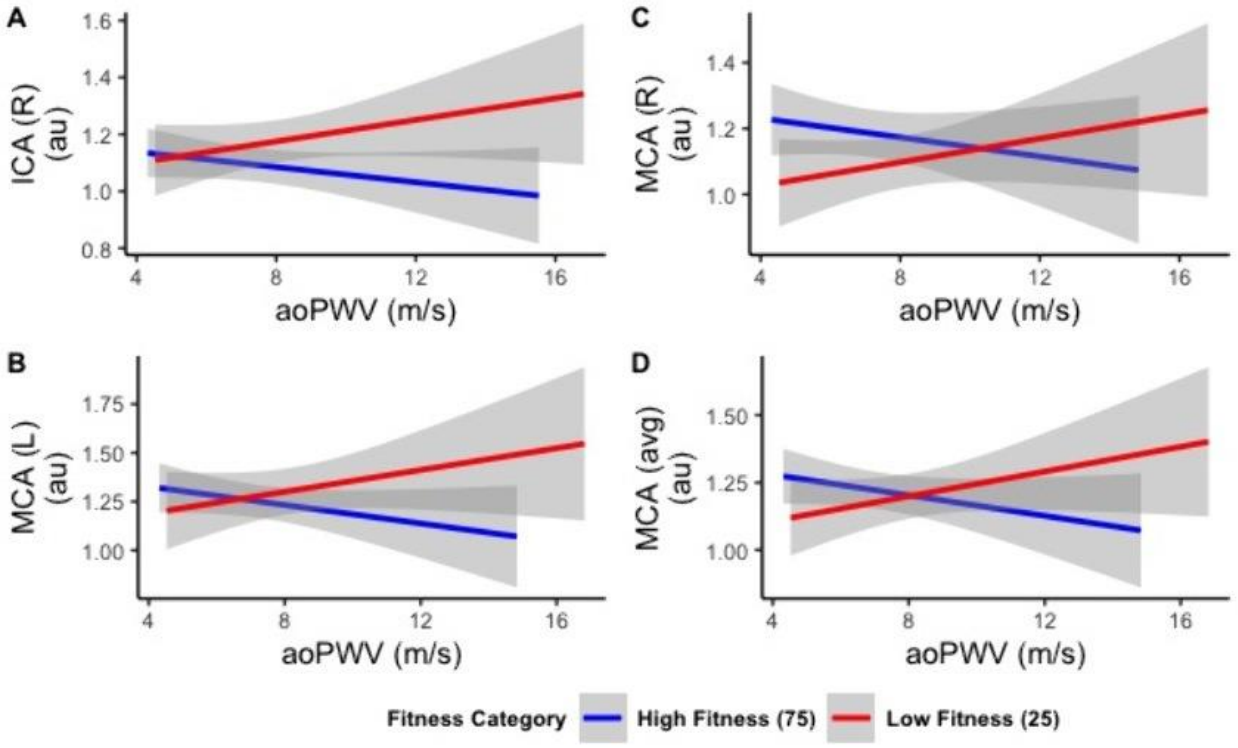
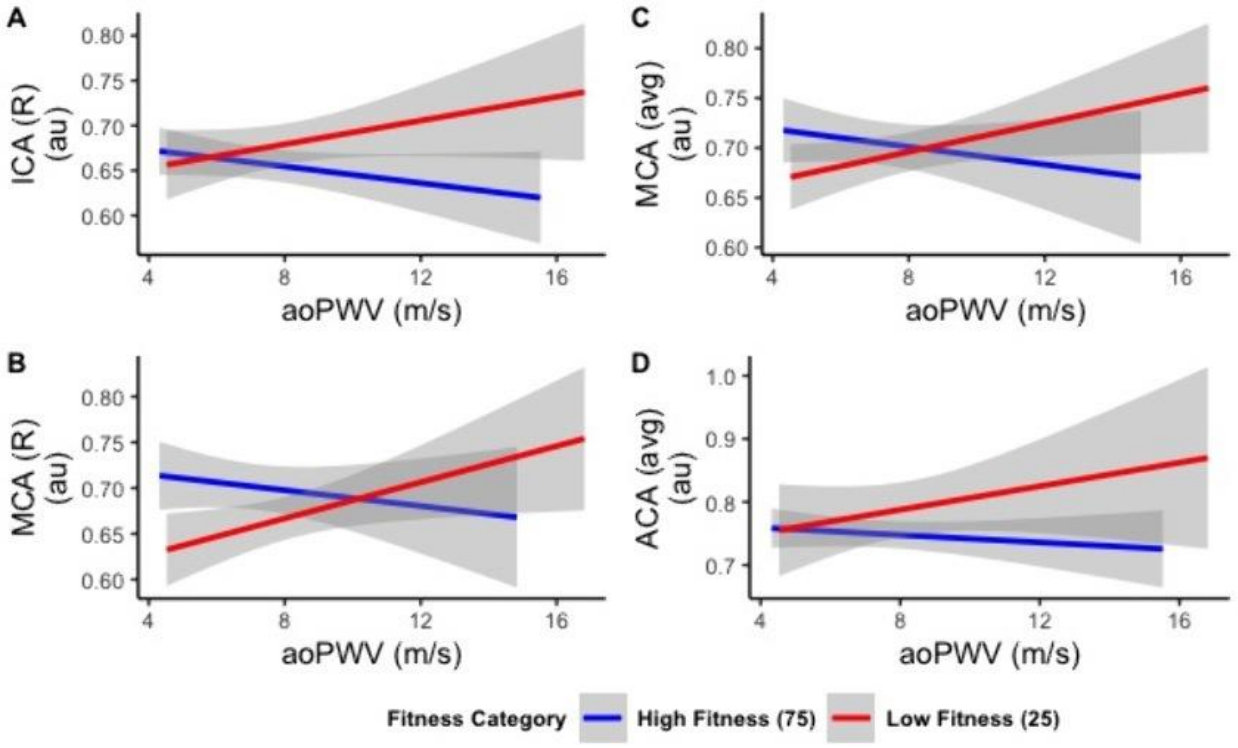


Figure 3. Resistive Index (RI)



Conclusions: Our results suggest that high fitness (>75th percentile) seems to be protective against the expected negative effects of arterial stiffness on cerebral hemodynamics

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0141 / #1565

Poster Topic: *Theme A: β-Amyloid Diseases / A01.l. Disease Mechanisms, Pathophysiology: Vasculature, microbleeds, hypertension, angiogenesis*

IMPACT OF THROMBOCYTOPENIA ON ALZHEIMER'S DISEASE PATHOLOGY IN APP23 TRANSGENIC MICE

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

Lili Donner, Lisa Stasch, Margitta Elvers
University Hospital Düsseldorf, Heinrich-Heine University, Department Of Vascular- And Endovascular Surgery, Duesseldorf, Germany

Aims: Deposits of Aβ in the brain parenchyma and cerebral vessels (known as cerebral amyloid angiopathy, CAA) are the pathological hallmarks of Alzheimer's disease (AD). Recently, we demonstrated that aged AD transgenic mice APP23, which develop amyloid-β deposits in the brain parenchyma and cerebral vessels, have pre-activated platelets in blood and enhanced integrin activation. Moreover, platelets adhere to vascular amyloid-β deposits and cause vessel occlusion in aged APP23 mice. A comprehensive analysis of these AD transgenic mice revealed that activated platelets directly contribute to vascular amyloid plaques by promoting the formation of Aβ aggregates. To investigate whether platelets play a role in influencing Aβ deposition in the brain parenchyma and neuroinflammation, AD transgenic mice APP23 were crossed with $Mpl^{-/-}$ mice to generate thrombocytopenic APP23 mice.
Methods: Histological analysis of AD pathology in 24-month-old male APP23/$Mpl^{-/-}$ mice compared to male age-matched controls
Results: APP23/$Mpl^{-/-}$ mice showed a slight trend towards a lower amyloid plaque burden in the brain parenchyma, but the reduction was not statistically significant. In line with our prior findings, we found significantly reduced CAA formation in APP23/$Mpl^{-/-}$ mice compared to APP23 mice. Moreover, thrombocytopenia had no impact on neuronal loss in the CA1 region. However, by evaluating neuroinflammation, immunofluorescence staining showed a significant reduction of activated microglia and reactive astrocytes in APP23/$Mpl^{-/-}$ mice compared to APP23 mice.
Conclusions: Thrombocytopenia does not have a significant impact on plaque formation in the brain parenchyma in male APP23 mice. However, a low platelet count significantly reduces the formation of CAA.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0142 / #1695

Poster Topic: *Theme A: β-Amyloid Diseases / A01.l. Disease Mechanisms, Pathophysiology: Vasculature, microbleeds, hypertension, angiogenesis*

INTERACTION BETWEEN MICROVASCULAR AND AD-RELATED PATHOLOGY IN THE MEDIAL TEMPORAL LOBE

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

Valentina Perosa[1], Francesco Bax[1], Jan Oltmer[1], Maarten Van Den Berg[1], Corinne Auger[2], Matthew Frosch[3], Steven Greenberg[1], Bradley Hyman[4], Susanne Van Veluw[1]
[1]Harvard Medical School/Massachusetts General Hospital, Neurology, Boston, United States of America, [2]Harvard Medical School/Massachusetts General Hospital, Massgeneral Institute For Neurodegenerative Disease, Boston, United States of America, [3]Harvard Medical School/Massachusetts General Hospital, Pathology, Boston, United States of America, [4]Massachusetts General Hospital, Neurology, Charlestown, United States of America

Aims: Background: Cerebral small vessel disease(CSVD), including cerebral amyloid angiopathy(CAA) and arteriolosclerosis, commonly co-occur with Alzheimer's disease and related dementias(AD/ADRD). The medial temporal lobe(MTL) is prone to harboring multiple pathologies, such as neurofibrillary tangles(NFTs), amyloid-β-plaques, TDP-43[1], and CSVD. Whether a causal relationship between these pathologies exists remains largely unknown, but one possible linking mechanism is the dysfunction of perivascular clearance. We aimed to analyze the burden of CSVD in the MTL of a pathological AD cohort and to determine the relationship between CSVD and enlarged perivascular spaces (EPVS), a marker of clearance dysfunction.
Methods: 156 subjects(79.4±10.9y, 90F), part of the pathological cohort of the Massachusetts Alzheimer's Disease Research Center(MADRC) were included in the study. One hemisphere was formalin-fixed, and samples from predefined regions of the hippocampal body and entorhinal cortex were cut in 5 mm thick sections, which were then stained for luxol fast blue with hematoxylin&eosin(LHE), amyloid-b, hyperphosphorylated tau(At8), and phosphorylated TDP-43, following standard histological protocols(Figure 1). Deep-learning models(Aiforiaâ) enabled the calculation of the burden of CAA, amyloid-β-plaques, NFTs, and pTDP-43 inclusions(Figure 2). Additionally, severity of arteriolosclerosis[2] and EPVS area[3] were assessed on the LHE sections.
Results: In linear mixed effects models CAA predicted the density of neurofibrillary tangles in the entorhinal cortex, and amyloid-β-plaques burden in all regions. The role of arteriolosclerosis remains unclear. CAA and arteriolosclerosis were both predictors of PVS-enlargement.
Conclusions: These results point towards an association between microvascular pathology and AD-related pathology, possibly mediated by clearance dysfunction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0143 / #2788

Poster Topic: *Theme A: β-Amyloid Diseases / A01.l. Disease Mechanisms, Pathophysiology: Vasculature, microbleeds, hypertension, angiogenesis*

UNDERSTANDING THE ROLE OF ENDOTHELIAL CELLS IN CEREBRAL AMYLOID ANGIOPATHY IN DOWN SYNDROME AND APP DUPLICATION.

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

Louis Valay[1], Amal Kasri[1], Vincent Fontaine[2], Stéphanie Bigoux[1], Charlie Arber[3], Selina Wray[3], Martin Irmler[4], Johannes Beckers[4], Marie-Claude Potier[1]
[1]Paris Brain Institute (ICM), Maladie D'alzheimer, Maladies à Prions, Paris, France, [2]ICAN/UMR1166, Ican Biocell Ips, Paris, France, [3]University College London, Neurodegenerative Diseases, London, United Kingdom, [4]Institute of Experimental Genetics, Helmholtz Zentrum München, Oberschleißheim, Germany

Aims: Sporadic Alzheimer's disease (sAD), familial AD with duplication of the Amyloid Precursor Protein gene (APPdup), and Down Syndrome (DS), the latter two with three copies of *APP*, share common hallmarks including amyloid and tau pathologies. However, the amount of Aβ peptides deposited in the wall of cerebral blood vessels leading to cerebral amyloid angiopathy (CAA) varies with higher CAA in APPdup compared to DS. Our aim was to characterize and understand the role of endothelial cells (ECs) forming the blood brain barrier (BBB) in CAA severity using human iPSC-derived-ECs (hiPSC-EC) from patients with APPdup and DS.
Methods: We analyzed the transcriptome of multiple independent hiPSC-ECs differentiations from APPdup and DS using RNAseq, measured Aβ using Multiplex ELISA and proteins from the tight- and adherent-junctions by immunocytochemistry, and measured the permeability of a monolayer of iPSC-ECs cultivated on Transwells.
Results: hiPSC-ECs with APPdup and DS had bigger size and secreted higher levels of Aβ compared to their isogenic controls. RNAseq analyses revealed dysregulated genes with a subset positively and negatively correlated with CAA in APPdup and DS respectively. We also identified opposite effects of APPdup and DS on the permeability of hiPSC-ECs (increase in APPdup and decrease in DS) highlighting the role of chromosome 21 genes to counterbalance the effects of APP overexpression on CAA.
Conclusions: These results could partly explain differences in CAA observed between postmortem brain tissue from APPdup and DS. Indeed, an increase of permeability of the blood brain barrier (BBB) in APPdup could favor the passage of peripheral Aβ species, soluble or aggregated, leading to vascular deposits thanks to the production of Aβ by the cerebrovascular unit. Individuals with DS would be protected by having a less permeable BBB.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0144 / #2626

Poster Topic: *Theme A: β-Amyloid Diseases / A01.l. Disease Mechanisms, Pathophysiology: Vasculature, microbleeds, hypertension, angiogenesis*

MEDIN AMYLOID - A POTENTIAL BIOMARKER AND THERAPEUTIC TARGET FOR CEREBROVASCULAR DYSFUNCTION AND CEREBRAL AMYLOID ANGIOPATHY.

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

Marleen Veit[1,2,3,4,5,6], Jessica Wagner[1,2,3,5,6], Karoline Degenhardt[1,3,6], Jasmin Hefendehl[7], Michael Candlish[7], Katleen Wild[6], Lisa M. Häsler[1,6], Marius Lambert[1,6], Regina Feederle[5,8], Benedikt Wefers[5], Wolfgang Wurst[5], Mathias Jucker[1,6], Jonas J. Neher[1,2,5,6,9]
[1]Hertie Institute for Clinical Brain Research, University of Tübingen, Cellular Neurology, Tübingen, Germany, [2]Biomedical Center, LMU Munich, Metabolic Biochemistry, Planegg, Germany, [3]University of Tübingen, Graduate School Of Cellular And Molecular Neuroscience, Tübingen, Germany, [4]LMU Munich, Graduate School Of Systemic Neuroscience, Planegg, Germany, [5]German Center for Neurodegenerative Diseases, Dzne, Munich, Germany, [6]German Center for Neurodegenerative Disease, Dzne, Tübingen, Germany, [7]Buchmann Institute for Molecular Life Sciences and Institute for Cell Biology and Neuroscience, Goethe University Frankfurt, Neurovascular Disorders, Frankfurt am Main, Germany, [8]Institute for Diabetes and Obesity, Helmholtz Zentrum München, Research Center for Environmental Health, Monoclonal Antibody Core Facility, Neuherberg, Germany, [9]LMU Munich, Munich Cluster For Systems Neurology (synergy), Munich, Germany

Aims: Vascular dysfunction is increasingly recognized as an important early event in sporadic Alzheimer's disease. Multiple lines of evidence associate medin amyloid, a fragment of MFG-E8, with vascular ageing and dysfunction and thus suggest that medin may be a vascular risk factor for dementia. This study aims to investigate the impact of medin amyloid on vascular amyloid-β deposition and explore its potential use as a biomarker and novel therapeutic target.
Methods: Using immunohistochemical and biochemical analyses of the brain and isolated cerebral blood vessels of APP transgenic mice, we examined whether genetic depletion of medin could modify amyloid-β aggregation *in vivo*. Additionally, we studied the effects of human medin (over-) expression on the vasculature both *in vivo* and *in vitro* using newly generated mouse lines of human medin pathology.
Results: Our data unveils a mechanistic link between vascular amyloid-β and medin amyloid pathology. Both MFG-E8 and medin are highly enriched in the vasculature, and their levels increase with the severity of vascular amyloid-β burden. Furthermore, we present the first mouse models for studying human medin pathology and reveal the functional consequences of MFG-E8 overexpression.
Conclusions: Our data strongly support medin amyloid as a driver of cerebral amyloid angiopathy. These findings highlight medin as a potential biomarker and novel therapeutic target for vascular dysfunction and cerebral amyloid angiopathy, warranting further evaluation in our newly generated model system.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0145 / #1478

Poster Topic: *Theme A: β-Amyloid Diseases / A01.l. Disease Mechanisms, Pathophysiology: Vasculature, microbleeds, hypertension, angiogenesis*

MEDIN: EXPLORING ITS ROLE IN ALZHEIMER'S DISEASE AND CEREBRAL AMYLOID ANGIOPATHY

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

Jessica Wagner[1,2,3], Karoline Degenhardt[1,2], Marleen Veit[1,2], Nikolaos Louros[4,5], Katerina Konstantoulea[4,5], Angelos Skodras[2,6], Katleen Wild[1], Ping Liu[1,2], Ulrike Obermüller[2], Vikas Bansal[7], Anupriya Dalmia[7], Lisa M. Häsler[2,6], Marius Lambert[2,6], Matthias De Vleeschouwer[4,5], Hannah Davies[8,9], Jillian Madine[9,10], Deborah Kronenberg-Versteeg[2,6], Regina Feederle[11,12], Domenico Del Turco[13], Peter Nilsson[14], Tammaryn Lashley[15,16], Thomas Deller[13], Marla Gearing[17], Lary C. Walker[17], Peter Heutink[7], Frederic Rousseau[4,5], Joost Schymkowitz[4,5], Mathias Jucker[2,6], Jonas J. Neher[1,2,3]
[1]German Center for Neurodegenerative Diseases (DZNE), Neuroimmunology And Neurodegenerative Disease, Tübingen, Germany, [2]Hertie Institute for Clinical Brain Research, University of Tübingen, Cellular Neurology, Tübingen, Germany, [3]Biomedical Center, LMU Munich, Metabolic Biochemistry, Munich, Germany, [4]KU Leuven, Department Of Cellular And Molecular Medicine, Leuven, Belgium, [5]VIB-KU Leuven Center for Brain and Disease Research, Switch Laboratory, Leuven, Belgium, [6]DZNE, Cell Biology Of Neurological Diseases, Tübingen, Germany, [7]German Center for Neurodegenerative Diseases, Dzne, Tübingen, Germany, [8]Institute of Life Course and Medical Sciences, Dpt. Of Cardiovascular And Metabolic Medicine, Liverpool, United Kingdom, [9]University of Liverpool, Liverpool Centre For Cardiovascular Sciences, Liverpool, United Kingdom, [10]Institute of Systems, Molecular and Integrative Biology, Dpt. Of Biochemistry And Systems Biology, Liverpool, United Kingdom, [11]Institute for Diabetes and Obesity, Helmholtz Zentrum München, Research Center for Environmental Health, Monoclonal Antibody Core Facility, Neuherberg, Germany, [12]German Center for Neurodegenerative Diseases, Dzne, Munich, Germany, [13]Institute of Clinical Neuroanatomy, Neuroscience Center, Goethe University, Dr. Senckenberg Anatomy, Frankfurt, Germany, [14]Linköping University, Dpt. Of Physics, Chemistry & Biology, Linköping, Sweden, [15]Queen Square Brain Bank for Neurological Disorders, Department Of Clinical And Movement Neuroscience, London, United Kingdom, [16]UCL Queen Square Institute of Neurology, Department Of Neurodegenerative Disease, London, United Kingdom, [17]Emory University School of Medicine, Dpt. Of Pathology And Laboratory Medicine And Dpt. Of Neurology, Atlanta, United States of America

Aims: Medin, a fragment of the protein MFG-E8, is known to aggregate in arteries of almost everybody over 50 years of age. Recently, medin was found in the vasculature of Alzheimer's disease (AD) patients but its role in AD pathogenesis remained unclear. In this study, we therefore investigated how medin may affect Amyloid-β (Aβ) pathology.
Methods: Building upon our previous research demonstrating that medin forms aggregates in the aorta and cerebral arteries of ageing wildtype mice, leading to arterial stiffening and consequential vascular dysfunction, we explored medin deposition in the brains of APP transgenic (tg) mice. We employed immunohistochemical and biochemical techniques to examine its influence on Aβ deposition and aggregate morphotype. To understand the underlying disease mechanism, we studied the interaction between medin and Aβ through genetic knockout of the medin-containing domain of MFG-E8 as well as seeding assays. Moreover, we assessed transcriptional and protein changes in human brain tissue.
Results: Our study provides evidence of a direct amyloid-amyloid interaction between medin and Aβ. Notably, we found that medin does not only co-localize with cerebral Aβ deposits but also alters onset and plaque morphotype in APP tg mice upon genetic deletion or exogenous addition. Interestingly, in line with its primary vascular localization in humans, elevated levels of MFG-E8 and medin correlate strongly

with CAA severity in both humans and mice. Furthermore, genetic medin deficiency reduces CAA and vascular damage by more than half in APP23 mice. Current work now focusses on proteomic and cellular alterations in isolated human and mouse cerebral vessels.

Conclusions: Our findings unveil a novel mechanism underlying age-associated vascular disease and amyloid deposition, highlighting medin as a potential therapeutic target and candidate for CAA biomarker development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0146 / #791

Poster Topic: *Theme A: β-Amyloid Diseases / A01.l. Disease Mechanisms, Pathophysiology: Vasculature, microbleeds, hypertension, angiogenesis*

ELUCIDATING THE ROLE OF PLACENTAL GROWTH FACTOR IN HYPERHOMOCYSTEINEMIA INDUCED VCID

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

Erica Weekman[1], Katelynn Krick[1], Colin Rogers[2], Tiffany Sudduth[2], Sherika Johnson[1], Teodoro Bottiglieri[3], Donna Wilcock[4]
[1]Indiana University School of Medicine, Stark Neurosciences Research Institute, INDIANAPOLIS, United States of America, [2]University of Kentucky, Sanders Brown Center On Aging, Lexington, United States of America, [3]Baylor Scott and White Research Institute, Institute Of Metabolic Disease, Dallas, United States of America, [4]Indiana University School of Medicine, Stark Neurosciences Institute, Indianapolis, United States of America

Aims: Vascular contributions to cognitive impairment and dementia (VCID) are the leading cause of dementia amongst the oldest old, making it critical to understand the mechanisms underlying VCID. We have identified placental growth factor (PlGF), an angiogenic mediator, to be associated with diffuse white matter disease in humans, which is a common manifestation of cerebral small-vessel disease (cSVD). PlGF is also upregulated in our mouse model of hyperhomocysteinemia (HHcy)-induced cSVD, which recapitulates many of the same pathologies as human cSVD, collectively suggesting a key role for PlGF in cSVD.
Methods: Using a novel mouse model with an inactive variant of PlGF (PlGF-KI), we induced HHcy for 8 weeks in 6-month-old mice. We determined levels of homocysteine-related metabolites in plasma, neuroinflammatory gene changes in brain tissue using qPCR, and microhemorrhage occurrence using Prussian blue staining.
Results: Interestingly, there were significant sex differences due to the loss of PlGF in HHcy induced VCID. The loss of PlGF increased weight loss in females, but less so in males, and there were significant sex effects in the homocysteine metabolism pathway with HHcy PlGF-KI females having decreased methionine, and increased HHcy, SAM and SAH compared to males. Male PlGF-KI mice also had reduced pro-inflammatory gene changes relative to females. However, these sex specific changes did not result in differences in microhemorrhages as the HHcy diet increased microhemorrhages in the PlGF-KI mice, regardless of sex.
Conclusions: In summary, it appears that PlGF impacts response to diet induction of HHcy in a sex-dependent manner. PlGF appears to have a significant impact on the neuroinflammatory response and cerebrovascular consequences of HHcy. Data from these studies continues to be assessed to further elucidate the role(s) of PlGF in cSVD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0147 / #418

Poster Topic: *Theme A: β-Amyloid Diseases / A01.l. Disease Mechanisms, Pathophysiology: Vasculature, microbleeds, hypertension, angiogenesis*

HYPERTENSION AND NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH DRUG-NAÏVE ALZHEIMER'S DISEASE

POSTERS: A01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS

Young Soon Yang
Soonchunhyang University College of Medicine, Cheonan Hospital, Neurology, SEOUL, Korea, Republic of

Aims: Neuropsychiatric symptoms (NPS) such as anxiety, depression, and delusions affect up to 90% of all patients with Alzheimer's disease (AD). NPS is associated with significant caregiver burden and patient distress. Given the severe burden of NPS in AD, it is critical to know potential modifiable risk factors of NPS in AD. This study explores the association between hypertension and NPS in patients with drug-naïve AD.
Methods: We reviewed medical records of 149 patients with AD with (n=80) and without (n=69) hypertension. NPS were assessed using the Korean version of Neuropsychiatric Inventory (K-NPI). Affective, psychotic, and behavior symptom clusters were assessed separately.
Results: The total score of K-NPI was not significantly different between patients with AD with and without hypertension. Among K-NPI domains, scores of depression/dysphoria (p=0.045), anxiety (p=0.022), and apathy/indifference (p=0.037) were significantly higher in patients with AD with hypertension. Systolic blood pressure (BP) was associated with higher total K-NPI and affective symptom cluster scores. Diastolic BP was associated with affective symptom cluster scores.
Conclusions: Results suggest that hypertension increases risk of specific NPS in patients with AD. Among NPS, hypertension was associated with affective symptom cluster.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0148 / #654

Poster Topic: *Theme A: β-Amyloid Diseases / A01.m. Disease Mechanisms, Pathophysiology: Blood-brain barrier*

HUMAN SERUM EXACERBATES AD PATHOLOGY IN CORTICAL ORGANOIDS: INSIGHTS INTO BLOOD-BRAIN BARRIER DYSFUNCTION

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

Declan Brennan[1], Haakon Nygaard[2]
[1]University of British Columbia, Neuroscience, Vancouver, Canada, [2]University of British Columbia, Neurology, Vancouver, Canada

Aims: In Alzheimer's disease (AD) patients, increased blood-brain barrier permeability is correlated with declining cognitive function. Previous studies have shown that human serum increases insoluble Amyloid-β (Aβ) and phosphorylated tau (pTau) in cortical organoids. It is possible that either a component in the blood exacerbates AD pathology or that AD patients are more susceptible to this insult. We sought to confirm that human serum exacerbates AD pathology in cortical organoids while also investigating the underlying mechanisms of this important effect.
Methods: Cortical organoids were generated from induced-pluripotent stem cells carrying either the APP London mutation (v717l) or its CRISPR-corrected isogenic line. Organoids were sliced every 30-40 days at 500 µm thickness before treatment with human serum at day 110. Human serum from young, elderly, and AD donors were either company bought or collected at the Clinic for Alzheimer's and Related Disorders. Aβ isoforms and pTau were measured using ELISA-based assays. Bulk RNA sequencing was done for each condition to analyze differentially expressed genes.
Results: Both mutant and control organoids exhibited increased Aβ deposits and reduced soluble Aβ after serum treatment, though mutant organoids had a greater number of large Aβ aggregates and higher pTau/Tau. This effect was consistent across donor demographics. APP mRNA levels remained unchanged, suggesting altered cleavage rather than increased expression. Reactive astrocyte markers were highly elevated, while APP cleavage proteins showed no significant changes in mRNA counts. This indicates that either altered APP cleavage occurs through signaling perturbations alone or that neurons and reactive astrocytes have an inverse change in expression in response to serum.
Conclusions: Human serum exposure induces AD-like expression patterns and pathology in cortical organoids, highlighting the pivotal role of blood-brain barrier integrity in AD progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0149 / #1324

Poster Topic: *Theme A: β-Amyloid Diseases / A01.m. Disease Mechanisms, Pathophysiology: Blood-brain barrier*

IN SILICO INVESTIGATION OF BLOOD-BRAIN BARRIER PERMEABILITY OF OCTOVESPIN GUIDED THROUGH A LIPID MEMBRANE.

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

Caio Costa[1], Yuri Só[2], Luana Cristina Camargo[3], Márcia Renata Mortari[3], Ricardo Gargano[2]
[1]University of Brasilia, Physics, Brasilia, Brazil, [2]Universidade de Brasília, Physics, Brasília, Brazil, [3]Institute of Biological Science, Department Of Physiology, Brasília, Brazil

Aims: The blood-brain barrier (BBB) plays a crucial role in controlling the balance in the neuronal microenvironment. To enable controlled drug delivery to the central nervous system, it is essential that drugs have the ability to cross this barrier. Many computational methods have been developed with the purpose of studying the transport of compounds across the BBB. However, some of these methods focus on analyzing the effects of the chemical structures of compounds during their interaction with biological receptors. In the present work was analyzed the potential of Octovespin in crossing the Blood-Brain Barrier, employing various computational tools for a detailed study of the process.
Methods: In this study, we opted for a different approach, using molecular dynamics techniques guided by a simplified model of the BBB for a detailed assessment of compound permeability during the transposition process. This methodology is based on creating a non-equilibrium system that includes a force field to guide the compounds through the membrane. In the present work, a peptide bio-inspired from the venom of the wasp *Polybia occidentalis*, called Octovespin, was tested in the BBB simplified model. This compound exhibited an ability in the disaggregation of senile plaques formed by amyloid-beta (Aβ) protein.
Results: Our results indicate that Octovespin has the ability to cross the blood-brain barrier (BBB), which makes it a promising candidate for the treatment of Parkinson's and Alzheimer's diseases.
Conclusions: This method stands out for its rapid implementation and affordable computational cost, which makes it a highly advantageous alternative for the analysis of various compounds. Additionally, it offers the opportunity to perform preliminary tests to evaluate the ability of drugs to successfully penetrate the BBB.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0150 / #614

Poster Topic: *Theme A: β-Amyloid Diseases / A01.m. Disease Mechanisms, Pathophysiology: Blood-brain barrier*

BRAIN OR BODY FIRST: MODELING INTERACTIONS AT THE BLOOD-BRAIN BARRIER WITH BRAIN-CHIP TECHNOLOGIES

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

Aurelie De Rus Jacquet[1,2], Martine Saint-Pierre[2], Kelvin Luk[3], Francesca Cicchetti[1,2]
[1]Universite Laval, Psychiatry And Neurosciences, Quebec, Canada, [2]Centre de recherche du CHU de Quebec-Université Laval, Neuroscience Axis, Quebec, Canada, [3]University of Pennsylvania, Pathology And Laboratory Medicine, Philadelphia, United States of America

Aims: Communication between the blood and the brain is a dynamic, complex process that occurs at the physical and molecular interphase formed by the blood-brain barrier (BBB). To sustain brain health, the neurovascular unit tightly regulates bidirectional exchanges between these two compartments, but BBB integrity is compromised in people with neurodegenerative disorders such as Parkinson's disease (PD). The objective is to leverage advanced tissue engineering approaches to model the complex cellular and molecular interactions occurring at the BBB in people with PD.
Methods: We established a microfluidic model of the BBB using patient-derived induced pluripotent stem cells (iPSCs) harboring PD-related mutations, including LRRK2 G2019S and SNCA triplication. To identify triggers of BBB dysfunction in PD, we exposed the model to reactive astrocytes harboring PD-related mutations and/or pathological proteins such as alpha-synuclein. We then evaluated changes to barrier integrity, neuroinflammation and neurodegeneration.
Results: We found that several mutations in genes associated with familial PD result in the increased vulnerability of the BBB and the extravasation of plasma proteins from the blood to the brain compartment of the model. In particular, we observed that pro-inflammatory astrocytes induce vessel enlargement and loss of barrier function, as observed in people with PD, but these features can be rescued upon pharmacological treatment.
Conclusions: Our novel PD-BBB model is a versatile tool to study the role of the BBB in disease onset and progression, and it is amenable to pharmacological testing.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0151 / #595

Poster Topic: *Theme A: β-Amyloid Diseases / A01.m. Disease Mechanisms, Pathophysiology: Blood-brain barrier*

BLOOD-BRAIN BARRIER REPAIR IN ALZHEIMER'S DISEASE WITH EPILEPSY

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

Anika Hartz
University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America

Aims: More than 25% of patients with Alzheimer's disease (AD) develop epilepsy as co-morbidity. In AD with epilepsy (ADxEpi), seizures accelerate cognitive decline and further reduce life expectancy compared to AD alone. One hallmark of both AD and epilepsy is blood-brain barrier dysfunction. We discovered that barrier dysfunction is more severe in ADxEpi patients compared to seizure-free AD patients. Collectively, our data suggest that a combination of Ab and seizure-released glutamate (Aβ/Glu) triggers a dual positive feedback loop which exacerbates barrier dysfunction, seizures, and cognitive decline in ADxEpi. Our goal is to define the mechanism that underlies barrier dysfunction in ADxEpi and to develop a therapeutic intervention.
Methods: We determine signaling steps that lead to Aβ/Glu-mediated barrier dysfunction using isolated mouse brain capillaries and verify these findings *in vivo*. We determine barrier dysfunction in brain tissue from ADxEpi patients and correlate the degree of barrier dysfunction with seizure burden and patient cognition scores. We develop an intervention therapy designed to repair barrier dysfunction using two rodent ADxEpi models.
Results: We found that Aβ/Glu exacerbates barrier leakage compared to Aβ or Glu alone. We also discovered that Aβ/Glu activates NOX/LOX/COX signaling, causing barrier leakage. Using patient samples, we show that ADxEpi patients have increased barrier leakage compared to seizure-free AD patients. Using two ADxEpi rodent models (mouse and rat) we further show that LOX/COX inhibitors combined with a ROS scavenger attenuate barrier dysfunction *in vivo*.
Conclusions: Based on our data we conclude that blocking Aβ/glutamate signaling by inhibiting NOX/LOX/COX repairs barrier dysfunction and has the potential to help reduce seizure burden and slow cognitive decline in AD with epilepsy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0152 / #1751

Poster Topic: *Theme A: β-Amyloid Diseases / A01.m. Disease Mechanisms, Pathophysiology: Blood-brain barrier*

INVOLVEMENT OF BLOOD-BRAIN-BARRIER ASSOCIATED MICROGLIA AND PERICYTES IN THE DEVELOPMENT OF AMYLOID B PATHOLOGY IN APPNL-G-F AD MICE.

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

Hao Li[1], Katrine Bjørnholm[2], Maarja Mäe[3], Christer Betsholtz[3,4], Helena Karlström[2], Michael Vanlandewijck[3,4], Per Nilsson[1]
[1]Karolinska Institutet, Neurobiology, Care Sciences And Society Division Of Neurogeriatrics, Stockholm, Sweden, [2]Karolinska Institutet, Neurobiology, Care Sciences And Society Division Of Neurogeriatrics, Stockholm, Sweden, [3]Uppsala University, Immunology, Genetics, And Pathology, Rudbeck Laboratory, Uppsala, Sweden, [4]Karolinska Institutet, Department Of Medicine, Huddinge, Stockholm, Sweden

Aims: Blood brain barrier (BBB) dysfunction in Alzheimer's disease (AD) is correlated to an accelerated progression of cognitive decline. It has been shown that pericytes in particular play an important role in neurovascular dysfunction in AD, but how this contributes to disease pathogenesis remains unknown. To elucidate this, we investigated the transcriptome of the cell types in the BBB, including the mural cells, in Amyloid Precursor Protein (*App*) knock-in (App^{NL-G-F}) mice with and without pericyte deficiency.
Methods: Cerebral microvasculature was isolated using CD31 panning, and the cells were analyzed by single cell RNA sequencing (scRNAseq) and subsequently validated using immunohistochemistry. Pericyte deficient $Pdgfb^{ret/ret}$ mice were crossed with App^{NL-G-F} mice and injected with tracer molecules to quantitatively measure BBB leakage. Aβ pathology was investigated by immunohistochemistry.
Results: ScRNAseq data from the cerebral micro vasculature of the App^{NL-G-F} revealed a population of disease-associated microglia characterized by high expression of Cst7. These were found to bridge between Aβ plaque and small and large blood vessels. Data analysis indicates that the point of contact in capillaries could be mural cells suggesting a role of pericytes in neuroinflammation. To further elucidate the role of pericytes on progression of Aβ pathology we studied a new pericyte deficient $App^{NL-G-F}xPdfgb^{ret/ret}$. The tracer studies showed a significant increase of BBB leakage in 3-month-old $App^{NLGFret/ret}$ mice compared to controls. This will be followed by tracer studied in other ages, evaluation of Aβ pathology, and scRNAseq of the BBB.
Conclusions: The BBB in App^{NL-G-F} mice is characterized by vascular associated DAMs. The combination of pericyte deficiency and Aβ amyloidosis increased the leakage of App^{NL-G-F} mice vasculature, which may impact the development of Aβ pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0153 / #2157

Poster Topic: *Theme A: β-Amyloid Diseases / A01.m. Disease Mechanisms, Pathophysiology: Blood-brain barrier*

BLOOD-BRAIN BARRIER PERMEABILITY MEASURED WITH ASL DIFFERS BETWEEN COGNITIVE STAGES AND AMYLOID STATUS

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

Beatriz Padrela[1,2], Sandra Tecelão[3], Oliver Geier[4], Markus Sneve[5], David Vállez García[1,2], Lene Pålhaugen[3,6], Bjørn-Eivind Kirsebom[7,8], Atle Bjørnerud[5,9], Anders Fjell[5,9], Kristine Walhovd[5,9], Frederik Barkhof[1,2,10], Per Selnes[3], Jan Petr[1,11], Tormod Fladby[3,6], Henk Mutsaerts[1,2]
[1]Amsterdam UMC, Radiology And Nuclear Medicine, Amsterdam, Netherlands, [2]Amsterdam Neuroscience, Brain Imaging, Amsterdam, Netherlands, [3]Akershus University Hospital, Department Of Neurology, Lørenskog, Norway, [4]Oslo University Hospital, Department Of Physics And Computational Radiology, Division Of Radiology And Nuclear Medicine, Oslo, Norway, [5]Center for Lifespan Changes in Brain and Cognition, University of Oslo, Department Of Psychology, Oslo, Norway, [6]Campus Ahus, University of Oslo, Institute Of Clinical Medicine, Oslo, Norway, [7]University Hospital of North Norway, Department Of Neurology, Tromsø, Norway, [8]UiT The Arctic University of Norway, Department Of Psychology, Faculty Of Health Sciences, Tromsø, Norway, [9]Division of Radiology and Nuclear Medicine, Oslo University Hospital, Computational Radiology And Artificial Intelligence, Oslo, Norway, [10]University College London, Queen Square Institute Of Neurology And Centre For Medical Image Computing (cmic), London, United Kingdom, [11]Institute of Radiopharmaceutical Cancer Research, Helmholtz-zentrum Dresden-rossendorf, Dresden, Germany

Aims: Blood-brain barrier (BBB) permeability changes may affect early mechanisms of Alzheimer's Disease (AD). We evaluate changes in BBB water permeability between cognitive and amyloid status, measured non-invasively using arterial spin labeling (ASL) MRI.
Methods: Participants older than 50 years were selected from the DDI and from the LCBC cohorts (Table 1). All LCBC participants were cognitively normal (CN), while DDI included both CN and mild cognitive impairment (MCI) participants. We separated the groups as CN_LCBC, CN_DDI, and MCI_DDI. A recently developed multi-delay multi-echo BBB-ASL MRI sequence was used to estimate cerebral blood flow (CBF) and time of exchange (Tex) maps of labeled water across the BBB. Lower Tex is a proxy of higher BBB water permeability. Amyloid status was defined from the available CSF amyloid-beta 42/40 ratio (cut-off ≤ 0.077). Tex and CBF associations with cognition and amyloid status were assessed using general linear models (GLMs) adjusted for age and sex. Statistical analyses were performed in R4.1.2.

Table 1: *Sample characteristics. Units are given as mean ± SD.*

	Total sample (n=116)	
	LCBC (n=77)	**DDI (n=39)**
Age (years)	64.6 ± 8.4	67.7 ± 7.94
Sex (female)	49 (64%)	20 (51%)
Cognitively normal (n)	77	24
MCI (n)	0	15
Total GM CBF (mL/100g/min)	58.3 ± 13.4	75.7 ± 23.2
Females (mL/100g/min)	61.4 ± 14.0	86.9 ± 21.9
Males mean value	52.9 ± 10.3	63.7 ± 18.2
Total GM Tex (s)	0.21 ± 0.04	0.18 ± 0.04
Females mean value	0.22 ± 0.04	0.20 ± 0.04
Males mean value	0.19 ± 0.02	0.17 ± 0.03

CBF: Cerebral blood flow; DDI: Dementia Disease Initiation; GM: Gray matter; LCBC: Center for Lifespan Changes in Brain and Cognition; MCI: Mild cognitive impairment; Tex: time of exchange (proxy of BBB water permeability).

Results: CBF tended to be higher in the A+ group but not statistically significant (t=-1.94, p=0.06, Figure 1). Tex was lower in A+ than A- (t=2.75, p=0.01, Figure 2). GLM analysis showed that both amyloid status and cognitive staging were predictive of BBB water permeability (Tex), with higher permeability in amyloid positive compared to amyloid negative groups when correcting for age, sex, and CBF (β = -35.2, $p < 0.001$) (Table 2). The same pattern was found in MCI subjects compared to healthy controls (Table 3).

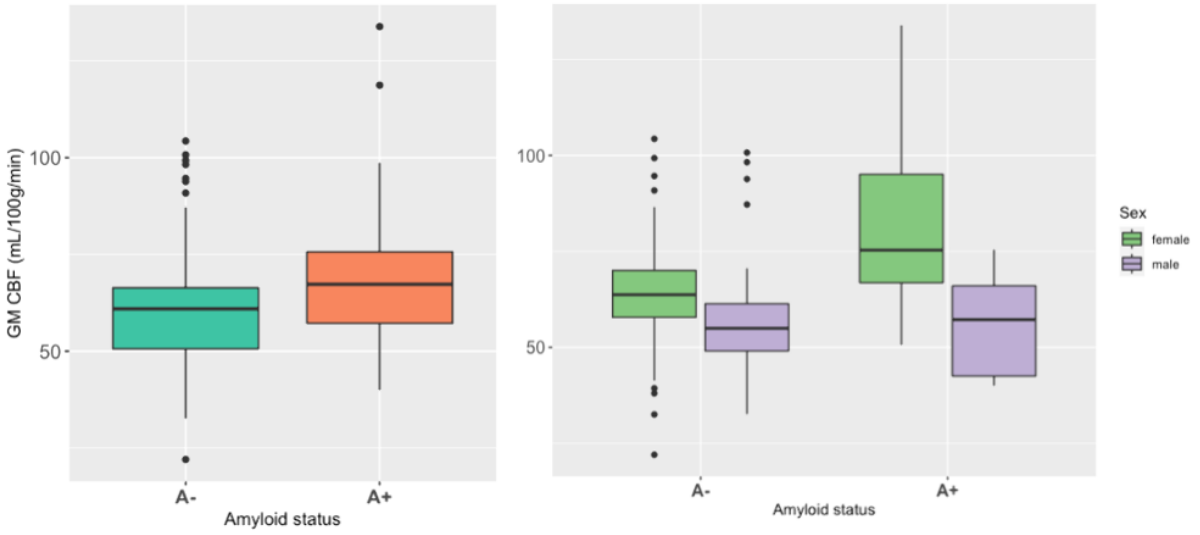


Figure 1 - Gray matter (GM) time of exchange (CBF) stratified by amyloid status and sex

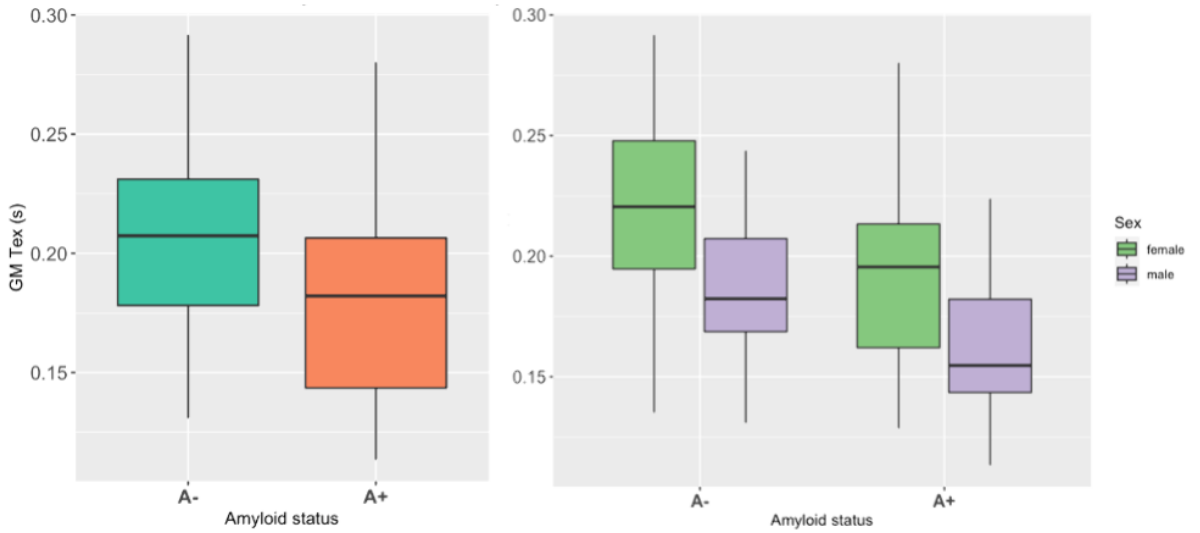


Figure 2 - Gray matter (GM) time of exchange (Tex) stratified by amyloid status and sex.

Table 2: *CBF and Tex GM values associated with amyloid status corrected for age and sex – and CBF in the case of Tex.*

	Amyloid status		Amyloid status + age + sex						Amyloid status + age + sex + CBF							
	β	p	β (A+)	p (A+)	β (age)	p (age)	β (male)	p (male)	β (A+)	p (A+)	β (age)	p (age)	β (male)	p (male)	β (CBF)	p (CBF)
CBF total GM	10.7	*	13.3	**	-0.5	*	-8.4	*	-	-	-	-	-	-	-	-
Tex total GM	-0.028	**	**-0.22**	*	-0.001	**	-0.028	***	**-0.035**	***	-0.001	N.S	-0.02	**	0.001	***

CBF: Cerebral blood flow; GM: Gray matter; NS: non-significant; Tex: time of exchange (proxy of BBB water permeability).
*p<0.05 *, p<0.01**, p<0.001***. Reference groups: A- for amyloid staging and female for sex*

Table 3: *CBF and Tex GM values associated with cognitive staging corrected for age and sex – and CBF in the case of Tex.*

	Cognitive staging				Cognitive staging + age + sex + CBF									
	β (CN)	p (CN)	β (MCI)	p (MCI)	β (CN)	p (CN)	β (MCI)	p (MCI)	β (age)	p (age)	β (male)	p (male)	β (CBF)	p (CBF)
CBF total GM	**19,17**	**	**-0.5**	*	-	-	-	-	-	-	-	-		
Tex total GM	**-0.22**	*	**-0.001**	**	**-0.053**	***	**-0.051**	***	-0.02	N.S.	-0.0002	N.S.	**0.0014**	***

CBF: Cerebral blood flow; CN: here, CN corresponds to cognitively normal subjects from DDI, since the reference group is CN from LCBC; GM: Gray matter; Tex: time of exchange (proxy of BBB water permeability).
*p<0.05 *, p<0.01**, p<0.001***. Reference groups: CN_LCBC for cognitive staging and female for sex*

Conclusions: Our findings suggest that BBB water permeability is increased in amyloid-positive and MCI participants compared to CN, suggesting that BBB water permeability is a potential early imaging biomarker in AD physiology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0154 / #1520

Poster Topic: *Theme A: β-Amyloid Diseases / A01.m. Disease Mechanisms, Pathophysiology: Blood-brain barrier*

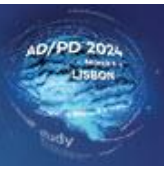
POST-TRANSLATIONAL MODIFICATIONS OF BETA-AMYLOID AFFECT ITS TRANSPORT ACROSS THE BLOOD-BRAIN BARRIER

POSTERS: A01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

Kseniya Varshavskaya, Irina Petrushanko, Vladimir Mitkevich, Alexander Makarov, Evgeny Barykin
Engelhardt Institute of Molecular Biology, Laboratory Of Protein Conformational Polymorphism In Health And Disease, Moscow, Russian Federation

Aims: Beta-amyloid (Aβ) undergoes post-translational modifications that alter its pathogenic properties. Aβ can enter the brain from circulation by binding to RAGE and trigger the pathology of Alzheimer's disease (AD). However, the transport of modified forms of Aβ across the blood–brain barrier (BBB) has not previously been studied. Here, we characterized the transport of phosphorylated (pS8-$Aβ_{42}$) and isomerized (isoD7-$Aβ_{42}$) Aβ across the BBB in comparison with unmodified Aβ.
Methods: Murine brain endothelial cells bEnd.3 seeded on transwell membrane were used as an *in vitro* model of the BBB. The transport of Aβ isoforms was estimated using ELISA. Endocytosis inhibitors and RAGE antagonist were used to characterize the involved mechanisms. Endothelial permeability was evaluated using sodium fluorescein. The parameters of the interaction of Aβ and its isoforms with RAGE were determined using microscale thermophoresis.
Results: IsoD7-$Aβ_{42}$ and pS8-$Aβ_{42}$ cross the BBB better than unmodified $Aβ_{42}$. The transport of all isoforms is caveolin-dependent, but the transport of isoD7-$Aβ_{42}$ is dependent on both caveolin- and clathrin-mediated endocytosis. The RAGE antagonist inhibits the transport of $Aβ_{42}$, but does not affect the transport of pS8-$Aβ_{42}$ and isoD7-$Aβ_{42}$. RAGE binds to isoD7-$Aβ_{42}$ an order of magnitude weaker than to $Aβ_{42}$. Higher levels of $Aβ_{42}$ were detected in cell lysates compared to isoD7-$Aβ_{42}$, suggesting the altered ratio between transport and degradation.
Conclusions: Post-translational modifications of Aβ increase the rate of its transport across the BBB and modify the mechanisms of the transport, which may be important for AD pathology and treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0155 / #723

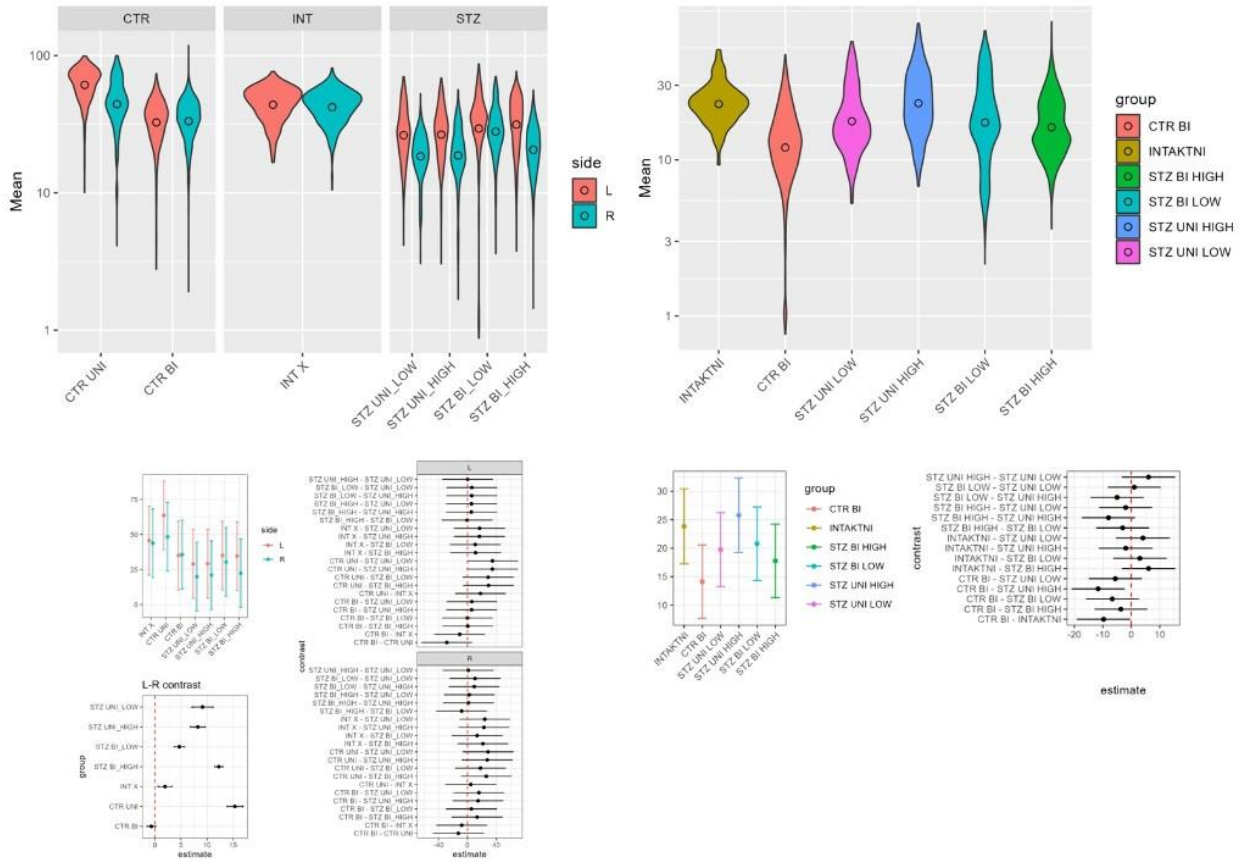
Poster Topic: *Theme A: β-Amyloid Diseases / A01.n. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

QUANTIFICATION OF TRANSTHYRETIN EXPRESSION, A PUTATIVE NEUROPROTECTIVE AGENT, ACROSS VARIOUS EXPERIMENTAL APPROACHES IN A WELL-ESTABLISHED RODENT MODEL OF SPORADIC ALZHEIMER'S DISEASE.

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Ana Babić Perhoč, Jan Homolak, Robert Kranjčec, Davor Virag, Ana Knezovic, Jelena Osmanovic Barilar, Melita Salkovic-Petrisic
University of Zagreb School of Medicine, Department Of Pharmacology And Croatian Institute For Brain Research, Zagreb, Croatia

Aims: Transthyretin (TTR), a tetrameric transport protein, commonly associated with aggregation disorders and amyloidosis, has recently been recognized as a potential neuroprotectant in various settings, including Alzeimer's disease (AD). Modeling sporadic AD with intracerebroventricular streptozotocin (STZ-icv) in rodents is widely used and well established in AD research. Here, we aimed to characterize the effects of STZ-icv on TTR in its production site, the choroid plexus (CP) and the hypothalamus (HPT), where it influences metabolism.
Methods: Seven groups with six 3-month-old C57BL/6 mice entered the experiment. Four different STZ-icv dosing regimens were employed; uni- and bi-lateral low (1,5 mg/kg) and high (3 mg/kg) doses with appropriate uni- and bi-lateral controls and intact animals. A month after STZ-icv administration, animals were euthanized and blood and brain samples taken. Plasma glucose and insulin were measured spectrophotometrically and by ELISA. Immunohistochemical staining with polyclonal anti-TTR antibody was performed on 14 µm thick Tissue-tek™-embedded sections.
Results: Plasma glucose and insulin were assessed to exclude systemic diabetes induced by streptozotocin and results were unchanged across all groups. Relative to unilateral controls, model-derived estimates showed both high- and low-dose STZ-icv to lower TTR expression at the injection side in the CP. Interestingly, across all STZ-groups, as well as in the unilateral controls, injection-side CP TTR expression was significantly higher, compared to the contralateral side, irrespective of STZ's impact on cell-count. In the HPT, TTR expression was paradoxically increased by STZ-icv compared to controls receiving vehicle
only.



Conclusions: TTR expression is affected by injection-injury, possibly increasing ipsilaterally as a compensatory measure; and STZ, with different effects depending on brain-site and STZ dose, in different regimens of a mouse model of sporadic AD. Research funded by Pfizer Inc. (73521469) and ZCI-Neuro (GA KK01.1.1.01.0007).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0156 / #2289

Poster Topic: *Theme A: β-Amyloid Diseases / A01.n. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

ALTERED AMINO ACID PROFILE IN PATIENTS WITH ALZHEIMER'S DISEASE: INTERACTION BETWEEN MALNUTRITION AND PATHOLOGY

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Matteo Cotta Ramusino[1], Roberto Aquilani[2], Alfredo Costa[3], Manuela Verri[2]
[1]IRCCS Mondino Foundation, Brain And Behavioral Sciences, Pavia, Italy, [2]University of Pavia, Department Of Biology And Biotechnology "lazzaro Spallanzani", Pavia, Italy, [3]University of Pavia, Irccs Mondino Foundation, Pavia, Italy

Aims: Background: Biochemical alterations linked to the neuronal/astroglial dysfunction affect the molecular composition of the interstitial fluid and of the cerebrospinal fluid (CSF). Nutritional status can influence the amino acids (AA) levels in subjects with Alzheimer's disease (AD). This work is aimed to investigate the alterations of AA in CSF and plasma of AD patients and to investigate the possible combined role of malnutrition and pathology on the observed alterations
Methods: In 54 patients with AD (69% males, 74.4 ± 8.2 years) and 17 age-matched control (CTRL) subjects, CSF and venous blood samples were taken for AA measurements. Patients were stratified according to the nutritional status (Mini Nutritional Assessment, MNA, scores).
Results: Compared to CTRL, AD patients showed reduced levels of aspartic acid, and increased levels of taurine and 3-methyl-histidine ($p<0.001$). In addition, amyloid correlated inversely with histidine levels while p-tau correlated positively with serine levels. In the combined group (CG) including malnourished AD (16.7%; MNA < 17) and AD at risk for malnutrition (36.6%, MNA 17−24), all CSF essential amino acids (EAAs) and 30% of non-EAAs were lower compared to the CTRL ($p < 0.018$ to 0.0001), whereas in normo-nourished ADs (46.7%, MNA > 24) the CSF levels of 10% EAAs and 25% non-EAAs were decreased ($p < 0.05$ to 0.00021). Compared to normo-nourished ADs, CG had lower levels of Branched-Chain AA both in plasma and CSF ($p<0.01$).
Conclusions: AD patients had low levels of AA in plasma and CSF, particularly EAA and BCAA. The amino acid profile is an expression partly of the metabolic signature of the disease partly of the nutritional status.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0157 / #1728

Poster Topic: *Theme A: β-Amyloid Diseases / A01.n. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

NEURONAL INSULIN RESISTANCE PROMOTES NON-AMYLOIDOGENIC APP PROCESSING

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Steven Alves[1], José João Mendonça Vitória[2], Diogo Trigo[3], Odete Da Cruz E Silva[1]
[1]Institute of biomedicine, University of Aveiro, Department Of Medical Sciences, Aveiro, Portugal, [2]Universidade de Aveiro, Departamento De Ciências Médicas, Aveiro, Portugal, [3]Institute of Biomedicine - iBiMED, Departamento De Ciências Médicas - Dcm, Aveiro, Portugal

Aims: Growing evidence shows that Type 2 diabetes patients are more likely to develop Alzheimer's disease (AD) with ageing. This means that neuronal insulin resistance (IR) must play a role in several key AD mechanisms. Here, we assessed if IR affects normal APP processing.
Methods: For that purpose, an IR model was developed, and APP processing monitored by western blot analysis of SH-SY5Y lysates and respective mediums, BACE1 activity and $A\beta_{1-42}$ secreted into the medium, by ELISA.
Results: IR had no impact in total APP intracellular levels, however it significantly increased by 2-fold the total secreted APP (sAPP) in the medium, implying an increase in APP processing. Furthermore, as seen with total sAPP, sAPPα similarly increased in IR cells. Moreover, no changes in both BACE1 activity and Aβ production were observed with IR, supporting the notion that increased APP processing occurred by promoting non-amyloidogenic cleavage.
Conclusions: Although IR may have a significant role in AD pathogenesis, it does not significantly affect Aβ levels. However, it does alter APP processing, which may affect homeostasis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0158 / #10

Poster Topic: *Theme A: β-Amyloid Diseases / A01.n. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

SEXUAL DIMORPHIC RESPONSES TO THERMOTHERAPY IN APP/PS1 MICE

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Kevin Hascup[1], Samuel Mcfadden[2], Mackenzie Peck[2], Erol Ikiz[2], Yimin Fang[2], Andrzej Bartke[3], Erin Hascup[4]
[1]Southern Illinois University School of Medicine, Dale And Deborah Smith Center For Alzheimer's Research & Treatment; Depts Of Neurology, Pharmacology, And Mmicb, Springfield, United States of America, [2]Southern Illinois University School of Medicine, Dale And Deborah Smith Center For Alzheimer's Research & Treatment; Dept. Of Neurology, Springfield, United States of America, [3]Southern Illinois University School of Medicine, Depts Of Internal Medicine And Mmicb, Springfield, United States of America, [4]Southern Illinois University School of Medicine, Dale And Deborah Smith Center For Alzheimer's Research And Treatment; Depts Of Neurology And Pharmacology, Springfield, United States of America

Aims: A thermoregulatory decline occurs with age due to changes in muscle mass, vasoconstriction, and metabolism that lowers core body temperature (Tc). Although lower Tc is a biomarker of successful aging, we have previously shown this worsens cognitive performance in the APP/PS1 mouse model of Alzheimer's disease (doi.org/10.1093/gerona/glac223). We hypothesized that elevating Tc with thermotherapy would improve metabolism and cognition in APP/PS1 mice.
Methods: From 6-12 months of age, male and female APP/PS1and C57BL/6 mice were chronically housed at 23 or 30°C. At 12 months of age, mice were assayed for insulin sensitivity, glucose tolerance, and spatial cognition. Plasma, hippocampal, and peripheral (adipose, hepatic, and skeletal muscle) samples were procured postmortem and tissue-specific markers of amyloid accumulation, metabolism, and inflammation were assayed.
Results: Chronic 30°C exposure increased Tc in all groups except female APP/PS1 mice (Fig 1A). Thermotherapy improved insulin sensitivity in all groups except male APP/PS1 mice that instead had improved glucose tolerance (Fig 1B-C). Plasma concentrations of insulin-like growth factor 1 (IGF-1) and leptin were decreased in male APP/PS1 mice while IGF-1 was increased in female APP/PS1 mice. **Figure 1**

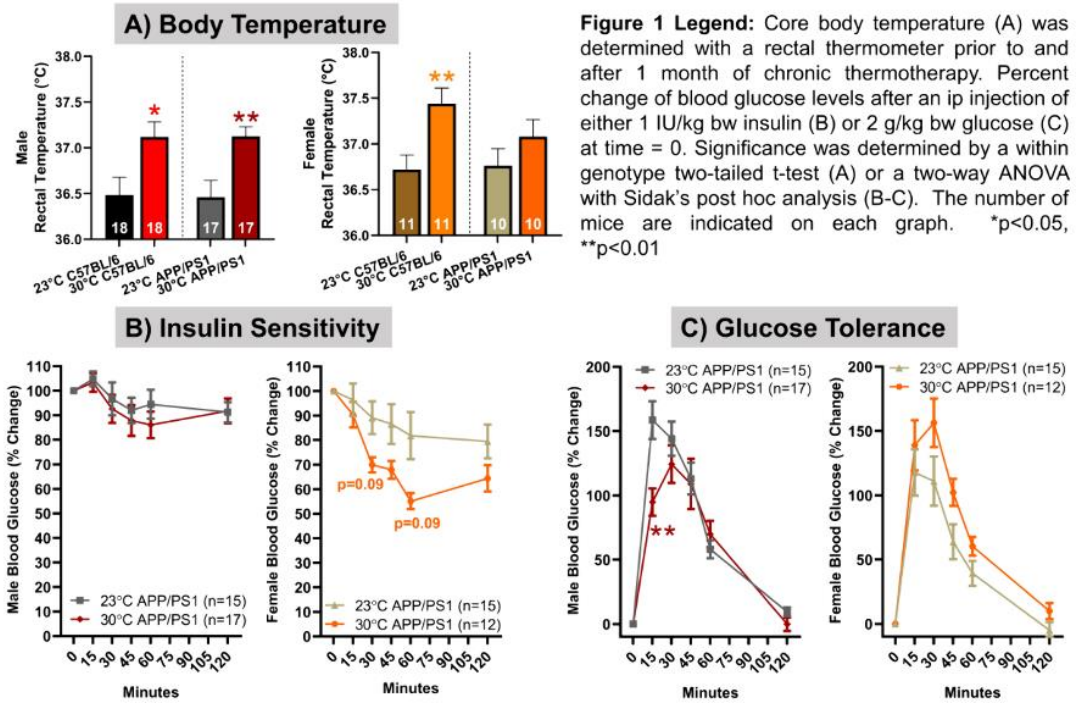


Figure 1 Legend: Core body temperature (A) was determined with a rectal thermometer prior to and after 1 month of chronic thermotherapy. Percent change of blood glucose levels after an ip injection of either 1 IU/kg bw insulin (B) or 2 g/kg bw glucose (C) at time = 0. Significance was determined by a within genotype two-tailed t-test (A) or a two-way ANOVA with Sidak's post hoc analysis (B-C). The number of mice are indicated on each graph. *p<0.05, **p<0.01

Thermotherapy improved spatial navigation in male mice, but this treatment had no effect in female C57BL/6 mice and worsened performance in female APP/PS1 mice (Fig 2). Thermotherapy had no effect on hippocampal amyloid accumulation but did reduce circulating proinflammatory cytokines. Additional mechanistic studies are ongoing to elucidate sex- and tissue-specific metabolic differences to thermotherapy. **Figure 2**

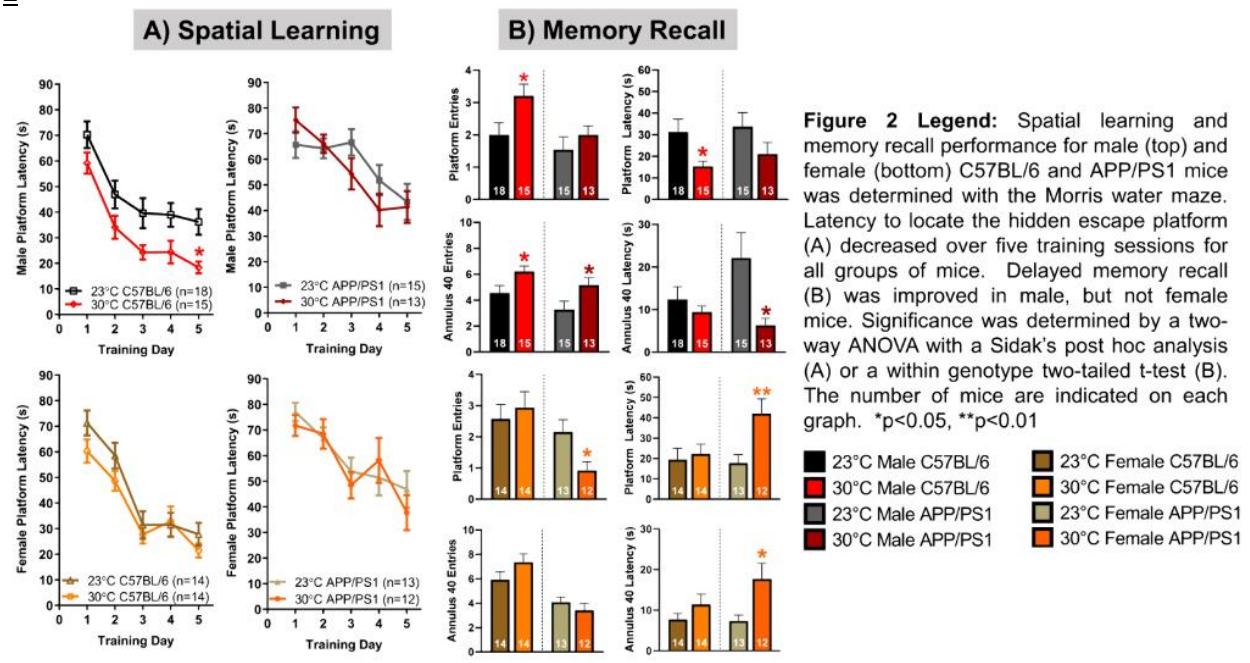


Figure 2 Legend: Spatial learning and memory recall performance for male (top) and female (bottom) C57BL/6 and APP/PS1 mice was determined with the Morris water maze. Latency to locate the hidden escape platform (A) decreased over five training sessions for all groups of mice. Delayed memory recall (B) was improved in male, but not female mice. Significance was determined by a two-way ANOVA with a Sidak's post hoc analysis (A) or a within genotype two-tailed t-test (B). The number of mice are indicated on each graph. *p<0.05, **p<0.01

Conclusions: Although chronic thermotherapy improved either glucose tolerance or insulin sensitivity in all groups, only male mice had better spatial learning and memory recall. Support came from the

NIH (R01 AG057767, AG061937), IDPH (03282005H), Smith Alzheimer's Center, and Kenneth Stark Endowment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0159 / #1034

Poster Topic: *Theme A: β-Amyloid Diseases / A01.n. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

STABILIZED HIF RESPONSE PROTECTS NEURONS IN AN ALZHEIMER'S DISEASE MODEL

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Margareta Kurkela[1], Elitsa Dimova[1], Henna Koivisto[2], Tuulia Ala-Nisula[1], Maiju Uusitalo[1], Petri Kursula[1,3], Johanna Myllyharju[1], Raisa Serpi[1], Heikki Tanila[2], Peppi Koivunen[1]
[1]University of Oulu, Biocenter Oulu, Faculty Of Biochemistry And Molecular Medicine, Oulu Center For Cell-matrix Research, Oulu, Finland, [2]University of Eastern Finland, A.i. Virtanen Institute For Molecular Sciences, Kuopio, Finland, [3]University of Bergen, Department Of Biomedicine, Bergen, Norway

Aims: Hypoxia-inducible factor (HIF) regulates transcription of hundreds of genes in pathways such as glycolysis, angiogenesis, and cell proliferation. In normoxic conditions, HIF is targeted for degradation by HIF prolyl 4-hydroxylases (HIF-P4Hs). When oxygen availability decreases, HIF escapes degradation and activates reading of the target genes. HIF-P4H inhibition is already a therapeutical target in anemia but has potential for other diseases since HIF stabilization has been shown to be highly beneficial especially for metabolic health. The aim of our study was to investigate whether genetic HIF stabilization interferes with the disease progression in an Alzheimer's disease model.
Methods: The behavioral phenotype of female *Hif-p4h-2* hypomorphic *APP*swe/*PSEN1*dE9 (*APP/PSEN1*) mice was investigated at 6, 9 and 12 months old using open field and dark light tests in comparison to the *Hif-p4h-2* wild type *APP/PSEN1* mice. Glucose tolerance test (GTT) was carried out at 11 months old, and at 12 months samples were collected for histological, protein and qPCR analyses.
Results: *Hif-p4h-2* hypomorphism in *APP/PSEN1* mice reduced anxiety and maintained activity levels in behavioral tests over the follow-up period in comparison to the *Hif-p4h-2* wild type *APP/PSEN1* mice. The hypomorphic *Hif-p4h-2 APP/PSEN1* mice displayed lowered insulin levels and improved results in GTT. The improved behavioral and metabolic parameters associated with improved neuronal health measured with reduced ATG9A positivity in histological analyses.
Conclusions: Stabilization of the HIF response in *APP/PSEN1* mice resulted in an improved behavioral phenotype, and metabolic health with emphasis on reduced insulin levels. Improved behavioral and metabolic health associated with improved neuronal health. These data suggest that stabilized HIF response improves neural tolerance to detrimental effects of Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0160 / #838

Poster Topic: *Theme A: β-Amyloid Diseases / A01.n. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

INSULIN RECEPTOR KNOCKDOWN IN CHOROID PLEXUS WORSENS PATHOLOGY IN APP/PSEN1 MICE

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Caio Mazucanti, Vernon Kennedy, Jane Tian, Josephine Egan
National Institute on Aging, Laboratory Of Clinical Investigation, Baltimore, United States of America

Aims: This work characterizes insulin signaling in choroid plexus and its possible implications in diseases of the brain by modulating insulin receptor expression in choroid plexus (CP) of APP/PSEN1 mice and assessing plaque burden and behavior.
Methods: Insulin signaling in the choroid plexus of 3-months old APP/PSEN1 mice was disrupted by intracerebroventricular injection of AAV5 carrying insulin receptor shRNA sequence. Tissue specificity of AAV5 infection was confirmed by icv injection of AAV5-Cre in Cre-reporter mice (Ai14), and downregulation of IR expression was confirmed by qPCR both *in vitro* and *in vivo.* Integrity of the tissue was assessed by H&E and immunofluorescence staining. Gross brain morphology was visualized by MRI. Brain sections were stained with Thioflavin-S for amyloid deposits. Nine months after viral injection, locomotor and cognitive behavior were assessed by home cage activity measurements and spontaneous alternation test, respectively.
Results: Intracerebroventricular injection of AAV5 results in exclusive infection of epithelial cells of the choroid plexus. A month after injection, blood-CSF barrier disruption resulted, as shown by ZO-1 and Na+/K+ ATPase immunofluorescence staining. Two months after injection, in vivo MRI imaging shows complete atrophy of CPs and ventricles. H&E staining revealed immune infiltration in CP of insulin receptor knockdown mice. In APP/PSEN1 mice, CP insulin receptor knockdown resulted in increased number of amyloid plaques throughout the brain and worsened behavioral measurements associated with this transgenic mouse model.
Conclusions: These results implicate insulin signaling in the maintenance of one of the most important barriers in the CNS, connecting metabolic conditions such as type 2 diabetes and insulin resistance to neurological disorders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0161 / #1372

Poster Topic: *Theme A: β-Amyloid Diseases / A01.n. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

TEMPORAL CORTEX DISPLAYS THE MOST PROMINENT RESPONSE TO INTRANASAL INSULIN IN A RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Jelena Osmanovic Barilar[1], Leonarda Vlahov[1], Ana Babić Perhoč[1], Davor Virag[1], Jan Homolak[2], Melita Salkovic-Petrisic[1], Ana Knezovic[1]
[1]School of Medicine University of Zagreb, Department Of Pharmacology And Croatian Institute For Brain Research, Zagreb, Croatia, [2]University of Zagreb, School of medicine, Croatia, Department Of Pharmacology And Croatian Institute For Brain Research, Zagreb, Croatia

Aims: Our knowledge regarding the effect of insulin in the brain is still modest. Impaired response to insulin in the brain has been linked to many neurodegenerative disorders like Alzheimer's disease (AD). In line with this finding, an animal model of sporadic AD has been developed by intracerebroventricular (icv) administration of streptozotocin (STZ), which given peripherally causes insulin resistance. To explore the brain insulin effect in the STZ-icv model, we used intranasal insulin (INS) targeting brain.
Methods: Wistar rats were injected icv with STZ (3 mg/kg) or vehicle only (CTR). One month after, INS was given intranasally in both nostrils and animals were sacrificed 3, 7.5, 15, 30, 60 and 120 minutes after administration. C-fos levels, insulin concentration, IRS-1 activation/inhibition were measured in the brain and plasma.
Results: INS increased c-fos levels in temporal cortex (TC) 120 minutes after administration in STZ-icv rats. In CTR, insulin concentration was found increased at earliest time point (3 min) in all observed brain regions and remained increased after 7.5 min only in TC. IRS1 activity increased in TC and hippocampus (HPC) and it was followed by increment of inhibitory phosphorylation of IRS1, and activation diminished through time (up to 30 min). Contrary to this finding, there was no change in IRS activation/inhibition in hypothalamus (HPT).
Conclusions: Most prominent effect of intranasal insulin was found in TC. IRS inhibition follows its activation promptly after INS application in HPC and TC. It seems that in HPT insulin has no effect on pathway including IRS-1. *Supported by HRZZ-IP-2018-01-8938 and co-financed by the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project"Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain",GA KK01.1.1.01.0007 funded by the European Union)*

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0162 / #593

Poster Topic: *Theme A: β-Amyloid Diseases / A01.n. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

PLASMA ADIPONECTIN IS ASSOCIATED WITH BIOMARKERS OF ALZHEIMER'S DISEASE: EVIDENCE FROM REAL-LIFE STUDY

POSTERS: A01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Louise Sindzingre[1], Elodie Bouaziz-Amar[2], François Mouton-Liger[1], Emmanuel Cognat[3], Julien Dumurgier[2], Agathe Vrillon[1], Matthieu Martinet[1], Claire Paquet[1], Matthieu Lilamand[1]
[1]Inserm U1144, Therapeutical Optimization In Neuropsychopharmacology, Paris, France, [2]Therapeutical Optimization in Neuropsychopharmacology, Inserm U1144, Paris, France, [3]Lariboisière-Fernand Widal Hospital GHU AP-HP Nord, Cognitive Neurology Centre, Paris, France

Aims: Adiponectin secreted by adipose tissue plays a role in the regulation of energy homeostasis, carbohydrate and lipid metabolism, as well as in the modulation of inflammation. The observation of a relationship between Alzheimer's disease (AD) and body mass index (BMI) has highlighted the role of metabolic disorders in its pathophysiology. However, the available body of evidence has reported conflicting results. The exact role and mechanisms of adiponectin in the pathophysiology of AD remain unclear. The aim of this study was to compare plasma adiponectin levels in patients with AD, confirmed by biomarkers, with those of neurological control subjects.
Methods: In a single-center, cross-sectional, observational study we performed chemiluminescent enzyme immunoassay of plasma adiponectin levels in patients diagnosed with AD or as neurological controls. We described the evolution of adiponectin concentration among the age categories in males and females. We also analyzed the relationship between adiponectin and AD using linear regression models including age, gender and BMI.
Results: Two hundred and six patients (142 patients with AD and 64 neurological controls) were included. The mean age of the patients was 69 years, and 56% were women. Plasma adiponectin levels were significantly higher in patients with AD compared with control patients ($p<0.001$). This association was modulated by age, gender and BMI, which were significantly and independently associated with plasma adiponectin levels, while adiponectin was no longer associated with AD in multivariate models. Higher adiponectin concentrations were observed in females and associated with aging.
Conclusions: Adiponectin was associated with the biological diagnosis of AD and may play a key pathophysiological role in AD. Nevertheless, adiponectin levels were strongly related to age, gender and BMI. Further studies are needed to better characterize the "hormonal signature" of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0163 / #1665

Poster Topic: *Theme A: β-Amyloid Diseases / A01.o. Disease Mechanisms, Pathophysiology: Neural networks, plasticity*

LOW CONCENTRATIONS OF AMYLOID-BETA PEPTIDES TRIGGER PREMATURE FUNCTIONAL AND GENE EXPRESSION ALTERATIONS IN HUMAN-INDUCED NEURONS

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

Marcos Costa
Institut Pasteur de Lille, Inserm U1167, Lille, France

Aims: Alzheimer's disease (AD) is the most prevalent cause of dementia in the elderly, characterized by the presence of amyloid beta (Aβ) plaques, neurofibrillary tangles, neuroinflammation, synapse loss and neurodegeneration in the brain. The amyloid cascade hypothesis postulates that deposition of Aβ peptides is the causative agent of AD pathology, but we still lack comprehensive understanding about the molecular mechanisms connecting Aβ peptides to neuronal dysfunctions in AD. In this work, we investigated the early effects of Aβ peptides accumulation on the functional properties and gene expression profiles of human-induced neurons (hiNs).
Methods: We exposed 6-weeks-old hiNs to low concentrations of cell-secreted Aβ oligomers or synthetic Aβ and performed time-lapse time microscopy to detect fast calcium transients as an indirect readout of neuronal electrical function. Next, we used single-nucleus RNA sequencing (snRNA-seq) to probe early Aβ-mediated gene expression alterations in hiNs and human-induced astrocytes (hiAs). Lastly, we leveraged snRNA-seq data to identify patterns of intercellular communication modulated by Aβ oligomers.
Results: We show that hiNs acutely exposed to low concentrations of both cell-secreted Aβ peptides or synthetic $A\beta_{1-42}$ exhibit alterations in the frequency of calcium transients suggestive of increased neuronal excitability. We also show that cell-secreted Aβ up-regulates the expression of several synaptic-related genes and down-regulates the expression of genes associated with metabolic stress mainly in glutamatergic neurons and to a lesser degree in GABAergic neurons and astrocytes. These neuronal alterations correlate with activation of SEMA5, EPHA and NECTIN signaling pathways, which are important regulators of synaptic plasticity.
Conclusions: Our findings indicate that slight elevations in Aβ concentrations are sufficient to elicit transcriptional changes in human neurons with long lasting consequences to neural network activity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0164 / #656

Poster Topic: *Theme A: β-Amyloid Diseases / A01.o. Disease Mechanisms, Pathophysiology: Neural networks, plasticity*

CORTICAL REGION CONFERS NEURON-TYPE-SPECIFIC VULNERABILITY TO HUMAN APP EXPRESSION

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

Annie Goettemoeller, Matthew Rowan
Emory University School of Medicine, Cell Biology, Atlanta, United States of America

Aims: Preventative treatment for Alzheimer's Disease is of dire importance, and yet, cellular mechanisms underlying early regional vulnerability in Alzheimer's Disease remain unknown. In human patients with Alzheimer's Disease, one of the earliest observed pathophysiological correlates to cognitive decline is hyperexcitability. In mouse models, early hyperexcitability has been shown in the entorhinal cortex, the first cortical region impacted by Alzheimer's Disease. The origin of hyperexcitability in early-stage disease and why it preferentially emerges in specific regions is unclear.
Methods: Using cortical-region and cell-type- specific proteomics and patch-clamp electrophysiology, we uncovered differential susceptibility to human-specific amyloid precursor protein (hAPP) in a model of sporadic Alzheimer's.
Results: Unexpectedly, our findings reveal that early entorhinal hyperexcitability may result from intrinsic vulnerability of parvalbumin interneurons, rather than the suspected layer II excitatory neurons. This vulnerability of entorhinal PV interneurons is specific to hAPP, as it could not be recapitulated with increased murine APP expression. Furthermore, the Somatosensory Cortex showed no such vulnerability to adult-onset hAPP expression, likely resulting from PV-interneuron variability between the two regions based on physiological and proteomic evaluations. Interestingly, entorhinal hAPP-induced hyperexcitability was quelled by co-expression of human Tau, at the expense of increased pathological tau species.
Conclusions: This study suggests early disease interventions targeting non-excitatory cell types may protect regions with early vulnerability to pathological symptoms of Alzheimer's Disease and downstream cognitive decline.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0165 / #685

Poster Topic: *Theme A: β-Amyloid Diseases / A01.o. Disease Mechanisms, Pathophysiology: Neural networks, plasticity*

DIVERSITY OF CA1 PYRAMIDAL PLASTICITY MODULATED BY FAST-SPIKING PV INTERNEURONS IN AN AD MOUSE MODEL

POSTERS: A01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS, PLASTICITY

Yan Zheng[1], Lijuan Li[1], Hanning Hu[1], Zizheng Chen[1], Jianliang Zhang[2]
[1]Capital Medical University, Department Of Physiology And Pathophysiology, Beijing, China, [2]Capital Medical University, Department Of Neurobiology, Beijing, China

Aims: Alzheimer's disease (AD) is a refractory disease with complex pathogenesis. The synaptic degeneration and decline in plasticity in the hippocampal circuit play a central role in AD. Previous studies have elucidated the role of hippocampal long-projecting circuits in the AD brain. Nevertheless, how the hippocampal microcircuits are involved in the AD process is unclear. The known pieces of evidence revealed that the fast-spiking parvalbumin (PV) positive basket interneurons (PVBCs) connect the adjacent deep CA1 pyramidal neurons (deep CA1PNs) and superficial CA1 pyramidal neurons (superficial CA1PNs) to form a recurrent inhibitory microcircuit relevant to learning and memory. This study examined how PVBCs regulate CA1 plasticity in an AD mouse model, considering neuronal heterogeneity in the CA1 microcircuit.
Methods: We conducted whole-cell recording on acute hippocampal slices to study individual long-term potentiation (LTP) in CA1 of 5xFAD mice. To evaluate and manipulate hippocampal functions in the AD mouse model, we employed Contextual Fear Conditioning, pharmacology, and optogenetics.
Results: We found that the LTP of superficial CA1PNs was selectively impaired, while deep CA1PNs remained normal in 5xFAD mice at six months, compared to their wild-type littermates. The CA1 PVBCs functioning as filters at higher frequencies were damaged in the 5xFAD mouse brain. In addition, the amplitude of NMDAR-EPSCs in PVBCs was enhanced in the mouse model brain. Intriguingly, the administration of memantine in acute hippocampal slices rescued the diminished LTP in superficial CA1PNs of 5xFAD mice compared to wild-type mice.
Conclusions: We suggest that PVBCs in CA1 are vulnerable to AD-like environments, leading to distinct changes in pyramidal LTP. This may lead to a promising approach of combining NMDAR inhibition and non-invasive electrophysiological modulation for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0166 / #1835

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

CHANGES IN PLASMA SMALL RNA TRANSCRIPTOME CAN BE DETECTED UP TO 12 YEARS PRIOR TO AD SYMPTOM ONSET

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Aleksandra Beric[1], Charissa Martin[1], Santiago Sanchez[1], Patricia Baldrich[2], Laura Ibanez[1]
[1]Washington University School of Medicine, Psychiatry, Saint Louis, United States of America, [2]The Donald Danforth Plant Science Center, Na, Saint Louis, United States of America

Aims: MicroRNAs (miRNAs) are known to be involved in Alzheimer's disease (AD), but little is known about the other classes of small RNAs (sRNAs) or their potential as early biomarkers. We performed the first comprehensive study of sRNAs in plasma of pre-symptomatic AD participants.
Methods: Sampling included 88 plasma samples from the Knight-ADRC cohort, 51% of which were pre-symptomatic AD participants, 58% female, and with a mean age of 78. After RNA extraction with a Maxwell RSC instrument, we generated sRNA libraries using the RealSeq®-AC sRNA kit version 2. Libraries were aligned to the reference genome and known small RNAs using Bowtie2. After stringent quality control we performed differential expression analyses using DESeq2. We integrated the sRNA data with RNA-seq data from the same samples to test whether any of the dysregulated sRNAs significantly correlate with known AD-genes.
Results: We identified six miRNAs (eg. miR-15b-5p and miR-505-5p) and 244 Piwi-interacting RNAs (piRNAs) that were significantly dysregulated in plasma of pre-symptomatic AD participants. Further, we identified dysregulated sRNAs that significantly correlate with AD associated loci identified by Bellenguez *et al*. HLA-DQA1 correlated positively to miR-15b-5p, miR-505-5p and miR-619, but associated with piR-409995 in the opposite direction. Additionally, we identified significant relationships between eight more piRNAs, and five other AD-related genes.
Conclusions: Our findings emphasize the importance of non-coding RNAs in AD. We showed that sRNAs beyond miRNAs are dysregulated in early stages of AD. Large-scale studies of sRNAs in plasma might be crucial to develop new, more easily accessible, screening tools for AD. Here, we described that several plasma sRNAs correlate with known AD genes up to 12 years prior to disease onset, and thus potentially capture the pathological processes happening in the brain.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0167 / #1893

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

TRANSCRIPTOMIC ANALYSIS OF THE PRESENILIN-1 G206A VARIANT IN ALZHEIMER DISEASE INDIVIDUALS FROM PUERTO RICO

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Katrina Celis[1], Farid Rajabli[1], Anthony Griswold[2], Larry Adams[1], Kara Hamilton-Nelson[1], Kyle Scott[1], Patrice Whitehead[1], Pedro Mena[1], Jose Sanchez[1], Heriberto Acosta[1], Gary Beecham[1], Briseida Feliciano-Astacio[1], Michael Cuccaro[1], Jeffery Vance[1], Derek Dykxhoorn[1], Juan Young[1], Margaret Pericak-Vance[1]
[1]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [2]University of Miami, John P. Hussman Institute For Human Genomics, Miami, United States of America

Aims: The variant G206A in the Presenilin-1 (*PSEN1*) gene has been identified almost exclusively in Alzheimer Disease (AD) Puerto Rican families. The G206A variant is associated with extreme variability in age of onset (AOO), ranging from 30 to 90 years, while other variations at the same amino acid of *PSEN1* have a tighter range of AOO (30-35 years). We aim to identify the molecular mechanisms involved in the age of onset (AOO) variability between *PSEN1* G206A mutation carriers through transcriptomic analysis from whole blood, brains and induced pluripotent stem cells (iPSCs).
Methods: We identified G206A carrying brains from the National Alzheimer Coordinating Center and AD Rapid Decline study. These brains will undergo Single Nucleus RNA sequencing (snRNA-seq) using 10X Chromium platform and will be analyzed using Seurat. iPSC of G206A carriers with different AOO were reprogrammed using non-integrating Sendai virus. RNA was extracted from whole blood and iPSC from G206A carriers and sequenced at 40 million reads/sample using the Illumina Novaseq 6000.
Results: We identified 43 carriers (39 AD and 4 cognitively unimpaired) as part of PRADI. A single African haplotype was identified in all carriers.To perform snRNAseq, we selected six autopsy brains from G206A carriers. Six iPSC line were reprogrammed successfully, all lines were screened using G-band Karyotype, factor loss analyses, genetic finger printing, immunocytochemistry and pluripotency markers. For bulk RNA sequencing, we included six iPSC lines (three with early and three with late AOO) and 28 samples from whole. Transcriptomic results are in progress.
Conclusions: The G206A variant, a founder effect in the Puerto Rican population, exhibits variable AOO. We propose to utilize these unique resources to identify the transcriptomic profile associated with AOO variability. Identification of transcriptome modifiers in G206A carriers could allow us to discover therapeutic targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0168 / #2035

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

TARGETING CIRCADIAN DYSFUNCTION TO AMELIORATE PATHOLOGY AND COGNITION IN MOUSE MODELS OF ALZHEIMER'S DISEASE.

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Daniel Whittaker[1], Daniel Carlin[1], Haylie Romero[1], Laila Akhmetova[1], David Welsh[2], Christopher Colwell[1], Paula Desplats[3]
[1]University of California Los Angeles, Neurosciences, Los Angeles, United States of America, [2]University of California San Diego, Psychiatry, La Jolla, United States of America, [3]University of California San Diego, Neurosciences, La Jolla, United States of America

Aims: Circadian disruptions impact nearly all patients with Alzheimer's disease (AD), who suffer reversal of sleep/wake cycles and evening agitation. Emerging evidence indicates that these alterations occur early in disease and aggravate pathology, thus supporting a causal role for circadian dysfunction in AD, and emphasizing a critical need to investigate the therapeutic potential of circadian-modulating interventions.
Methods: We applied multi-omic profiling to evaluate epigenomic and transcriptomic changes associated with circadian regulation in the brain of APP23 Tg and non-transgenic mice. We tested a circadian and metabolic intervention consistent on time-restricted access to food (TRF) with a 6 h feeding/18 h fasting regimen, without caloric restriction, and with feeding aligned to the active period. We evaluated cage activity, sleep, transcription, pathology and cognition in comparison to mice with *ad libitum* access to food.
Results: We identified progressive circadian disruptions in the APP23 TG mice, including excessive wakefulness, altered behavioral circadian rhythms, and severe deregulation of rhythmic expression of many genes associated with AD pathology and neuroinflammation. TRF improved diurnal locomotor activity patterns and behavioral circadian rhythms and increased total sleep. TRF also normalized the transcription of genes associated with AD, neuroinflammation, lipid processing, and autophagy in the hippocampus of APP23 TG mice. Critically, TRF had a major impact on neuropathology, reducing plaque burden, amyloid deposition, and improving memory in treated mice.
Conclusions: We demonstrated the efficacy of a circadian intervention based on time-restricting feeding in rescuing pathology and behavior in two mouse models of AD. Our study unveils for the first time the pleiotropic nature of timed feeding on AD. Since TRF can substantially modify disease trajectory, this intervention has immediate translational potential for AD patients, as an accessible approach to halt disease progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0169 / #885

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

INHIBITION OF BACH1 AS A NOVEL STRATEGY TO ATTENUATE PROGRESSIVE NEUROPATHOLOGY IN ALZHEIMER'S DISEASE.

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Debashis Dutta[1,2], Joyce Meints[3], Navneet Kaidery[1], Manuj Ahuja[4], Razaul Karim[3], Cenxiao Fang[3], Otis Attucks[5], Carmen Valcarce[5], Mitsuyo Matsumoto[6], Akihiko Muto[6], Kazuhiko Igarashi[6], Sudarshana Sharma[7,8], Michael Lee[3], Bobby Thomas[1]
[1]Medical University of South Carolina, Department Of Pediatrics, Charleston, United States of America, [2]Medical University of South Carolina, Darby's Children Research Institute, Charleston, United States of America, [3]University of Minnesota, Department Of Neuroscience, Minneapolis, United States of America, [4]Bristol-Meyers Squibb, Na, New Jersey, United States of America, [5]vTv Therapeutics LLC, Na, High Point, United States of America, [6]Tohoku University Japan, Department Of Biochemistry, Sendai, Miyagi, Japan, [7]Medical University of South Carolina, Department Of Biochemistry, Charleston, United States of America, [8]Medical University of South Carolina, Hollings Cancer Center, Charleston, United States of America

Aims: Alzheimer's disease (AD) is the most prevalent form of dementia. A decline in the expression of the redox-dependent transcription factor Nrf2 is observed in AD brains. Although Nrf2 activation is a promising therapeutic strategy, the current Nrf2 activators suffer from side effects and tolerability issues in patients. BTB and CNC homology 1 (Bach1) is a known transcriptional repressor of the Nrf2 pathway and is elevated in human AD brains and APP/PS1 mouse model of AD. It suggests that Bach1 inhibition might be neuroprotective in AD. The present study aims to validate if genetic deletion of Bach1 and pharmacological inhibition by a newly identified non-electrophilic molecule (HPPE) attenuates AD-like neuropathology in the APP/PS1 mouse model.
Methods: APP/PS1 mice were crossed with Bach1$^{-/-}$ mice to generate Bach1 ablated APP/PS1 mice. Cohorts of post-symptomatic APP/PS1 mice were administered with HPPE for 45 days (20 mg/kg twice a day, 12 h apart). Cognitive performance of mice was evaluated by Barnes maze and novel object recognition tests. Amyloid pathology and microglial activation were monitored by immunohistochemical analyses. The Bach1-regulated pathways were identified by sn-RNA-seq analysis.
Results: Deletion of Bach1 in APP/PS1 mice attenuated cognitive impairment, Abeta plaque formation and microglial activation in the hippocampus. Accordingly, HPPE treatment significantly inhibited amyloid pathology and cognitive dysfunction in the APP/PS1 mice. Single nuclei- functional genomics analysis demonstrated that the neuroprotective effects of Bach1 inhibition in APP/PS1 mice was due to upregulation of genes involved in oxidative phosphorylation in neurons and downregulation of pro-inflammatory genes in oligodendrocytes, astrocytes and microglia.
Conclusions: Present findings suggest that genetic deletion and pharmacologic inhibition of Bach1 attenuates progression of AD-like pathology and that Bach1 inhibition is a promising therapeutic approach.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0170 / #2235

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

MIR-129-5P AS A BIOMARKER FOR PATHOLOGY AND COGNITIVE DECLINE IN ALZHEIMER'S DISEASE

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Sang-Won Han[1], Jung-Min Pyun[2], Paula Bice[3,4], David Bennett[5], Andrew Saykin[4], Sangyun Kim[6], Young Ho Park[7], Kwangsik Nho[4]
[1]Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Neurology, Chuncheon, Korea, Republic of, [2]Soonchunhyang University Seoul Hospital, Neurology, Seoul, Korea, Republic of, [3]Indiana University School of Medicine, Radiology And Imaging Sciences, Indianapolis, United States of America, [4]Indiana University School of Medicine, Department Of Radiology And Imaging Sciences, Indianapolis, United States of America, [5]Rush University Medical Center, Rush Alzheimer's Disease Center, Chicago, United States of America, [6]Seoul National University Bundang Hospital, Neurology, Seongnam-si, Korea, Republic of, [7]Seoul National University Bundang Hospital, Neurology, Seongnam, Korea, Republic of

Aims: Integrative network and machine learning analysis of microRNA (miRNA) can provide insights into Alzheimer's dementia (AD) pathology and prognostic/diagnostic biomarkers.
Methods: We performed co-expression network analysis to identify network modules associated with AD, neuropathology markers, and cognition using brain tissue miRNA profiles from the Religious Orders Study and Rush Memory and Aging Project (ROS/MAP) (N=702) as a discovery dataset. We performed association analysis of hub miRNAs with AD, neuropathology markers, and cognition. For replication, we performed a consensus miRNA co-expression network analysis using the ROS/MAP dataset and an independent dataset (N=16) from the Gene Expression Omnibus (GEO). Furthermore, we performed a machine learning approach to assess the performance of hub miRNAs for AD classification.
Results: Network analysis identified a glucose metabolism pathway-enriched module (M3) as significantly associated with AD and cognition. Five hub miRNAs (miR-129-5p, miR-433, miR-1260, miR-200a, and miR-221) of M3 had significant associations with AD clinical and/or pathologic traits, with miR129-5p by far the strongest across all phenotypes. Consensus network analysis identified two AD-associated consensus network modules, and two hub miRNAs (miR-129-5p and miR-221). Machine learning analysis showed that the AD classification performance (area under the curve (AUC)=0.807) of age, sex, and *apoE* ε4 carrier status was significantly improved by 6.3% with inclusion of five AD-associated hub miRNAs.
Conclusions: Integrative network and machine learning analysis identified miRNA signatures, especially miR-129-5p, as associated with AD, neuropathology markers, and cognition, enhancing our understanding of Alzheimer's disease pathogenesis and leading to better performance of AD classification as potential diagnostic/prognostic biomarkers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0171 / #588

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

MIRNA EXPRESSION DYSREGULATION IN SYNAPSES OF ALZHEIMER'S DISEASE BRAIN TISSUE

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Laia Lidón[1], Raúl Núñez[2], Danna Perlaza[1], Alba Cervantes[1], Natalia Valle[1], Sara Serrano[1], Érika Sánchez-Aced[1], Sònia Sirisi[1], Maria Florencia Iulita[1], Oriol Dols[1], Alberto Lleó[1], Rocío Pérez[3], Olivia Belbin[1]
[1]Hospital of Sant Pau, Neurology, Barcelona, Spain, [2]ACE Alzheimer Center Barcelona, Research Center And Memory Clinic, Barcelona, Spain, [3]ISABIAL, Universidad Miguel Hernández-CSIC, Instituto Neurociencias, Alicante, Spain

Aims: Knowing that synapse loss is the major neuropathologic correlate of cognitive impairment in Alzheimer's disease (AD) and that microRNA (miRNA) play an important role in the regulation of synaptic plasticity, our objective was to study the expression of synapse-specific miRNA in AD post-mortem brain tissue.
Methods: We obtained synaptosomes (SYN) and homogenates (H) from temporal cortex from 10 AD (mean age=77.4±4.2) and 10 healthy controls (CN; mean age=72.3±5.9). We extracted and quantified miRNA using the mirVana™ and TaqMan® Advanced miRNA Assay. We performed linear regression to identify differentially expressed miRNA across groups, considering fold changes <0.8 or >1.2 (adj.p<0.05) in AD vs CN. We searched two predictive databases (TargetScan and miRDB) for gene targets of the DE miRNA and performed pathway analysis using the Panther database (PantherDB.org).
Results: We detected 411 miRNA in H and 432 in SYN of the total 751 included on the Openarray. To study the synapse-enriched miRNA, we took forward the 47 miRNA with >1.2-foldchange (adj.p<0.2) in SYN compared to H in either AD or CN. We found that miR-132-3p and miR-132-5p were under-expressed (0.17-fold, p=0.001 and 0.35-fold, p=0.006, respectively) and miR-181a-3p was over-expressed (2.13-fold, p=0.04) in AD vs CN. The gene targets of miR-181a-3p (594), miR-132-3p (474) and miR-132-5p (1230) were overrepresented in pathways regulating synaptic and mitochondrial function. Targets of miR-132 also were overrepresented in pathways related to tau pathology, Aβ production, interleukin production, apoptosis and oxidative stress.
Conclusions: We identified 3 synapse-specific miRNA that are differentially expressed at synapses of AD temporal cortex. Their target genes are involved in pathways related to AD pathogenesis. Future studies will focus on the validation of these miRNA in other brain areas and the potential of these miRNA as therapeutic targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0172 / #893

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

EFFECTS OF DNMT3A OVEREXPRESSION/KNOCKDOWN ON SYNAPTIC TRANSMISSION IN THE 5XFAD MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Yanzhi Liu[1], Chi Him Poon[1], Charlotte So[1], Benjamin Chun-Kit Tong[2], King-Ho Cheung[2], Harry Steinbusch[3], Lee Wei Lim[1]
[1]The University of Hong Kong, School Of Biomedical Sciences, Pok Fu Lam, Hong Kong PRC, [2]Hong Kong Baptist University, School Of Chinese Medicine, Kowloon City, Hong Kong PRC, [3]Maastricht University, Department Of Neuroscience, Maastricht, Netherlands

Aims: Growing evidence suggests that dysregulations in DNA methylation contribute to the pathogenesis of AD. In this study, we aim to investigate the effects of overexpressing/knockdown DNA methyltransferase 3A (DNMT3A) in the hippocampus of both wildtype mice and the 5xFAD mouse model of AD. The effects of DNMT3A manipulation on the memory performances, CA3-CA1 synaptic transmission and serotonergic neurotransmission are investigated.
Methods: rAAV containing either an overexpression vector or shRNA were used to overexpress/knockdown DNMT3A. Mice (male, 4-6 mo) received bilateral infusion of the virus into the dorsal hippocampus. Behavioral tests (Y-Maze, Morris Water Maze, Open Field and Light Dark Box) were conducted starting from 43 days post-surgery. On day 52, mice were sacrificed, and their brains were harvested for either field electrophysiology or molecular analysis. For field electrophysiology, long-term potentiation and paired pulse facilitation/inhibition were tested on the CA3-CA1 synapse. 5HT fibre density in the hippocampus were assessed by immunohistochemistry. Transcript levels of DNA methylation regulators and 5HT receptors were assessed by RT-qPCR.
Results: 5xFAD mice showed memory impairments in Morris Water Maze test (MWM) compared to WT mice. DNMT3A overexpression and knockdown both led to memory impairments in wildtype (WT) and 5xFAD mice in MWM. 5xFAD mice displayed synaptic hyperexcitability as assessed by field electrophysiology, which was normalized by DNMT3A overexpression. DNMT3A overexpression and knockdown led to differential changes in the expression of DNA methylation regulators, 5HT fiber density and 5HT receptor expression in the hippocampus.
Conclusions: Normal physiological level of DNMT3A is crucial for memory functions in WT and 5xFAD mice. Perturbances in DNMT3A expression led to memory impairments and changes in synaptic excitability, 5HT fiber density and widespread changes in the DNA methylation regulators expression in the hippocampus.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0173 / #1509

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

INTEROGATING DNA METHYLATION IN LEWY BODY DEMENTIA IN A CROSS BRAIN-REGION AND MULTI-COHORT STUDY

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Katie Lunnon[1], Joshua Harvey[1], Jennifer Imm[1], Byron Creese[1], Leonidas Chouliaras[2], Emma Dempster[1], Clive Ballard[1], John O'Brien[2], Dag Aarsland[3], Jonathan Mill[1], Lasse Pihlstrøm[4], Ehsan Pishva[1,5]
[1]University of Exeter, Department Of Biomedical And Clinical Sciences, Exeter, United Kingdom, [2]University of Cambridge, Department Of Psychiatry, Cambridge, United Kingdom, [3]Institute of Psychology, Psychiatry & Neuroscience (IoPPN), King's College London, Department Of Old Age Psychiatry, London, United Kingdom, [4]Oslo University Hospital, Department Of Neurology, Oslo, Norway, [5]University of Maastricht, Department Of Psychiatry & Neurophysiology, Maastricht, Netherlands

Aims: The Lewy body dementias are a class of neurodegenerative diseases classified by the accumulation of alpha-synuclein in neurons, forming Lewy bodies (LB). We hypothesize that the development of LB pathology is associated with epigenetic changes, as measured by DNA methylation within the brains of patients with Parkinson's disease and Dementia with Lewy bodies.
Methods: In our discovery cohort we profiled 921 DNA samples from the anterior cingulate gyrus and prefrontal cortex of 474 unique donors on the Illumina EPIC array, generating a quantitative measure of DNA methylation for over 850,000 CpG sites. A mixed model was used to identify loci significantly associated with neuropathology as measured by Braak LB staging, controlling for confounding demographic, processing and neuropathological variables. We then meta-analyzed the findings from this cohort with an independent published cohort of 322 frontal cortex samples.
Results: In a cross cortical mixed model analysis in our discovery cohort we found one Bonferroni-corrected significant differentially methylated position (cg13847853, $p = 3.41 \times 10^{-8}$) and a further nine that passed our suggestive association threshold, the second most significant residing within the *PTPRN2* gene (cg10257673, $p = 8.88 \times 10^{-7}$). Our meta-analysis combining a second independent cohort identified nine significant loci after correcting for multiple testing.
Conclusions: We have interrogated the epigenetic basis of neuropathological progression in Lewy body dementia and found a number of associated loci in both our cross-cortex discovery analysis, and meta-analysis. One of the most associated loci resided in the *PTPRN2* gene. *PTPRN2,* which has been has been previously implicated in a number of independent DNA methylation studies of PD, including in blood (Chuang, et al., 2019), brain tissue (Young, et al., 2019) and cortical neurons (Kochmanski, et al., 2021).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0174 / #1537

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

SPATIALLY-RESOLVED TRANSCRIPTIONAL CHANGES IN THE HIPPOCAMPUS OF AN AMYLOID MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Katie Lunnon[1], Millie Sander[1], Ella Margetts-Smith[1], Adam Smith[1], Valentin Laroche[2], Ehsan Pishva[1,2], Jon Brown[1]
[1]University of Exeter, Department Of Biomedical And Clinical Sciences, Exeter, United Kingdom, [2]University of Maastricht, Department Of Psychiatry & Neurophysiology, Maastricht, Netherlands

Aims: A key pathological trait of Alzheimer's disease (AD) is the accumulation of amyloid plaques in the brain. J20 mice harbour mutations in the amyloid precursor protein gene known to be associated with familial AD. These mice exhibit AD-associated pathology and transcriptional changes in the hippocampus. Spatial transcriptomic technology presents a unique and novel opportunity to investigate spatially-resolved transcriptomic changes in tissue of interest. Here, we aimed to identify changes in gene expression, and associated functional pathways, throughout sub-regions of the J20 mouse hippocampus.
Methods: 10µm slices of fresh-frozen tissue were collected from the brains of both J20 and WT mice. All sample preparation, imaging and sequencing protocols were conducted following the 10x Genomics Visium guidelines. Spatial clusters were created based on gene expression profiles, and hippocampal clusters were subset for analysis. Cell deconvolution was conducted in order to assess cell-type composition of said clusters. Differential expression analysis and network analysis were conducted using Seurat and hdWGCNA respectfully. Pathway enrichment analysis was conducted in order to associate said changes with functional outcomes.
Results: Six clusters were found to correspond with known sub-regions of the hippocampus, and were conserved between samples. Cluster-specific differentially expressed genes (DEGs) were identified between J20 and WT mice. Five hdWGCNA models were identified, which exhibited spatially-defined co-expression signatures. Three of these modules were significantly differentially expressed between J20 and WT mice. Both DEGs and significant hdWGCNA modules were found to correspond with distinct biological pathways.
Conclusions: The hippocampus of J20 mice exhibit region-specific transcriptomic changes. Biological pathways associated with these changes provide insight as to the functional and pathological changes occuring throughout the hippocampus during AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0175 / #1825

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

MAPPING ANCESTRY-SPECIFIC GENOMIC REGULATORY ARCHITECTURE OF IPSC-DERIVED OLIGODENDROCYTE-ENRICHED NEURAL SPHEROIDS IN THE CONTEXT OF ALZHEIMER'S DISEASE

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Aura Ramirez[1], Jihanne Shepherd[1], Lauren Coombs[1], Shaina Simon[1], Sofia Moura[1], Brooke Derosa[1], Farid Rajabli[1], Patrice Whitehead[1], Larry Adams[1], Takiyah Starks[2], Pedro Mena[1], Maryenela Illanes-Manrique[3,4], Sergio Tejada[1], Goldie Byrd[2], Mario Cornejo-Olivas[4], Briseida Feliciano-Astacio[5,6], Liyong Wang[1], Wanying Xu[7], Fulai Jin[7], Margaret Pericak-Vance[1], Anthony Griswold[8], Derek Dykxhoorn[1], Juan Young[1], Jeffery Vance[1]
[1]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [2]Wake Forest University School of Medicine, Maya Angelou Center For Health Equity, Winston-Salem, United States of America, [3]Global Brain Health Institute (GBHI), Atlantic Fellow For Equity In Brain Health At, San Francisco, United States of America, [4]Universidad Científica del Sur, Neurogenetics Working Group,, Lima, Peru, [5]Universidad Central del Caribe, -, Bayamón, Puerto Rico, [6]Universidad Central Del Caribe, Department Of Internal Medicine, Bayamon, Puerto Rico, [7]Case Western Reserve University, Department Of Genetics And Genome Sciences, Cleveland, United States of America, [8]University of Miami, John P. Hussman Institute For Human Genomics, Miami, United States of America

Aims: This study aimed to establish ancestry-dependent differences in the genomic regulatory architecture (GRA) of oligodendrocytes in the context of Alzheimer's disease (AD) using induced pluripotent stem cell (iPSC)-derived neural spheroids with African, Amerindian, and European ancestral backgrounds. The objective was to provide ancestry-specific insights into the chromatin structure and gene regulation of oligodendrocytes and expand functional resources for gene identification studies in African American and Hispanic/Latino populations.
Methods: iPSCs were derived from individuals with AD or without cognitive impairment, with >85% global ancestry of each ancestral background. The iPSCs were differentiated into oligodendrocyte (OL) enriched neural spheroids using a protocol promoting oligodendroglia development. Multiomic profiling was performed on day 76 of differentiation, involving analysis of chromatin accessibility and transcriptome through Single Cell ATAC and Single Cell RNA-seq techniques. Chromatin interactions were investigated using Hi-C analyses.
Results: Various stages of OL lineage cells were identified, ranging from cycling progenitors and OL precursor cells to fully mature myelinating OLs. Comparisons across ancestries, considering AD cases and controls as well as APOE genotypes, revealed ancestry-dependent differential gene expression in several oligodendroglia clusters, including AD GWAS hits such as *SORL1*, *PLCG2*, and *JAZF1*. Ongoing analyses of other oligodendroglia clusters, astrocytes, and neurons are underway.
Conclusions: This study provides ancestry-specific insights into the chromatin structure and gene regulation of oligodendrocytes in the context of AD. The findings contribute to our understanding of this previously overlooked cell lineage and expand the available functional resources for gene identification studies in African American and Hispanic/Latino populations. The comprehensive characterization of GRA in oligodendrocytes enhances our ability to interpret the variability associated with AD risk genes across populations and supports the development of personalized approaches for AD diagnosis and treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0176 / #286

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

MIR-425-5P AS POTENTIAL GENE REGULATOR FOR IMMUNOLOGICAL PROCESSES IN BRAIN WHITE MATTER LESIONS

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Sandra Van Der Auwera, Sabine Ameling, Katharina Wittfeld, Stefan Frenzel, Robin Bülow, Matthias Nauck, Henry Völzke, Uwe Völker, Hans Grabe
University Medicine Greifswald, Department Of Psychiatry And Psychotherapy, Greifswald, Germany

Aims: White matter lesions (WML) emerge as a consequence of vascular injuries in the brain reflecting ischemic damage. While they are commonly observed in the aging brain, associations have been established with both neurodegenerative and neurological disorders such as dementia or stroke. Despite substantial efforts, biomarkers indicating WMLs are still lacking.
Methods: Leveraging data from the general population Study of Health in Pomerania (SHIP), our objective was to identify circulating micro-RNAs (miRNAs) associated with WMLs, thus providing a foundation for a comprehensive biological model. Different regression models as well as extensive biobank search and the usage of bioinformatic tools were used to disentangle the role of miRNAs on WML and elucidate the possible biological pathways.
Results: In 647 individuals we identified *hsa*-miR-425-5p as a key miRNA regulating various genes associated with WML, Alzheimer's Disease, and stroke, with particular emphasis on the *SH3PXD2A* gene. Furthermore, miR-425-5p was found to exert effects on immunological processes based on both human and mouse data. Through interaction analyses, additional noteworthy miRNAs associated with WMLs were identified, primarily moderated by factors such as sex or smoking status. All identified miRNAs exhibited a strong over-representation in neurodegenerative and neurological diseases, as well as pathways related to brain signaling and longevity.
Conclusions: In conclusion, we introduced *hsa*-miR-425-5p as a promising key regulator, implicating its involvement in immunological pathways. Mir-425-5p holds the potential to serve as an early indicator of WMLs shedding light on potential mechanisms and pathways to vascular dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0177 / #1343

Poster Topic: *Theme A: β-Amyloid Diseases / A01.p. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

DEFICIENCY OF MIR-223-3P RESULTS IN SEX-BIASED ELEVATION OF CLASS II MAJOR HISTOCOMPATIBILITY COMPLEX AND INFLAMMATORY GENES IN MICROGLIA

POSTERS: A01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Wang-Xia Wang[1,2], Paresh Prajapati[2], Urim Geleta[2]
[1]University of Kentucky, Spinal Cord And Brain Injury Research Center, Lexington, United States of America, [2]University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America

Aims: Class II major histocompatibility complex (MHC II) molecules are constitutively expressed on antigen presenting cells, including microglia. Aberrant class MHC II expression has been linked to various diseases and pathological conditions such as Alzheimer's Disease (AD) and Parkinson's disease (PD). MicroRNAs (miRNAs) play a key role in regulation of many biological and pathological events including immunity and inflammation. MiR-223-3p is an X-chromosome resided miRNA and its expression enriched in macrophages/microglia. However, the role of miR-223-3p in immunity and neuroinflammation in the context of neurodegenerative diseases is unknown. The objectives of the current study are to understand the regulatory role of miR-223-3p in immune and inflammatory response in microglia.
Methods: MiR-223-3p knockout (KO) and genetic background matched wildtype (WT), female and male mice were used in the studies. Microglia were isolated from the brain tissues of 3-week-old pups using a procedure that included density gradient centrifugation and further selection using the EasySep™ Mouse CD11b Positive Selection Kit. The isolated microglia were then cultured in Microglia culture media for 2 weeks before subject to treatments with interferon gamma and lipopolysaccharide. Following 12 hours incubation, microglia were then harvested, and RNAs were isolated for RT-qPCR quantification of MHC II genes and inflammatory markers.
Results: Our data demonstrated that deficiency of miR-223-3p resulted in elevation of MHC II master transactivator *CII2A*, MHC II (*H2-Aa, H2-Eb1*), and inflammatory (*NLRP3, CTSE, CD86, TNFα*, and *CCL17)* genes in both female and male miR-223-3p KO microglia. Moreover, the elevation of these genes was significantly more pronounced in female relative to male KO microglia.
Conclusions: The current study indicated that miR-223-3p regulates sex-biased expression of MHC II and inflammatory genes, which may contribute to the sexual dimorphic phenomenon observed in neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0178 / #1222

Poster Topic: *Theme A: β-Amyloid Diseases / A01.q. Disease Mechanisms, Pathophysiology: Autophagy, apoptosis, cell death*

EFFECTS OF A NOVEL NOTCH-SPARING PRESENILIN 1 MUTATION ON NEURONAL CELL DEATH

POSTERS: A01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

Isabel Bestard-Lorigados[1], Qinxin Zhu[2], Keenan Sterling[1], Fang Cai[2], Weihong Song[1,2]
[1]University of British Columbia, Psychiatry, Vancouver, Canada, [2]Wenzhou Medical University, Institute Of Aging, Wenzhou, China

Aims: Presenilin 1 (PS1) mutations are the primary cause of familial Alzheimer's disease (AD). These pathogenic mutations increase beta-amyloid levels while inhibiting Notch cleavage and signalling. Recently, our lab identified a unique mutation, called $PS1_{\Delta S169}$, that unlike other PS1 mutations, does not affect Notch signalling, making it an ideal therapeutic target. This study aims to investigate the mechanisms underlying $PS1_{\Delta S169}$'s effect on AD pathogenesis, particularly on neuronal cell death, using *in vitro* and *in vivo* models.
Methods: To examine these effects on neuronal cell death, PS1 plasmids corresponding to the PS1 wild-type (control) and five AD-related PS1 mutations, including the Notch-sparing $PS1_{\Delta S169}$, were transfected into a PS1-knockout neuro2A cell line called N2A-KO cells; thus, corresponding to six experimental groups. The *in vivo* study included three experimental groups corresponding to two knockin mouse models with two different PS1 mutations, including $PS1_{\Delta S169}$, compared to the wild-type control. Various molecular techniques were performed to determine how each PS1 mutation affects cell viability and neurotoxicity, including Western Blots for protein expression, and cell death assays.
Results: Overall, our findings indicate that these pathogenic PS1 mutations significantly decreased cell viability in N2A-KO cells, except in the MTS assay for $PS1_{\Delta S169}$. Furthermore, using N2A-KO cells, we found that the pathogenic PS1 mutations differentially affected cell death markers related to pyroptosis, apoptosis and autophagy. Similarly, synaptic markers were affected in our PS1 knockin models.
Conclusions: Our findings provide novel insights into the pathological effects of the PS1 mutations on different cell death pathways, and these results offer a foundation to further define how the Notch-sparing PS1 mutation affects neurotoxicity and neuronal death as part of the AD pathogenesis process.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0179 / #1760

Poster Topic: *Theme A: β-Amyloid Diseases / A01.q. Disease Mechanisms, Pathophysiology: Autophagy, apoptosis, cell death*

LIPID PEROXIDATION ELICITS DIVERGENT INFLAMMATORY RESPONSE PATHWAYS BETWEEN HUMAN NEURONS AND ASTROCYTES

POSTERS: A01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

Elizabeth Calzada[1], Kaitlyn Demeulenaere[1], Pamela Tapia[2], Brenton Laing[2], Eulim Kang[1], Yeka Aponte[2], Christopher Ramsden[1]
[1]National Institute on Aging, Lipid Peroxidation Unit, Laboratory Of Clinical Investigation, Baltimore, United States of America, [2]National Institute on Drug Abuse, Intramural Research Program, Baltimore, United States of America

Aims: Cellular exposure to lipid peroxidation products and reactive aldehydes such as acrolein and crotonaldehyde modifies lipids, proteins, and nucleic acids through chain reactions of free radical propagation and/or biomolecular modification of susceptible chemical groups. Lipid peroxidation, reactive lipid aldehydes, and protein carbonylation have been implicated in Alzheimer's disease pathogenesis; however, whether these by-products drive or are a result of neurodegeneration is unclear. Here, we compared biochemical signaling pathways to aldehyde exposure between human astrocytes and iPSC-derived neurons to evaluate response pathways between cell populations associated with disease pathology.
Methods: Human induced pluripotent stem cells were differentiated to cortical neurons. After neural maturation, cells were exposed to aldehydic products of lipid peroxidation, acrolein and crotonaldehyde, and chemicals known to stimulate lipid peroxidation, cumene hydroperoxide and RSL3, to evaluate cytotoxicity and the molecular effects of these toxins in culture. Parallel experiments were conducted in human post-mortem astrocytes as a comparison. Western blot analysis was used to quantitate expression of proteins involved in cell survival, death, and inflammatory response pathways.
Results: Notably, pre-differentiated neural stem cells were highly sensitive to aldehyde-induced cell death with an approximate median lethal dose of 12.5μM in acrolein and 100μM in crotonaldehyde while differentiated neurons were more resistant to crotonaldehyde and acrolein toxicity (median lethal dose ~200μM and 100μM, respectively). In comparison, astrocyte cultures displayed a median lethal dose of 50μM in acrolein and 200μM in crotonaldehyde. Exposure of astrocytes to chemical agents that perpetuate lipid peroxidation damage consistently elicited an acute heme-oxygenase 1 protein overexpression that was not pronounced in neurons.
Conclusions: This sensitized antioxidant response in astrocytes highlights their reactivity to ameliorate lipid peroxidation damage in the brain and suggests that sustained exposures may prolong activation of anti-inflammatory signaling pathways.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0180 / #2582

Poster Topic: *Theme A: β-Amyloid Diseases / A01.q. Disease Mechanisms, Pathophysiology: Autophagy, apoptosis, cell death*

AUTOPHAGIC ROLES OF TRIM22 AND ITS ASSOCIATION WITH ALZHEIMER'S DISEASE

POSTERS: A01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

Hansol Heo[1], Hyungsun Park[2], Myung Shin Lee[1], Jongyoon Kim[2], Juyeong Kim[1], Seongju Lee[2], Jaerak Chang[1,3]
[1]Ajou University School of Medicine, Department Of Biomedical Sciences, Suwon, Korea, Republic of, [2]Inha University, Department Of Anatomy, College Of Medicine, And Program In Biomedical Science & Engineering, Incheon, Korea, Republic of, [3]Ajou University School of Medicine, Department Of Brain Science, Suwon, Korea, Republic of

Aims: The primary aim was to investigate the role of TRIM22 in autophagy regulation. We sought to understand how TRIM22 contributes to the autophagic process and whether it has implications for neurodegenerative diseases.
Methods: We examined the effect of TRIM22 on autophagosome-lysosome fusion and the clearance of protein aggregates. These experiments involved molecular and cellular techniques to uncover the underlying mechanisms.
Results: The research revealed a novel function of TRIM22 in autophagy regulation. We found that TRIM22 plays a pivotal role in promoting autophagosome-lysosome fusion by facilitating the association between GABARAP family proteins and PLEKHM1. This, in turn, enhances the autophagic clearance of protein aggregates. Importantly, this function is independent of TRIM22's E3 ubiquitin ligase activity.
Conclusions: The findings demonstrate that TRIM22 acts as a crucial regulator of autophagy, orchestrating the fusion of autophagosomes and lysosomes by serving as a scaffold for autophagy-related proteins. This discovery has significant implications for our understanding of autophagy and its relevance to TRIM22-associated early-onset familial Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0181 / #856

Poster Topic: *Theme A: β-Amyloid Diseases / A01.q. Disease Mechanisms, Pathophysiology: Autophagy, apoptosis, cell death*

ELUCIDATING INTERACTIONS OF SLEEP LOSS AND PROTEOSTASIS FAILURE AS PREDICTORS OF COGNITIVE DECLINE IN ALZHEIMER'S DISEASE

POSTERS: A01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

Christopher Morrone[1], Darcy Wear[1,2], Arielle Tsang[1], Maria Akkawi[1,2], Wai Haung Yu[1,2,3]
[1]Centre for Addiction and Mental Health, Brain Health Imaging Centre, Toronto, Canada, [2]University of Toronto, Department Of Pharmacology And Toxicology, Toronto, Canada, [3]Centre for Addiction and Mental Health, Geriatric Mental Health Research Services,, Toronto, Canada

Aims: Proteostasis, including autophagy, and sleep are implicated in Alzheimer's disease (AD), especially in early disease stages. In light of recent evidence describing their linkage, our central aims are to interrogate the potential positive-feedback-loop between sleep loss and proteostasis impairment in AD, elucidating contributions to cognitive impairment, and to discern neuronal populations vulnerable to failed autophagy and rampant proteinopathy.
Methods: App^{NL-G-F}xMAPT double knock-in (dKI) mice were tested at 3 ages (4-, 8-, 12-month) and compared to MAPT (no major pathology) single knock-ins. Mice were surgically implanted with EEG/EMG headcaps and tested for sleep and neuronal function, before and after sleep disruption. Spatial learning, memory and executive function were assessed in the Barnes maze. Brain tissue was collected for immunohistochemistry.
Results: Immunohistochemistry for β-amyloid (6F3D) and tau (PHF1) demonstrated progressive accumulations, with cortical plaque and neuritic tau from 4-months, moderate hippocampal pathology at 8-months and robust accumulation at 12-months. Neuronal integrity (NeuN) in hippocampus and entorhinal cortex is preserved until the 12-month stage at which dKI mice exhibit loss compared to MAPTs. Sleep impairment including circadian arrhythmicity and loss of rapid eye movement sleep begins at 4-months in dKI mice (compared to MAPTs), and progressively declines over age, more prominently in female mice. Memory and executive function impairments follow sleep loss, starting at 12-months and more prominently in males. Intervening to disrupt sleep increases proteinopathy and disrupts proteostasis (p62) in mouse hippocampus. Conversely, activating autophagy therapeutically with trehalose improves sleep and memory.
Conclusions: Understanding the linkage between sleep and proteostasis, and neuronal populations vulnerable to autophagy impairments, is valuable to predict cognitive decline especially considering sex differences in the behavioural phenotype. Future work can evaluate modulating these processes for AD treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0182 / #2459

Poster Topic: *Theme A: β-Amyloid Diseases / A01.q. Disease Mechanisms, Pathophysiology: Autophagy, apoptosis, cell death*

CEREBROSPINAL FLUID ENDOTHELIN LEVELS ARE ASSOCIATED WITH PROAPOPTOTIC IMBALANCE IN ALZHEIMER'S DISEASE.

POSTERS: A01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

Caterina Motta, Chiara Giuseppina Bonomi, Francesca Bernocchi, Alessandro Martorana
University of Rome Tor Vergata, Memory Clinic, Rome, Italy

Aims: Endothelin-1 (ET-1) is a potent vasoconstrictive peptide, primarily secreted by endothelial cells, and is involved in mechanism of neuronal cell death. Our objective was to explore the association between cerebrospinal fluid (CSF) levels of ET-1, core Alzheimer's disease (AD) biomarkers and molecules linked to proapoptotic and antiapoptotic pathways.
Methods: CSF samples of 68 patients belonging to the AD continuum (ADc) and 16 healthy subjects (A-T-) were analyzed: amyloid-β 42 (Aβ42), amyloid-β 40 (Aβ40), Aβ42/Aβ40 ratio (amyR), phosphorylated-tau (p-tau), total tau (t-tau), ET-1, BCL-2, BCL-X, p53. Statistical analyses were calculated for non-parametric comparisons, Pearson's correlations, and mediation analyses.
Results: CSF levels of ET-1 were slightly higher in ADc, although not significantly different respect to A-T-, and no difference was found in CSF levels of BCL-2, BCL-X and p53. Age-adjusted Pearson's analyses in ADc patients showed a significant and positive correlation between ET-1 and p53 (rho=0.40, $p<0.001$), a negative correlation between ET-1 and BCL-X (rho=-0.46, $p<0.001$) and no correlation between ET-1 and BCL-2. The correlation analyses also showed a slight positive correlation between ET-1 and amyR (rho=0.25, p=0.040), as well as between amyR and p53 (rho=0.024, p=0.035). The mediation analysis confirmed a significant total effect of amyR on p53 (p=0.009) not mediated by ET-1 (ACME p=0.131), and a significant total effect of ET-1 on p53 (p=0.004) not mediated by amyR (ACME p=0.215).
Conclusions: We showed for the first time in AD patients that ET-1 CSF levels are associated to the activation of proapoptotic pathways and to the inactivation of antiapoptotic pathways. On the other hand ET-1 and p53 levels appear to be independently correlated with amyR, suggesting a possible compensatory role for amyloid peptides in restoring the apoptotic balance.

P0183 / #2055

Poster Topic: *Theme A: β-Amyloid Diseases / A01.q. Disease Mechanisms, Pathophysiology: Autophagy, apoptosis, cell death*

EVALUATING NEUROPROTECTIVE POTENTIAL OF BERGENIA LIGULATA AND NELUMBO NUCIFERA AGAINST ALUMINUM CHLORIDE-INDUCED NEUROTOXICITY IN RATS

POSTERS: A01.Q. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

Dr. Nilay Solanki, Yamini Patel
Ramanbhai Patel College of Pharmacy, Pharmacology, Changa, India

Aims: Neurodegenerative disorders are characterized by the accumulation of proteins with altered physicochemical characteristics in the brain and surrounding tissues, as well as the gradual loss of neurons. Neurotoxicity occurs when exposure to dangerous chemicals alters the nervous system's normal activities. This may eventually cause disruption or even the death of neurons, which are essential for sending and processing signals in the brain and other regions of the nervous system. Alzheimer's disease (AD) is a brain illness that gradually decreases one's capacity for remembering things, thinking, and doing even the most fundamental tasks. Our present research focused on the possible synergistic neuroprotective effects of Bergenia ligulata and Nelumbo nucifera in rats with neurotoxicity brought on by aluminum chloride.
Methods: The fourty six rats were separated into a number of groups. All groups got AlCl3, which caused neurotoxicity, with one exception. Then Nelumbo nucifera and Bergenia ligulata are supplied as a combined therapy. Numerous factors are assessed, including behavioral testing, AChE estimates, oxidative stress markers, and apoptotic markers.
Results: AChE was elevated by AlCl3 and then decreased throughout therapy. Additionally, it lowers the levels of GSH, SOD, and catalase while raising MDA levels. The opposite result of the therapy was a decrease in oxidative stress. AlCl3 also affects apoptosis by raising caspase-3 levels while decreasing Bcl-2 levels. By reducing caspase-3 levels and improving Bcl-2 levels, the therapy decreased apoptosis pathways.
Conclusions: This leads to the conclusion that Bergenia ligulata and Nelumbo nucifera combined therapy proved neuroprotective in AlCl3-induced neurotoxicity in rats by reducing AChE level, caspase-3 levels and improving Bcl-2 levels.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0184 / #2448

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

THE ASSOCIATION BETWEEN FRAILTY INDEX AND ALZHEIMER'S DISEASE BIOMARKERS.

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Simona Buscarnera[1], Federica Ribaldi[2], Valentina Garibotto[2], Giovanni Frisoni[3]
[1]Università la Sapienza di Roma, Dipartimento Di Neuroscienze Umane, Roma, Italy, [2]Geneva Memory Center, Department Of Rehabilitation And Geriatrics, Geneve, Switzerland, [3]University Hospitals of Geneva, Memory Centre, Division Of Geriatrics And Rehabilitation, Geneva, Switzerland

Aims: Frailty has been associated with an increased risk of dementia. Frailty represents the overall organism's aging characteristics and it can be measured using Frailty index (FI). Alzheimer's disease (AD) is the primary cause of dementia. Its pathology could be assessed through in vivo biomarkers as β-amyloid (A) and phosphorylated tau (T). The aim of this study was to investigate the association between frailty and AD biomarkers in a Memory clinic population.
Methods: Data of 269 patients were collected from the Memory Center of the Geneva University Hospital, including individuals cognitively unimpaired, with mild cognitive impairment and dementia. A 36-items FI was developed. A and T positivity, assessed through PET amyloid and tau when available, or CSF ab42 and ptau if missing, was dichotomized and used as A+/A- or T+/T-. Pearson correlations was used to investigate the association between demographics and clinical features and FI. Mann-Whitney test was used to explore the difference of FI in A and T profiles.
Results: Participants had a mean age of 70 (SD 8.6) years, mean education of 14(SD 4) years, and 52% were women. We found a significant positive correlation between age ($r=0.25$, $p<0.001$), depression and anxiety ($r=0.17$, $p=0.008$) and FI, and a trend toward negative correlation between education and FI($r=-11$, $p=0.081$). FI was higher in subjects A- and T- compared to A+ and T+ separately ($p<0.01$).
Conclusions: The results show that FI increases with age in different populations. Cognitive resilience, assessed using education as a proxy, seems to decrease with high FI. FI is higher in people with low levels of brain AD pathology. Next steps include to assess the prognostic value of FI in persons with or without AD biomarkers positivity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0185 / #2162

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

LATE SPLENIC B-CELL DYSREGULATION IN APP/PS1 MICE

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Amit Fruitman, Karin Vardy, Sophie Shirenova, Ravit Madar, Eitan Okun
Bar-Ilan University, Life Sciences, Ramat-Gan, Israel

Aims: The role of adaptive immunity in Alzheimer's disease (AD) remains poorly understood. To date, most attention has addressed T cells, as the CSF and brain parenchyma of AD patients contain potentially harmful and clonally expanded CD8 T cells, especially around amyloid-b (Ab) related plaques. B cells, however, have thus far been thought of as beneficial in AD due to their involvement in humoral responses against Ab. The presence of B cells was recently shown to exacerbate the inflammatory state of disease-associated microglia (DAM). In addition, the presence of B cells or their immunoglobulins in the brain parenchyma is inversely associated with microglial TGF-b1 expression, which is detrimental, as microglial TGF-b1 signaling is critical for tissue homeostasis. Because of their importance in phagocytosis and inflammation suppression, and contrary to current understanding, we hypothesize that parenchymal B cells exacerbate the over-activated state of DAM, thereby promoting AD progression.
Methods: We have characterized age-associated alterations in B cell sub-sets in APP/PS1 mice, which model early onset AD by immuno-profiling sub-sets of B cells using spectral flow cytometry in the blood, spleen, and deep cervical lymph nodes (dcLNs), brain and meninges.
Results: While no significant differences were observed in 12m old APP/PS1 mice compared with WT mice, significant age-associated changes were observed in splenic B cells of 18m old APP/PS1 mice.
Conclusions: Since significant Ab-related pathology appears relatively early in these mice (4 months), these changes could appear relatively late in splenic B cell subsets as secondary to changes in CNS draining lymph nodes such as the dcLNs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0186 / #1885

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

DNA DAMAGE AND NEURONAL SENESCENCE: DIFFERENTIAL VULNERABILITIES OF NEURONS IN DIFFERENT CORTICAL LAYERS

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Gnanesh Gutta, Jiaan Xie, Eliana Brenner, Rody Kingston, Fulin Ma, Karl Herrup
University of Pittsburgh School of Medicine, Neurobiology, Pittsburgh, United States of America

Aims: The risk of Alzheimer's disease (AD) goes up with age as does the accumulation of unrepaired DNA damage. Increased genomic damage increases pressure to re-enter a cell cycle, which leads to expression of senescence markers. Our objective is to uncover how these events link to the pathogenesis of AD.
Methods: Immunohistochemistry for amyloid (6E10), DNA damage (53BP1,
Results: In unaffected human control samples, neurons with DNA damage increased in density with increasing distance from the pial surface. In AD, this pattern was overlaid with a substantial increase in DNA damage in the more superficial cortical layers. The distribution will be correlated with the location of amyloid plaques which varies from region to region. Senescence markers were common in both control and AD neurons, but their subcellular localization changed. For example, the p16 marker was nuclear in controls; in AD the staining shifted cytoplasmic but remained perinuclear. While the expression of senescence markers occurred in the absence of DNA damage, DNA damage was virtually always accompanied by expression of senescent markers.
Conclusions: There is a natural gradient of DNA damage in the aging cerebral cortex. The distribution of senescent markers was broader than expected and was most prominent in neurons with DNA damage. This correlation suggests that the two processes are related but in vitro studies will be required to rigorously determine if this reflects a causal pathway.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0187 / #530

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

AMYLOID-BETA: LINKING ALZHEIMER'S PATHOGENESIS TO PERIPHERAL METABOLIC DYSFUNCTION

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Ju-Hee Kang, Keren Mantik, Sujin Kim, Sohee Moon, Bonsang Gu
College of Medicine, Inha University, Pharmacology, Michuhol-gu, Korea, Republic of

Aims: Amyloid precursor protein is expressed both in the central nervous system and peripheral organs, including skeletal muscle and adipose tissues. While midlife obesity is associated with development of dementia, weight loss is linked to dementia severity and progression of Alzheimer's disease (AD). Moreover, AD is often accompanied by sarcopenia and/or cachexia. Nevertheless, the potential involvement of pathogenic amyloid-beta$_{1\text{-}42}$ (Aβ) in the dysfunction of metabolic organs remains unclear. In this study, we examined the effect of Aβ on myocyte and adipocyte dysfunction.
Methods: We treated C2C12 and 3T3-L1 cells with Aβ-oligomer (Aβo) to assess its impact on the metabolic function of peripheral tissues. Our evaluation encompassed effects of Aβo on cell differentiation, signaling pathways contributing to myogenesis/adipogenesis, muscle atrophy and lipolysis/lipogenesis, myokine/adipokine expression, and mitochondrial function. Additionally, in animal models, we measured Aβ concentration in skeletal muscle and white adipose tissue.
Results: Aβo inhibited the differentiation of C2C12 and downregulated the levels of myogenic transcriptional factors in C2C12 myotubes. Aβo-treated myoblasts induced cellular senescence, as measured by SA-β-gal staining. Specifically, Aβo-treated muscle cells displayed significant pathogenic changes, including mitochondrial dysfunction, apoptosis, and cellular senescence, which are common mechanisms observed in AD and sarcopenia. In differentiated 3T3-L1 adipocytes, Aβo reduced lipid accumulation, which was accompanied by upregulation of lipolysis signaling pathways. In addition, Aβo induced ER stress signaling, inflammatory adipokine expression, and disrupted autophagy progression.
Conclusions: Our results suggest that an increase in Aβ42 levels in peripheral organs as the AD progresses may accelerate sarcopenia/cachexia. Dysregulation of peripheral metabolic organs in advanced AD patient may lead to a "vicious cycle", wherein AD progresses more rapidly in sarcopenic/cachexic individuals.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0188 / #2635

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

IDENTIFICATION OF THE ENZYMATIC CLEAVAGE RELATIONSHIP BETWEEN ANTI-AGING PROTEIN A-KLOTHO AND ALZHEIMER'S DISEASE BIOMARKER BACE1

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Xiang Gao, Zuoli Sun, Yuhong Li, Rena Li
Capital Medical University, Beijing Anding Hospital, Beijing, China

Aims: The anti-aging protein α-Klotho is known to be involved in longevity and various age-related diseases, including cognitive impairment. BACE1, an important enzyme associated with the pathological process of Alzheimer's disease (AD), serves as a biomarker for predicting changes in cognitive function. Although both proteins are closely linked to age-related cognitive function, the mechanism of their interaction remains unclear.
Methods: This study included elderly (n = 30, 65-80 years) and young (n = 45, 30-40 years) healthy adults. The cleavage product was identified using Coomassie blue staining, Western blot, and MALDI-TOF mass spectrometry. Plasma levels of α-Klotho and BACE1 were measured using ELISA.
Results: After the digestion reaction between BACE1 and α-Klotho, a new protein product was identified. BACE1 cleaved the α-Klotho peptide 951-981 at the F-T residues. When the FT residues in the peptide were replaced with KK, BACE1 was unable to cleave the mutant peptide. The plasma levels of soluble α-Klotho protein were significantly lower in elderly participants than in young participants ($P < 0.0001$). However, there was no significant difference in plasma BACE1 protein levels between elderly and young participants ($P = 0.164$). In elderly healthy adults, there was a significant positive correlation between plasma BACE1 protein level and α-Klotho protein level ($P = 0.009$, $r = 0.469$), while this correlation was not observed in young healthy adults ($P = 0.170$, $r = -0.208$).
Conclusions: Anti-aging proteinα-Klotho is the substrate of BACE1 with special cleavage site FT, BACE1/α-Klotho pathway may serve as a common axis for age-related cognitive decline.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0189 / #1384

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

PRESENILIN1ΔE9 MUTATION IN THE MOUSE: A MODEL OF EARLY COGNITIVE AGING?

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Nathalie Macrez, Azza Sellami, Fanny Tixier, Aline Marighetto
Université de Bordeaux, Neurocentre Magendie - Inserm U1215, Bordeaux, France

Aims: While Presenilin1 (PSEN1) ΔE9 mutation produces early familial forms of Alzheimer's disease (AD), it does not produce AD phenotype in mice. However, co-expression of PSEN1ΔE9 mutation accelerates the appearance of AD-like (cognitive and amyloid) phenotype in the APPswe mouse model. In addition, the PSEN1 mutation was found to decrease cerebral vascular reactivity in middle-aged mice (Toussay et al 2017) resembling those appearing during Cerebral Small Vessel Disease and age-related dementia (Staszewski et al 2021, Li et al 2020). Hence, we hypothesized that PSEN1 mutation may accelerate brain aging.
Methods: To test this hypothesis, we compared neurocognitive changes induced by combined mutations of APP and PSEN1 and by mutation PSEN1 alone to those associated with normal aging in mice. To evaluate cognitive alterations, the animals were trained in a radial-maze task of working memory which interweaves memory and active forgetting to mimic and study peculiarities and complexity of memory function in everyday life (Al Abed et al, 2016; Stevens et al, 2023).
Results:). In this task, middle-aged (10-11 months) PSEN1 mutants display an aging-like cognitive impairment compared to their littermate controls, performing the task at a level close to old (19-20 months) controls, while APP/PS1 mice at young age (5-6 month) display a more severe, AD-like cognitive impairment. Preliminary results of immunohistochemical analyses of Fos protein expression (as a marker of neuronal activation) and vascular network performed post-training in the hippocampus of the same animals also indicate that PSEN1 mutation induces some functional alterations similar to those observed during normal aging.
Conclusions: Altogether our findings suggest that PSEN1 mice could mimic accelerated aging and provide a model of early cognitive aging that turns into AD-like dementia when PSEN1 is co-expressed with human APP.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0190 / #2385

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

AMYLOID BETA OLIGOMERS INDUCE SENESCENCE IN HUMAN FIBROBLASTS – INFLUENCE OF HISTONE DEACETYLASE INHIBITORS

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Daniela Marinho[1], Ildete L. Ferreira[1], George Kelly[2], Penny Lovat[3], Viktor Korolchuk[2], A. Cristina Rego[1]
[1]University of Coimbra, Cnc-center For Neuroscience And Cell Biology, Coimbra, Portugal, [2]Newcastle University, Biosciences Institute, Newcastle upon Tyne, United Kingdom, [3]Newcastle University, Institute Of Cellular Medicine, Newcastle upon Tyne, United Kingdom

Aims: Aging is known to be the most important risk factor for sporadic form of Alzheimer's disease (AD). Evidence of post-mitotic neuronal and glial senescence has been recently described in AD. Senescence, a cell phenotype of aging, is characterized by irreversible cell-cycle arrest, pro-inflammatory phenotype, senescence-associated-secretory-phenotype (SASP), mitochondrial dysfunction, among others. Interestingly, mitochondrial dysfunction drives and maintains cell senescence, while cell senescence inducers can promote senescence-associated mitochondrial dysfunction. Moreover, transcription regulation of pro-inflammatory cytokines drives SASP. Therefore, we aimed to evaluate the potential efficacy of transcriptional modifications exerted by histone deacetylase inhibitors (HDACis) in rescuing cell senescence in AD cell models.
Methods: Cell senescence was induced by exposing human fibroblasts to amyloid beta1-42 peptide oligomers (AbetaO) for five consecutive days and the effect of HDACis (sodium butyrate [SB] and tacedinaline [Tac]) was analysed for 24h after AbetaO exposure. HDACis were also tested prior to AbetaO exposure for 24h in human fibroblasts and mouse hippocampal-derived HT22 cells. AD-like senescence phenotype was evaluated by following several cellular markers of senescence by immunocytochemistry. We also assessed mitophagy using mito-Keima, and the transcription activity of key senescence modulators and mRNA levels of selected target genes.
Results: Our results evidence a decrease in Ki67 labelling, along with increased p21 and nuclei area, which was counteracted by SB, and at a lower extent by Tac. Both HDACis prevented the decrease in mitophagy induced by 24h exposure to AbetaO. Under similar conditions, Tac was also shown to reduce NFAT transcriptional activity, which regulates p21. Moreover, Tac was shown to control the mRNA levels of proteins relevant for mitochondrial calcium uptake.
Conclusions: Our data support that HDACis may act as serotherapeutic compounds in AD cell models.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0191 / #2417

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

GENOMIC INSIGHTS INTO AGE-RELATED CHANGES IN FRONTAL CORTEX: IMPLICATIONS FOR NEURODEGENERATIVE DISEASES AND STRESS RESILIENCE

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Ashlesh Patil[1], Satyendra Tripathi[2], Vishwajit Deshmukh[3], Jaya Tripathy[4]
[1]AIIMS Nagpur India, Physiology, Nagpur, India, [2]AIIMS Nagpur, Biochemistry, Nagpur, India, [3]AIIMS Nagpur, Anatomy, Nagpur, India, [4]AIIMS Nagpur, Community Medicine, Nagpur, India

Aims: Brain aging is a gradual process characterized by cognitive decline and an increased susceptibility to neurodegenerative diseases. This study aims to investigate the genetic and pathway changes associated with aging in the frontal cortex.
Methods: Two independent datasets were analysed from the Gene Expression Omnibus (GEO) database, GSE53890 for discovery and GSE11882 for validation. Gene expression profiles of adult human brain samples from frontal cortical region were compared between young (<60 years) and old (>60 years) using unpaired t test with Benjamini & Hochberg false discovery rate for multiple testing corrections.
Results: 38 genes were significantly up/downregulated with age in the discovery dataset. 8 genes *(AQP1, CD44, FKBP5, GFAP, HBA2, HBB, SLC14A1, TXNIP)* out of 18 genes in discovery dataset were also found to be significantly upregulated with age in the validation group. 20 genes *(ARPP21, C11orf87, CAMKK2, CBLN4, CRH, FREM3, GPR26, HS6ST3, KCNV1, LINC00507, MAL2, MFSD4A, NECTIN3, NGEF, PAK1, PPP4R4, PRKCB, RGS4, SSTR1, VIP)* were significantly downregulated with age in both datasets.
Conclusions: Genes implicated in neurodegenerative/neuropsychiatric diseases like Alzheimer Disease (*CD44, TXNIP*), Huntington disease (*SLC14A1*), Parkinson's disease (*ARPP21*), Schizophrenia (*CAMKK2*) are altered with age >60 years. Increased *FKBP5* in frontal cortex with age suggests better ability in handling of stress and reducing PTSD like events.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0192 / #2172

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

STEREOLOGICAL QUANTIFICATION OF THE IMPACT OF AGING ON DOPAMINERGIC AND CHOLINERGIC NEURONS

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Hannah Phelps[1], Merritt Reece[1], Matthew Burns[2]
[1]University of Florida, Neuroscience, Gainesville, United States of America, [2]University of Florida, Neurology, Gainesville, United States of America

Aims: Parkinson's disease (PD), Dementia with Lewy Body (DLB) and Multiple System Atrophy (MSA) are common and rapidly growing neurodegenerative disorders, with age being the major risk factor. As a result, aged animal models have become increasingly valuable as representative models of disease. Loss of dopaminergic and cholinergic neurons in the substantia nigra and basal forebrain, respectively, are pathological hallmarks of PD, DLB, and MSA, but have also been associated with normal aging, making the use of aged animals for quantification of cell loss associated with disease potentially problematic. Comparing dopaminergic and cholinergic neurons in the young and aged rat brain using unbiased stereological quantification has not been well studied. We aimed to quantify the dopaminergic and cholinergic neurons in the substantia nigra and basal forebrain, respectively, in young and aged rats.
Methods: Using 5 month and 23-month-old Fischer 344 x Brown Norway F1 hybrid rats of both sexes, immunofluorescence and stereology was completed. Immunofluorescence was used to stain for tyrosine hydroxylase (TH) and choline acetyltransferase (ChAT), dopaminergic and cholinergic cell bodies were quantified using the Optical Fractionator probe within Microbrightfield's Stereoinvestigator software.
Results: Preliminary data suggest that the number of dopaminergic cells in the substantia nigra and ventral tegmental area decrease with age, indicating the aging process in rats is similar to that in humans. In addition, female rats possessed more dopaminergic cells than male rats.
Conclusions: These results inform future stereological studies in age-related disease models, particularly PD, DLB, and MSA studies. Although cell loss has been used in animal models as a marker of neurodegenerative disease, these data suggest that there may be age and sex-dependent cell loss to consider in animal models of disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0193 / #1146

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

THE ROLE OF EXTREMELY LONG-LIVED PROTEINS IN AGING AND ALZHEIMER'S DISEASE

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Jeffrey Savas, Nalini Rao, Ewa Bomba-Warczak, Anika Wilen
Feinberg School of Medicine, Northwestern University, Neurology, Chicago, United States of America

Aims: Loss of proteostasis is a hallmark of aging, and aging is the greatest risk factor for Alzheimer's disease (AD). Deterioration in function and accumulation of damage to the proteome are to a large extent repaired by protein turnover. These turnover mechanisms are particularly important in long-lived postmitotic neurons, which cannot dilute toxic proteins through cell division. We aimed to identify extremely long-lived proteins (ELLPS) that persist for several months or longer across the aging continuum in wild-type mice and in AD mouse models. We hypothesize that these ELLPs represent key points of vulnerability to the decline of the aging proteome and critical substrates of amyloid pathology.
Methods: To identify ELLPs, we used whole-animal metabolic stable isotope labeling of wild-type and App KI mice combined with bottom-up proteomic analysis using liquid chromatograph-tandem mass spectrometry. The results were verified and followed up using biochemical, molecular, and electrophysiological methods.
Results: In wild-type mice we discovered that the brain proteome uniquely undergoes dynamic global turnover fluctuations during aging compared to heart and liver tissue. Parallel analyses of the insoluble fraction revealed that several protein sub-complexes experience impaired turnover, in part due to misfolding. Finally, we discovered that age-associated fluctuations in the activity of the ubiquitin proteasome system are linked to the turnover of the catalytic core subunits. In App KI mice, the turnover of presynaptic proteins is selectively impaired in the early stages of Abeta accumulation. Synaptic vesicle (SV)-associated proteins, have elevated levels, misfold in plaque-independent manner, and interact with APP and Abeta. We also found an enlargement of the SV pool and an increase in presynaptic potentiation.
Conclusions: The identification of ELLPs provides an opportunity to uncover Achillies heals of aging and initial substrates of amyloid pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0194 / #1889

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

SEX AND AGE SPECIFIC CSF PROTEOMIC SIGNATURES IDENTIFY DISTINCT CLUSTERS LINKED TO NEURODEGERATION

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Da Hun Seo[1], Cheolmin Lee[2], Gyujin Heo[3], Jigyasha Timsina[3], Lihua Wang[3], Ruiz Agustin[4], Taesung Park[1], Carlos Cruchaga[3], Yun Ju Sung[3]
[1]Seoul National University, Department Of Statistics, Seoul, Korea, Republic of, [2]Northwestern University, Health Sciences Integrated Program, Chicago, United States of America, [3]Washington University School of Medicine, Department Of Psychiatry, St. Louis, United States of America, [4]Universitat Internacional de Catalunya, Ace Alzheimer Center Barcelona, Barcelo, Spain

Aims: Sex and age are major risk factors for neurodegeneration. Studies on age-related molecular changes in plasma provided insights into age-related disease biology. Cerebrospinal fluid (CSF) proteomics can reveal additional insights into brain aging and neurodegeneration.
Methods: Using over 7,000 proteins in CSF obtained from 998 cognitively normal individuals (43-91 years old) across three cohorts (Knight-ADRC, ADNI, FACE), we performed regression to identify sex and age associated proteins (at FDR < 0.05). Similarly, plasma proteome from 1,382 individuals in Knight-ADRC was examined. Weighted gene co-expression network analysis was performed to group proteins with similar sex and aging trajectories. Enrichment for cell-type, disease ontology, and gene ontology was also performed.
Results: We identified 4,682 CSF proteins associated with age and 1,587 proteins with sex difference (1,172 affected by both). Aging effects and sex differences in CSF proteome were weakly correlated with those in plasma proteome. Network analysis identified 16 modules. Module 2 had 723 proteins (including APOE, APP; higher in females and decreasing with ages), enriched in microglia and macrophage. Along with negative regulation of apoptotic process, they were related to cerebral amyloid angiopathy, subarachnoid hemorrhage, and multi-infarct dementia (FDR = 0.029). Module 6 had 234 proteins (including LRRK2, SERPINA3, TREML2) with the strongest sex difference (high in males) and increasing with ages, enriched in endothelial cells. Along with complement activation and phagocytosis, they were related to many diseases including complement deficiency (FDR=2.14E-09), ischemic stroke (FDR=2.0E-7) and mild cognitive disorder (FDR=8.4E-03).
Conclusions: We identified two clusters of CSF proteins with sex and aging signatures related to neurodegeneration, which also show enrichment for other aging diseases. They explain comorbidity across multiple aging diseases, which may help promoting healthy aging and longevity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0195 / #332

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

DEVELOPMENT OF DEMENTIA AND OPIOID EXPOSURE FOR NON-CANCER PAIN CONTROL: A POPULATION-BASED COHORT STUDY

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Tak Youn[1], Hyong Sook Jun[2], Youngmin Cho[1]
[1]Dongguk University International Hospital, Psychiatry, Goyang, Korea, Republic of, [2]Baewha University, Dept. Of Office Administration, Seoul, Korea, Republic of

Aims: Opioids are linked to cognitive impairment and induce neurotoxicity by modulating various cognitive processes through the mu- and kappa-opioid receptor-ligand systems, as well as multiple cellular and molecular mechanisms. Therefore, opioid exposure can influence the development of dementia. In a previous cohort study(Moradi-Lakeh et al. 2015), individuals with the highest level of exposure to opioids had a slightly elevated risk of developing dementia compared to the general population. We aim to investigate the association between opioid exposure for non-cancer pain control and the development of dementia in patients with chronic non-cancer pain in South Korea.
Methods: This study is a population-based cohort study using big data from National Health Insurance Service database in South Korea. From 2017 to 2021, patients diagnosed with musculoskeletal diseases and chronic non-cancer pain but without psychiatric diseases were included. Patients who had been regularly and continuously prescribed opioids for ≥90 days were classified as opioid users.
Results: A total of 1,176,057 patients with chronic non-cancer pain without psychiatric diseases were included in the final analysis, and among them, 19,375(1.64%) were opioid users. A total of 32,073(2.72%) patients with chronic non-cancer pain were newly diagnosed with dementia from January 2017 to December 2021. Opioid users showed a 15% increased likelihood of developing dementia in comparison to opioid-naïve patients. In addition, compared to opioid-naïve patients, opioid users showed a 16% higher risk of developing Alzheimer's disease and a 15% higher risk of unspecified dementia. However, no significant differences were observed for vascular dementia.
Conclusions: Chronic non-cancer pain patients without psychiatric illness who were opioid users had a higher risk of developing alzheimer dementia compared to opioid-naïve patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0196 / #2291

Poster Topic: *Theme A: β-Amyloid Diseases / A01.r. Disease Mechanisms, Pathophysiology: Aging*

PLASMATIC CLUSTERIN AS A PERIPHERAL BIOMARKER OF LATE ONSET ALZHEIMER'S DISEASE

POSTERS: A01.R. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Dina Zekry[1], Benjamin Tournier[2], Kelly Ceyzériat[2,3,4], Antoine Marteyn[1], Quentin Amossé[5], Aurélien Badina[5], Stergios Tsartsalis[2], Francois Herrmann[1], Philippe Millet[2]
[1]Division of Internal Medecine for the aged/Geneva University Hospitals, Rehabilitation And Geriatrics, Thonex, Switzerland, [2]University Hospitals of Geneva, Psychiatry, Geneva, Switzerland, [3]University of Geneva, Cibm Center For Biomedical Imaging, Geneva, Switzerland, [4]University of Geneva, Laboratory Of Child Growth And Development, Geneva, Switzerland, [5]University of Geneva, Psychiatry, Geneva, Switzerland

Aims: Background: Early diagnosis of late onset Alzheimer's disease (LOAD) by peripheral biomarkers remains a challenge; many have been proposed, but not have been evaluated in a prospective manner. Clusterin (CLU), a chaperone protein expressed in the brain and found in relatively high concentrations in plasma is a promising candidate. CLU contributes to the elimination of beta amyloid, is associated to neurofibrillary tangles, is involved in apoptosis and neuroinflammation and is associated to the genetic risk for LOAD. **Objectives:** To assess the risk of developing LOAD based on the dynamics of plasma CLU.
Methods: Methods: A longitudinal measurement of CLU was performed in 4 cohorts of 10 old individuals (interval between measurements 28.3±14.9 months) including healthy controls, MCI and AD. Comparison was performed between groups of subjects that presented a cognitive decline vs those that remained stable.
Results: Results: Repeated two-way ANOVA showed an effect of group, time and the group x time interaction. At baseline, controls have the same CLU rates, whether they subsequently convert to AD or not. Control and MCI patients did not differ in CLU concentrations. In contrast, conversion from control or MCI status to AD was both associated with a significant increase in CLU concentration ($p<0.0001$). Individuals that remained in the same diagnostic category showed no significant CLU changes. To validate that the elevation in CLU is associated with conversion to AD, a replication study showed, in a second group MCI patients converting to AD in the follow-up (20.3±9 months) that CLU levels increased in 16/19 individuals (fold change: 3.5± 2.74; $p<0.01$).
Conclusions: Plasma CLU seems to be a promising marker of cognitive decline, and its association with AD may be a useful complementary diagnostic tool.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0197 / #1021

Poster Topic: *Theme A: β-Amyloid Diseases / A01.s. Disease Mechanisms, Pathophysiology: Microbiome*

CHARACTERIZATION OF THE HUMAN MICROBIOME ISOLATES ON HOST PROTEOSTASIS REVEALS PROTEOTOXIC AND PROTEOPROTECTIVE BACTERIA THAT NON-SPECIFICALLY AFFECT PROTEINS ASSOCIATED WITH NEURODEGENERATIVE DISEASES

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

Alyssa Walker, Rohan Bhargava, Michael Bucher, Amanda Brust, Daniel Czyz
University of Florida, Microbiology & Cell Science, Gainesville, United States of America

Aims: Neurodegenerative protein conformational diseases (PCDs), such as Alzheimer's, Parkinson's, and Huntington's, are a leading cause of death and disability worldwide and have no known cures or effective treatments. Emerging evidence suggests a role for the gut microbiota in the pathogenesis of neurodegenerative PCDs; however, the influence of specific bacteria on the culprit proteins associated with each of these diseases remains elusive, primarily due to the complexity of the microbiota. We employed the *Caenorhabditis elegans* model to characterize the effect of all culturable bacterial isolates from the Human Microbiome Project. The aim of this study is to decipher the role of the identified proteotoxic and proteoprotective bacteria on disease pathogenesis.
Methods: In the present study, we employed a single-strain screening approach to identify human bacterial isolates that enhance or suppress the aggregation of culprit proteins and the associated toxicity in *C. elegans* expressing Ab_{1-42}, a-synuclein, and polyglutamine tracts.
Results: We reveal the first comprehensive analysis of the human microbiome for its effect on proteins associated with neurodegenerative diseases.
Conclusions: Our results suggest that bacteria affect the aggregation of metastable proteins by modulating host proteostasis rather than selectively targeting specific disease-associated proteins. These results reveal bacteria that potentially influence the pathogenesis of PCDs and open new promising prevention and treatment opportunities by altering the abundance of beneficial and detrimental microbes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0198 / #2138

Poster Topic: *Theme A: β-Amyloid Diseases / A01.s. Disease Mechanisms, Pathophysiology: Microbiome*

GUT MICROBIAL PERTURBATIONS AFTER THE ONSET OF AMYLOID PLAQUE FORMATION EXACERBATES PATHOLOGIES IN A MOUSE MODEL OF AB AMYLOIDOSIS.

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

Wade Self, Emily Franke, David Weiner, David Holtzman
Washington University School of Medicine, Neurology, Saint Louis, United States of America

Aims: Multiple studies have corroborated the phenomenon that the presence of gut bacteria early in life regulates amyloid plaque formation and associated neuroinflammation in transgenic mouse models of Aβ amyloidosis. In this study, we aimed to understand how gut microbiota influence the progression of amyloid-associated pathologies at an age where amyloid plaques are present in the mouse brain.
Methods: We treated 5 month old APPPS1-21 mice daily by oral gavage with water or a broad-spectrum antibiotics cocktail containing kanamycin, gentamicin, colistin, vancomycin, and metronidazole for three consecutive days. On the fourth day, we administered either normal drinking water to water-gavaged mice or water containing the antibiotics cocktail at 1/50th the concentration administered via oral gavage to antibiotics-gavaged mice. At 7 months of age, animals were sacrificed and analyzed for changes in amyloid plaque-associated pathologies.
Results: Across independent experiments by two separate investigators, APPPS1-21 mice treated with antibiotics showed increases in amyloid plaque burden and dense-core plaques, neuritic dystrophy, microgliosis and astrocytosis compared to water-treated mice. We observed these results in both male and female mice. Additional analyses will aim to understand changes in gut microbial composition and function and biological pathways after antibiotics treatment that influences the increase in amyloid load.
Conclusions: These findings suggest that the alteration of the gut microbiome induced by antibiotics in adult mice with established amyloid pathology differentially impacts amyloid plaque formation and neuroinflammation compared to manipulations earlier in the animal lifespan. Studying the effects of the altered microbiome in this experimental paradigm may suggest new pathways as to how microbial dysbiosis contributes to AD pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0199 / #314

Poster Topic: *Theme A: β-Amyloid Diseases / A01.s. Disease Mechanisms, Pathophysiology: Microbiome*

HSV1 INFECTION TRIGGERS THE PRODUCTION OF AMYLOID-BETA (AB) PROTEIN IN BOTH MOUSE AND HUMAN NEURONAL CELLS

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

Ya Gao[1], Ahmad Mahmoudikouhi[1], Ignacio Agúndez[2], Kathlyn Laval[1]
[1]Ghent university, Department Of Translational Physiology, Infectiology And Public Health, Merelbeke, Belgium, [2]Universidad Politécnica De Madrid, Ingeniería Agronómica, Alimentaria Y De Biosistemas, Madrid, Spain

Aims: Alzheimer's Disease (AD) is a degenerative brain disease and the most common cause of dementia affecting 55 million people worldwide. So far, there is no cure and current treatments are not effective in delaying the progression of the disease. The cause of AD is unknown, but there is growing evidence suggesting that viruses, in particular, Herpes simplex virus type 1 (HSV1), are involved in the pathogenesis of AD. HSV1 is a ubiquitous human pathogen that commonly causes cold sores. This DNA virus initiates a lifelong latent infection in the peripheral sensory neurons of its host. The infection can be reactivated periodically by various factors, including sun exposure or stress. Here, we hypothesize that HSV1 directly contributes to the initiation of AD by specifically triggering the production of amyloid-beta (Aβ) in neurons.
Methods: To test this hypothesis, we compared the kinetics of HSV1 replication with the kinetics of Aβ protein production in both mouse (N2A) and human (SY-SY5Y) neuronal cells. This work was performed by viral titration and immunofluorescence staining techniques.
Results: We found that HSV1 induces the production of Aβ protein in both cell types starting from 9 hpi. Interestingly, no Aβ protein was expressed in mock-infected cells. The Aβ protein accumulated in neurons at later stage of infection (24 hpi) and was found to colocalize with HSV1 immediate-early (ICP0) viral protein in the cell cytoplasm. Finally, we demonstrated that the Aβ protein production efficiency in neuronal cells was viral strain-dependent.
Conclusions: Overall, our findings demonstrate that HSV1 infection initiates the production of Aβ protein in both mouse and human neuronal cells. These results provide increase support for the direct role of HSV1 in the pathogenesis of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0200 / #2210

Poster Topic: *Theme A: β-Amyloid Diseases / A01.s. Disease Mechanisms, Pathophysiology: Microbiome*

ASSOCIATION BETWEEN COGNITIVE AND ORAL STATUS AND MARKER GERMS OF PERIODONTITIS IN PERSONS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

Katharina Häberle[1], Christiane Von Ohle[2], Christoph Laske[3]
[1]University Clinic for Dentistry, Oral an Maxillofacial Surgery, Dental Conservation, Tübingen, Germany, [2]University Clinic for Dentistry, Oral and Maxillofacial Surgery, Dental Conservation, Tübingen, Germany, [3]Eberhard Karls University, Department Of Psychiatry And Psychotherapy, Tübingen, Germany

Aims: To investigate the association of marker germs causing periodontitis and the severity of cognitive impairment.
Methods: In the present study we examined 97 individuals with mild cognitive impairment (MCI), Alzheimer's disease (AD) and controls for their oral state and presence and severity of periodontitis. A sample of microbial tooth plaque was taken from all test subjects, in case of periodontitis additionally a subgingival sample from the pathologically deepened areas below the gum line. The quantity of seven marker germs were compared to the severity of cognitive impairment examined by the Mini-Mental-Status-Examination (MMSE) and AD biomarkers in cerebrospinal fluid (CSF).
Results: Periodontitis was significantly more present in AD patients (p = 0,003) compared to controls. Additionally, the severity of periodontitis (increased gingival sulcus depth) was inversely correlated with MMSE score (r = -0,304; p = 0,003) in all participants. Marker germs showed no significant association with AD biomarkers in CSF. In MCI patients we found significantly increased subgingival levels of *Prevotella intermedia* (p = 0,014) compared to controls, and *Porphyromonas gingivalis* (p = 0,042), *Treponema denticola* (p = 0,038), *Prevotella intermedia* (p = 0,012) and *Tanerella forsythia* (p < 0,001) compared to AD patients. Using receiver operating characteristics (ROC) curve analysis we found an area under the curve (AUC) of 0.82 for *Prevotella intermedia* and 0.71 for *Porphyromonas gingivalis* discriminating between MCI patients from controls, and 0.61 for *Prevotella intermedia* discriminating between AD patients and controls.

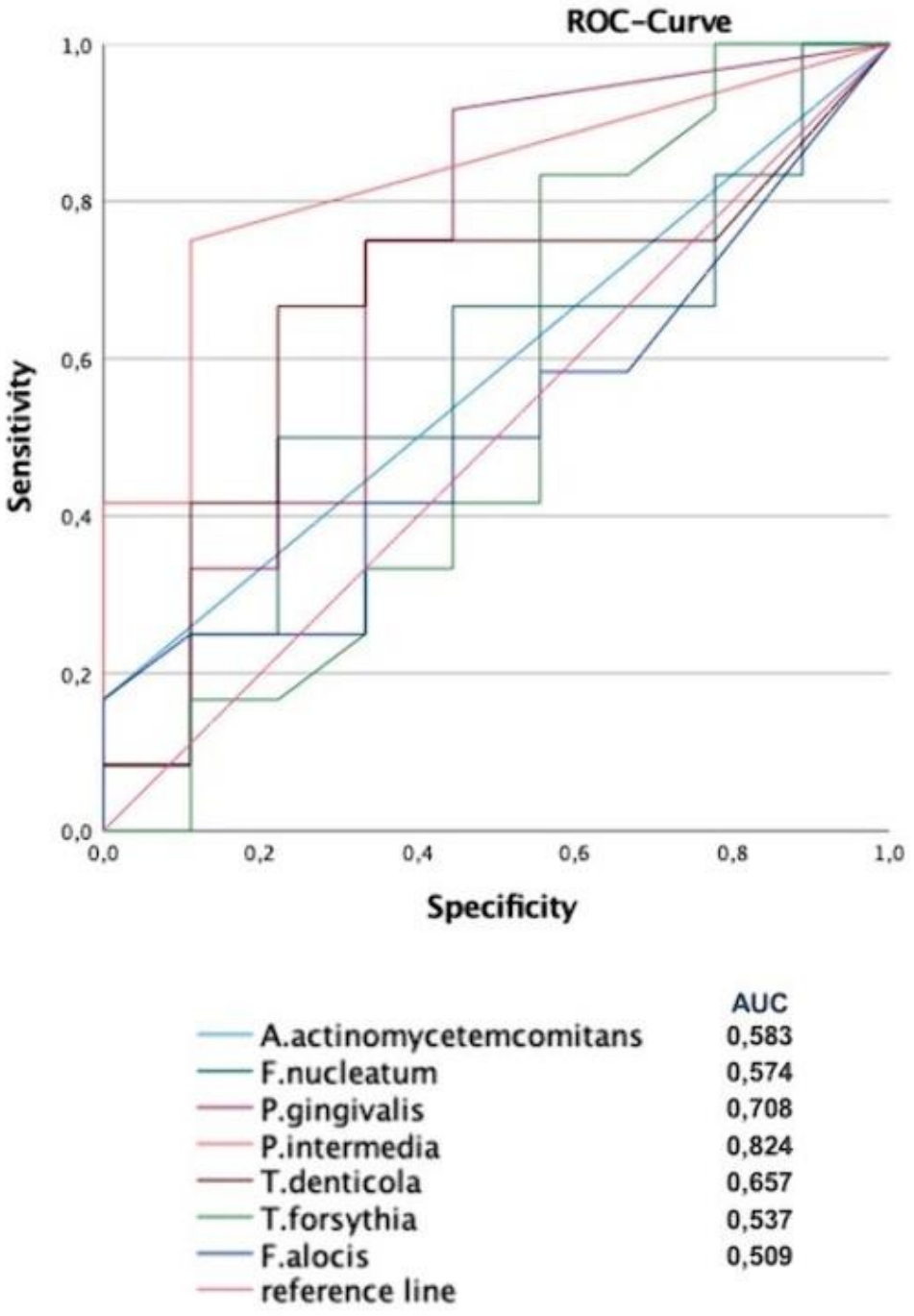


Image 1: ROC-Curve controls to MCI compared to marker germs

Conclusions: Periodontitis marker germs may represent an innovative diagnostic supplement for identification of patients with MCI and AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0201 / #1549

Poster Topic: *Theme A: β-Amyloid Diseases / A01.s. Disease Mechanisms, Pathophysiology: Microbiome*

PERIODONTAL MICROBE EFFECT ON THE ENDOTHELIAL TRANSCRIPTOME RESEMBLES CHANGES OBSERVED IN PATIENTS WITH ALZHEIMER'S DISEASE

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

Kamelija Horvatović[1], Andrea Gelemanović[2]
[1]Faculty of Science, University of Zagreb, Molecular Biology, Zagreb, Croatia, [2]Mediterranean Institute for Life Sciences, Bioinformatics, Split, Croatia

Aims: Among various familiar etiopathologies of Alzheimer's disease (AD), periodontitis is one of the most recent factors suspected to be affecting the onset of this disorder. This in silico study aims to test whether the transcriptomic changes in endothelial cells (EC) induced by common periodontal pathogens such as Fusobacterium nucleatum (FN) or Porphyromonas gingivalis (PG) match changes detected in the EC of AD patients.
Methods: RNA-seq datasets GSE222136 and GSE125050 were acquired from the NCBI GEO database. Differentially expressed genes (DEGs) between different pathologies (FN, PG or AD) and untreated or healthy controls were identified following the DESeq2 pipeline, while the weighted gene co-expression network analysis (WGCNA) pipeline was used to identify highly correlated gene modules. Functional enrichment analysis was performed on DEGs and modules of interest.
Results: In total 15 gene modules were identified of which six modules with 89 key genes were significantly correlated with PG treatment, and four modules with 352 key genes with FN treatment, with most notable change being interferon signaling. 553 and 834 DEGs were identified in PG- and FN-treated ECs, respectively, while 1384 were significantly altered in ECs of AD patients. After comparing all the results, MIRHG1, SLC24A40, and ABHD13 were detected as shared significantly upregulated DEGs in all three pathologies indicating altered RNA interference mechanisms, affected ion channels, and cell adhesion.
Conclusions: This integrated study identified several potential gene candidates of underlying microbe-driven pathological changes in EC physiology that might be key players in AD onset and/or progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0202 / #937

Poster Topic: *Theme A: β-Amyloid Diseases / A01.s. Disease Mechanisms, Pathophysiology: Microbiome*

PROGNOSTIC VALUE OF GUT MICROBIOME FOR CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE DEMENTIA WITHIN 4 YEARS: RESULTS FROM THE ALZBIOM STUDY

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

Christoph Laske[1], Silke Peter[2], Ulrich Schoppmeier[2]
[1]Eberhard Karls University, Department Of Psychiatry And Psychotherapy, Tübingen, Germany, [2]Eberhard Karls University, Department Of Microbiology, Tuebingen, Germany

Aims: A growing body of evidence suggests that dysbiosis of the gut microbiome is associated with the pathogenesis of Alzheimer`s disease (AD) and can be used as a diagnostic measure. However, longitudinal changes of gut microbiome and its prognostic significance for the development of AD are still unknown. In the present study we investigated the ability of taxonomic and functional gut microbiome data and their combination with clinical data to predict the progression from mild cognitive impairment (MCI) to AD dementia on the basis of clinical classification at 4 years follow-up (4yFU).
Methods: In the present study we investigated intestinal microbiome in 49 MCI patients participating at the AlzBiom study over a mean (SD) follow-up of 3.7 (0.6) years. At the end of the 4yFU, 27 MCI patients converted to AD dementia and 22 MCI patients remained stable. Gut microbiome was measured using shotgun metagenomics. Statistical models were built with features from baseline data that best discriminated between AD dementia converters and stable MCI patients using an ANOVA like test.
Results: The best taxonomic model at baseline for discrimination of AD dementia converters from stable MCI patients included 24 genera, yielding an area under the receiver operating characteristic curve (AUROC) of 0.87. The best functional model at baseline included 33 KO (Kyoto Encyclopedia of Genes and Genomes [KEGG] ortholog) features with an AUROC of 0.79. The combined use of these two models including a clinical model with the 4 parameters age, gender, BMI and ApoE yielded an AUROC of 0.93.
Conclusions: We identified a novel gut microbiome algorithm able to accurately predict progression to AD dementia in individuals with MCI over a 4 years follow-up. Gut microbiome represents an innovative prognostic supplement in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0203 / #2032

Poster Topic: *Theme A: β-Amyloid Diseases / A01.s. Disease Mechanisms, Pathophysiology: Microbiome*

GUT MICROBIOTA GENUS NETWORK REFLECTS ALZHEIMER'S DISEASE CLINICAL STAGES

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

Amanda Muliterno Domingues Lourenço De Lima[1], Marco Antônio De Bastiani[1], Morghana Machado Da Rosa[2], Luiza Santos Machado[3], Eduardo R Zimmer[1]
[1]Department of Pharmacology, Graduate Program in Biological Sciences: Biochemistry (PPGBioq) and Phamarcology and Therapeutics (PPGFT), Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil, [2]Federal University of Health Sciences of Porto Alegre, Medicine, Porto Alegre, Brazil, [3]Universidade Federal do Rio Grande do Sul, Biochemistry, Porto Alegre, Brazil

Aims: We hypothesized that dysfunctional associations between the bacterial groups of the gut microbiota could be associated with AD clinical stages. Thus, we aimed to compare the gut-microbiota networks in cognitively unimpaired (CU), mild cognitive impaired (MCI), and AD dementia individuals.
Methods: We selected 16S rRNA gene sequencing data from fecal samples of CU, MCI and AD (n = 30, per group) available at NCBI repository (PRJNA489760). Individuals of both sexes aged between 57 and 73 years were included in the study. Adaptors were removed from the FASTQ files using the Trimmomatic tool for each sample and submitted to the DADA2 pipeline. Briefly, after filter and trimming, amplicon sequence variants (ASVs) were inferred using the *dada* function, taxonomic assignment was implemented using the SILVA resource and normalized by rarefaction without replacement. Afterward, normalized centered-log ratio transformed abundance data were used to construct correlation networks between genus for CU, MCI, and AD.
Results: We observed different correlation patterns between bacterial genera in CU, MCI, and AD. More especially, we found a progressive increase in network density toward AD clinical progression. Genus reportedly associated with cerebral amyloidosis and tau show few connections in the CU individuals, which are increased in MCI and highly connected in AD. Interestingly, we also noted that the opportunistic pathogen *Escherichia_Shigella*, strongly associated with AD pathology, was exclusively present in the AD network and showed a negative correlation with *Faecalibacterium*, a reportedly indicator of health.
Conclusions: Microbial association networks at the genus level reflect different pathological stages of AD and could provide insights into preventive therapeutic strategies aiming to delay disease progression through the modulation of the gut microbiota.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0204 / #1853

Poster Topic: *Theme A: β-Amyloid Diseases / A01.s. Disease Mechanisms, Pathophysiology: Microbiome*

MICROBIOME DYSBIOSIS IN NEURODEGENERATIVE DISEASES: INSIGHTS FROM PARKINSON'S DISEASE AND IDIOPATHIC RAPID-EYE-MOVEMENT SLEEP BEHAVIOR DISORDER

POSTERS: A01.S. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROBIOME

Polina Novikova, Júlia Ortís Sunyer, Oskar Hickl, Velma Aho, Susheel Busi, Tuesday Lowndes, Benoît Kunath, Cédric Laczny, Patrick May, Paul Wilmes
University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Esch-sur-Alzette, Luxembourg

Aims: The study aims to utilize multiomics strategies to explore the gut microbiome's role in neuroinflammation, aiming to clarify its impact on both PD and iRBD.
Methods: Using our previously developed methodological framework, we performed a systematic multiomics analysis of DNA, RNA, proteins, and metabolite fractions isolated from a total of 122 flash-frozen fecal samples obtained from PD (46), iRBD (27) patients and healthy controls (49).
Results: Beyond taxonomic differences, we detected significant molecules like β-glutamate, ceramides, arsenite, and flagella-related proteins in PD and iRBD. Glutamate pathways were disturbed, with increased β-glutamate levels in disease cases. Ceramide pathways were down-regulated. Genes linked to arsenate reduction were also altered. Notably, flagellar biosynthesis-related genes displayed significant depletion at the gene level.
Conclusions: The findings from this research will not only enhance our understanding of the microbiome's role in PD but also increase the potential therapeutic targets for addressing the disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0205 / #2732

Poster Topic: *Theme A: β-Amyloid Diseases / A01.t. Disease Mechanisms, Pathophysiology: Cholinergic*

DEMENTIA-THERAPEUTIC EFFECTS OF AN EXOSOMES-RICH CONDITIONED MEDIUM FROM AMNIOTIC MEMBRANE STEM CELLS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A01.T. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CHOLINERGIC

Khan-Erdene Tsolmon[1], Chanho Noh[1,2], Hye-Rim Seong[2], Seong-Jun Lee[2], Sunhwa Jeong[2], Seon Myeong Go[2], Seok Jin Hong[2], Uk Lee[2], Ah-Young Lee[2], Tae Myoung Kim[1,2], Ehn-Kyoung Choi[2], Yun-Bae Kim[1,2]
[1]Chungbuk National University, Department Of Veterinary Medicine, Cheongju-si,, Korea, Republic of, [2]Designed Cells Co., Ltd., Central Research Institute, Cheongju, Korea, Republic of

Aims: Acetylcholine depletion due to amyloid β (Aβ)-induced cholinergic degeneration is a main etiology of Alzheimer's disease (AD). Acetylcholinesterase (AChE) inhibitors do not delay or reverse the disease progress. Antibodies specific for Aβ induce microbleeding and brain edema. We obtained an exosome-rich conditioned medium (ERCM) containing large amounts of functional molecules such as Aβ-degrading neprilysin (NEP) as well as neuroprotective and neuroregenerative growth factors (GFs) and neurotrophic factors (NFs), and assessed its therapeutic effects in AF64A-induced AD model animals.
Methods: The enzymatic activity of NEP in ERCM was assayed for Aβ degradation, and cytoprotective activity was assessed for the production of choline acetyltransferase (ChAT) in F3 neural stem cells. To induce cognitive deficit, mice were injected ICV with a cholinotoxin AF64A, and treated IV once or 4 times with ERCM. Cognitive function was assessed via passive avoidance and Morris water-maze performances, and neuroprotective effects were evaluated by analyzing brain acetylcholine and Aβ concentration, GFs and NFs, and microscopic findings.
Results: ERCM exhibited NEP activity and up-regulated ChAT (acetylcholine-synthesizing enzyme) production in F3 cells. ERCM treatment recovered cognitive function of AD mice, in which repeated treatment was more effective than single injection. The hippocampal pyramidal cell loss and Aβ accumulation induced by AF64A challenge was prevented by treatment with ERCM, in parallel with the recovery of functional molecules such as acetylcholine, GFs and NFs, NEP, and ChAT. In addition, ERCM exerted neuroregenerative activity, as confirmed by increased host nestin-positive neural stem cells and ChAT-positive cholinergic neurons, and decreased GFAP-positive astrocytes.
Conclusions: ERCM ameliorated AF64A-induced dementia. The results indicate that ERCM rich in NEP and GFs/NFs recovers learning and memory functions via amyloid β elimination as well as neuroprotection and neuroregeneration.

P0206 / #769

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

THERAPEUTIC EFFECT OF BIOINSPIRED WASP VENOM PEPTIDE FRATERNINE-10 IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Luana Cristina Camargo, Letícia Gomes, Gabriel Campos, Adolfo Carlos De Souza, Márcia Renata Mortari
University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil

Aims: Alzheimer Disease (AD) is characterized by the accumulation of Amyloid-β (Aβ) and TAU peptides, which aggregate and become toxic to neurons. Current AD treatments are still limited; therefore, the development of new drugs for AD treatment is necessary. Animal venom compounds are known to be very specific for unique targets, especially for central nervous system receptors, due to evolutionary pressures. Fraternine-10 was bioinspired from Fraternine, a peptide isolated from *Parachartergus fraternus* wasp venom.In this context, we evaluated the potential of Fraternine-10 as a treatment in an AD Aβ-induced mouse model.
Methods: Aβ was infused (400 pmol/animal) into brain lateral ventricle by a neurosurgery. Aβ- infused mice were then treated with three doses of Fraternine-10 (4, 8, and 12 mg/kg; intraperitonial) (n= 7, 9 and 8, respectively) or saline (n=12) one hour after Aβ infusion and for six consecutive days. Then, all groups underwent the Novel Object Recognition Test (ORT), the Open Field test, and the Morris Water Maze (MWM), which consisted of four trials with six sections followed by the test without the platform. Thioflavin T staining was performed to evaluate Aβ aggregation.
Results: The Fraternine-10 (12 mg/kg) exacerbated memory impairment due to Aβ toxicity in the ORT ,while, no improvement was observed in the MWM. No differences amoung groups were observed in the Open Field test. Moreover, Fraternine-10 did not reduce Aβ aggregation in the cortex and hippocampus. Hence, it is likely that Fraternine-10 was degraded over time and lost its potential therapeutic effect.
Conclusions: Further studies are necessary to understand the pharmacokinetic properties of Fraternine-10 and explore possible improvements. Finally, Fraternine-10 could serve as a starting point for developing a promising drug for AD treatment after further modifications.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0207 / #1916

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

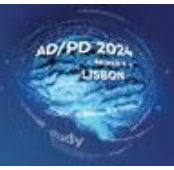
APP EXON17 SKIPPING AS AN ALTERNATIVE STRATEGY TO DOWNREGULATE APP IN AD

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Allen Chen, Dominic Walsh, Thierry Bussiere
Biogen, Neurodegenerative Disease Research Unit, Cambridge, United States of America

Aims: The proteolytic processing of the Amyloid Precursor Protein (APP) by β- and γ-secretase generates the Amyloid β-peptide (Aβ) that is deposited in the brains of Alzheimer's disease (AD) patients. Removal of aggregated Aβ by immunotherapy has shown clinical efficacy, making APP a promising target in AD. However, knockdown of APP may lead to safety issues, as knockout mice exhibit certain adverse phenotypes, including reductions in brain and body weight, reduced grip strength, and impairments in spatial learning and long-term potentiation. These phenotypes can be rescued with the soluble fragment of APP generated by α-secretase shedding (sAPPα). Here we examine a novel approach to target APP via skipping of exon17. Exon17 encodes for the transmembrane domain of APP which includes the C-terminus of Aβ. Removal of this exon is predicted to produce a secreted form of APP (APP ΔE17) incapable of generating Aβ. APP ΔE17 is highly similar to sAPPα and may retain its function while attenuating any phenotypes associated with loss of APP. Thus this strategy could prevent generation of Aβ while retaining sAPPα function.
Methods: Cell lines expressing APP ΔE17 were examined for APP secretion as a C-terminal intact protein. Processing by α-/β-secretase was determined by measuring the levels of APP C-terminal fragments and impact of inhibitors on full-length protein. sAPP function on basal neurotransmission was assayed by fEPSP on acute hippocampal slices.
Results: Deletion of exon17 resulted in the secretion of APP with no detectable cleavage by the secretases. However, APP ΔE17 did not retain sAPPα function and, furthermore, led to the accumulation of APP in the conditioned media.
Conclusions: Exon17 skipping does not appear to be a suitable strategy for the downregulation of Aβ production.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0208 / #863

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

BRAIN METABOLIC CONNECTOMICS OF ADUCANUMAB PHARMACODYNAMICS IN 5XFAD MICE

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Paul Territo[1], Charles Burton[2], Scott Persohn[2], Ethan Miner[2], Kierra Eldridge[2], Sara Quinney[1], Andi Masters[1], Katherine Haynes[3], Kristen Onos[4], Mike Sasner[5], Gareth Howell[5], Gregory Carter[5], Adrian Oblak[2], Bruce Lamb[6], Stacey Sukoff Rizzo[3]
[1]Indiana University School of Medicine, Medicine, Indianapolis, United States of America, [2]Indiana University School of Medicine, Stark Neuroscience, Indianapolis, United States of America, [3]University of Pittsburgh, Medicine, Pittsburgh, United States of America, [4]The Jackson Laboratory, Medicine, Bar Harbor, United States of America, [5]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America, [6]Indiana University School of Medicine, Stark Neuroscience Research Institute, Indianapolis, United States of America

Aims: Objective: The MODEL-AD Preclinical Testing Core established a rigorous drug testing strategy for unbiased assessments. To validate this pipeline, chimeric aducanumab (chAdu) in aged 5XFAD mice was tested. To elucidate the pharmacodynamics (PD), metabolic connectomic modeling was performed.
Methods: Methods: chAdu was synthesized by transfection and qualified by standard methods. To determine the dosing strategy, PK studied were conducted in 9 mos 5XFAD mice of both sexes dosed with chAdu from 0.1 to 30 mg/kg, and blood sampled every 3 days between 0 and 27 days. PK/PD modeling predicted dose levels of 0.1 to 30 mg/kg at Q1W. Brain PD was determined at baseline and conclusion of chronic treatment via 18-FDG PET/CT. Images were registered to the Paxinos-Franklin atlas, extracted, and network connectivity determined by z-score transformation, pairwise covariance analysis. Networks were modularized via multi-resolution-consensus clustering (MRCC), where region set enrichment was conducted. Whole brain and module level statistics were conducted between sexes and across doses.
Results: Results: chAdu showed high purity and stability with freeze/thaw. PK/PD modeling revealed $T_{1/2}$ of ~2.5 days and informed the PD dose regimen (0.1-30 mg/kg Q1W, IP). 12-week treatment with chAdu resulted in dose- and sex-dependent dependent reversal of glycolytic loss in key brain regions. Whole brain covariance analysis of regional 18F-FDG PET uptake thresholded at the $p<0.05$ level, revealed a dose and sex dependent changes in network degree, density, positive and negative connection strength, and clustering coefficient. Network MRCC modules composition and distribution showed dose and sex dependency.
Conclusions: Conclusions: These data indicate that chAdu was selective and stable, and resulted in sex and dose dependent relevant metabolic network changes consistent with neuromodulation, and demonstrate the value of metabolic connectomic modeling for evaluating drug efficacy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0209 / #557

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

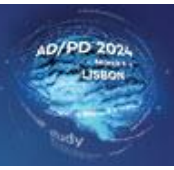
PLASMA EXCHANGE REDUCES ABETA LEVELS IN PLASMA AND AMYLOID PLAQUES IN THE BRAIN OF A MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Suelyn Koerich, Santiago Ramirez, Natalia Astudillo, Nicole De Gregorio Carbonell, Rabab Al-Laham, Tyler Allison, Natalia Pessoa Rocha, Fei Wang, Claudio Soto
UTHealth Science Center at Houston, Neurology, Houston, United States of America

Aims: In the present study, we investigated the effectiveness of repeated plasma exchange (PE) in removing Aβ peptides from the plasma and decreasing Aβ accumulation in the brain.
Methods: 300 µL of blood was obtained once a month from APP/PS1 mice from the jugular vein. Subsequently, blood was centrifuged to remove plasma, and the same volume was replaced with 5% mouse albumin and reinfused into the jugular. PE started at 3 months of age and animals were euthanized at 7 months. For biochemical and histological analysis, brains were dissected. The right hemisphere was fixed for histological examinations, and the left was snap-frozen in liquid nitrogen. For histology, 10 µm sections were stained with thioflavin S (ThS), or incubated with anti-Aβ 4G8, anti-GFAP, and anti-Iba1 antibodies. Images were analyzed using Image J software. Plasma concentrations of Aβ were measured by ELISA.
Results: show that PE avoids the increase of Aβ levels in mice plasma at 7 months. Also, these animals have less ThS burden in the cortex and hippocampus, as well as a significantly lower number of plaques. This reduction in amyloid pathology measured by histological staining was supported by results showing that PE reduced the accumulation of insoluble Aβ in the brain. Finally, the burden area positive for the microglia and astrocyte was significantly lower in PE-treated animals compared to controls.
Conclusions: The precise mechanism through which PE reduces amyloid pathology in this model remains unclear. The decrease in cerebral amyloid deposition occurred in parallel with a reduction in the concentration of Aβ in plasma, indicating that the mobilization of Aβ from the brain to the bloodstream may play a role in reducing the amyloid burden induced by PE.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0210 / #2761

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

LECANEMAB LABELS EXTENSIVE VASCULAR AMYLOID DEPOSITION IN DOWN SYNDROME BRAINS

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Lei Liu[1], Adriana Saba[1], Jesse Pascual[2], Michael Miller[3], Frederick Schmitt[4], Jordan Harp[4], Jasmeer Chhatwal[5], Dennis Selkoe[1], Elizabeth Head[2]
[1]Brigham and Women's Hospital, Neurology, Cambridge, United States of America, [2]University of California Irvine, Pathology & Laboratory Medicine, Irvine, United States of America, [3]Brigham and Women's Hospital, Pathology, Boston, United States of America, [4]University of Kentucky, Sanders-brown Center For Aging, Department Of Neurology, Lexington, United States of America, [5]Massachusetts General Hospital, Neurology, Boston, United States of America

Aims: Leqembi (Lecanemab), a humanized monoclonal antibody targeting amyloid β, has secured FDA approval as a treatment for early Alzheimer's disease (AD). There is growing interest in using it for AD in Down syndrome (DS), given over 90% of DS eventually develop AD. However, Leqembi comes with a critical consideration—Cerebral-Amyloid-Angiopathy (CAA)-related hemorrhage. CAA involves amyloid buildup within the brain vasculature. People with DS have a notably higher CAA prevalence compared to the general population, heightening this risk of adverse side effects during Leqembi treatment. To address this pressing clinical concern, our study aimed to determine if Leqembi can detect CAA structures in post-mortem brain tissues from people with DS.
Methods: Since Lecanemab is a human antibody, conducting immuno-histochemical staining on human tissue without significant background staining presented a technical challenge. We have developed a novel method using fragment antigen-binding regions (Fab) to block the endogenous level of human IgG in the brain tissue for reducing the general background caused by human-on-human immunohistochemical staining. We compared 12 brains from people with DS (Ages 49 to 68) to 5 brains from late onset AD (ages 83 to 96).
Results: First, Lecanemab labels a diverse phenotype of amyloid plaques in DS brains, with different plaque morphologies, including coarse-grained, cotton wool, and classic cored structures. Second, Lecanmab labels extensive vascular amyloid deposition in all 12 DS cases. Lecanemab labels particularly widespread leptomeningeal and cortical amyloid angiopathy, including blood vessel and capillary amyloid angiopathy in the cortex. There are also diffuse parenchymal Aβ deposits around the blood vessels.
Conclusions: This discovery raises heightened concerns regarding the safety and suitability of Leqembi's use in people with DS over the age of 50 years, underscoring the need for careful evaluation in clinical applications.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0211 / #1904

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

EVALUATION OF THE NEUROPROTECTIVE ACTION OF A NANOENCAPSULATED PEPTIDE IN A MOUSE MODEL OF ALZHEIMER'S DISEASE INDUCED BY THE ASS PEPTIDE

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Isabela Mota[1], Pedro Morais[2], Maria Clara Resende[3], Gabriely Penha[4], Lucas Campos[1], Julia Kozuma[3], Natasha Melo[2], Adolfo Carlos De Souza[4], Danilo De Oliveira[4], Luana Cristina Camargo[2], Gabriel Campos[4], Márcia Renata Mortari[4]
[1]University of Brasília, Physiological Sciences, Brasília, Brazil, [2]Institute of Biological Science, Department Of Physiology, Brasília, Brazil, [3]Institute of biological sciences/ University of Brasilia, Department Of Physiological Sciences, Brasília, Brazil, [4]University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil

Aims: This studyaims to evaluate the neuroprotectiveaction of a new peptideanalogous to Octovespina, a waspvenompeptide with neuroprotectiveeffects in Alzheimer's Disease (DA)
Methods: In a30-days experimental design, different animalgroupsunderwentstereotaxicsurgery on the first day, with administration of Aß or vehicle, and weretreatedintranasally for evaluationof the peptide in a chronicmodel, with the free or nanoencapsulatedpeptide, in a dose of 2µg/2µL. On the lastfivedays of protocol, the animalsweresubmitted to the Morris WaterMaze test (MWM), consisting of fourdays of training and one day of test. On the fourdays of training, each animal wasput on the watermaze for one minute, in six different sections to find anunderwaterplatform. On the test day, the platformwasremoved and the time spentwithin the platformquadrantwasevaluated.

Results: Whencompared to the control groups, the peptidewasablebringcognitiveimprovement to the animalsevaluated in the Morris WaterMaze at a dose of 2ug/2ul, nanoencapsulated and free. The resultsshowed similar efficacybetween the nanoencapsulated and non-nanoencapsulated doses in terms of improving the cognitivecapacity of the animals in this model, whencompared to the negative control group.
Conclusions: Thesefindingssuggest that the peptideis promising in the treatment of DA, in addition, furtherstudies are underway to betterevaluate the effects of the peptide in otherbehavioraltests andother doses (0,2µg/µL and 20µg/2µL), and at last, deeperevaluate the nanotechnology. This studywasfunded by FAPDF, CNPQ and CAPES.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0212 / #632

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

SIGNATURES OF MODIFIED ABETA VARIANTS IN ALZHEIMER'S DISEASE, DEMENTIA WITH LEWY BODIES AND VASCULAR DEMENTIA

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Sarah Schrempel[1], Anna Kottwitz[2], Maike Hartlage-Rübsamen[1], Anke Piechotta[2], Jochen Walter[3], Stephan Schilling[2], Steffen Roßner[1]
[1]University of Leipzig, Paul Flechsig Institute For Brain Research, Leipzig, Germany, [2]Fraunhofer Institute for Cell Therapy and Immunology, Department Of Drug Design And Target Validation, Halle (Saale), Germany, [3]University of Bonn Medical Center, Department Of Neurology, Bonn, Germany

Aims: The aggregation of amyloid beta (Abeta) and post-translationally modified Abeta in particular is a neuropathological feature in brains of Alzheimer's disease (AD) patients. In other types of dementia, such as dementia with Lewy bodies (DLB) and vascular dementia (VAD), a role of Abeta in the pathology is hypothesized. We propose distinct pathogenic profiles of Abeta post-translational modifications (PTMs) in AD and other types of dementia.
Methods: We employed novel and established monoclonal antibodies for comparative analyses of different Abeta PTMs in *post mortem* human brain tissue of pre-symptomatic and symptomatic AD cases, of subjects who suffered from DLB and VAD, respectively, and of control subjects. Using machine learning protocols, we quantified immunohistochemical stainings of Abeta PTMs and compared the results with the quantification of Abeta variants employing ELISAs. For the latter technique, tissue fractions were prepared based on differential solubility of Abeta variants in detergents and formic acid. Furthermore, histopathological findings were correlated with clinical data.
Results: In human brain tissue, labeling with antibodies raised against Abeta PTMs isoaspartate 7 (isoD7), pyroglutamate 3 (pE3) or phosphoserine 8 (pSer8) showed a lower percentage of stained plaque area compared to labeling of total Abeta. The isoD7-Abeta variant was the most abundant among the Abeta PTMs investigated. Both the total plaque load and abundance of Abeta variants were highest in AD cases, followed by DLB and pre-symptomatic AD, and lowest in VAD cases.
Conclusions: Abeta plaque pathology in general and the percentage of Abeta variants compared to total Abeta can be quantified using single labeling immunohistochemistry and machine learning protocols. Abeta PTMs, and in particular the abundant isoD7-Abeta variant, might be considered for diagnostic and therapeutic approaches in different types of dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0213 / #1510

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

CHARACTERIZATION OF AMYLOID-BETA SPECIES IN ALZHEIMER'S DISEASE BRAIN AND THE UNIQUE BINDING PROPERTIES OF LECANEMAB

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Linda Söderberg[1], Malin Johannesson[1], Eleni Gkanatsiou[1], Emily Button[1], Anne-Sophie Svensson[1], Nicolas Fritz[1], Patrik Nygren[1], Adeline Rachalski[1], Olof Zachrisson[1], Gunilla Osswald[1], Charlotte Silfverhielm[1,2], Christer Möller[1]
[1]BioArctic AB, Research & Development, Stockholm, Sweden, [2]Uppsala University, Department Of Public Health/geriatrics, Uppsala, Sweden

Aims: Immunotherapy against amyloid-beta has been shown as a promising treatment option for Alzheimer's disease (AD). In a phase 3 clinical trial in early AD subjects, lecanemab demonstrated disease-modifying effects on clinical endpoints and clearance of amyloid-beta plaques in the brain. Lecanemab is a humanized IgG1 monoclonal antibody, selectively targeting amyloid-beta protofibrils. Soluble amyloid-beta protofibrils are believed to be the most toxic species of amyloid-beta. Immunotherapy with antibodies targeting amyloid-beta is associated with amyloid-related imaging abnormalities with edema (ARIA-E). The incidence of ARIA-E might correlate with antibody binding to amyloid-beta in cerebral amyloid angiopathy (CAA) in vessels. Here we have studied binding of lecanemab and other amyloid-beta-binding antibodies to different amyloid-beta species isolated from AD brain.
Methods: Amyloid-beta species were measured in human postmortem brain isolated from parenchymal and meningeal tissue. MSD/ELISA and mass spectrometry were used for measurement and characterization. Binding studies with amyloid-beta antibodies were carried out using immunoprecipitation.
Results: Soluble amyloid-beta protofibrils were mainly composed of amyloid-beta-42 and levels were significantly elevated in AD brains compared to non-demented controls. Amyloid-beta 40 was identified as the major amyloid-beta species in CAA. Pyroglutamate-3 modified amyloid-beta was significantly elevated in insoluble brain fraction at later Braak stages as compared to lower Braak stages. Lecanemab showed strong binding to all sizes of amyloid-beta protofibrils isolated from AD brains, and showed low binding to amyloid-beta fibrils prepared from CAA.
Conclusions: Lecanemab has a unique binding profile with a high selectivity for soluble amyloid-beta protofibrils. This was shown when different amyloid-beta antibodies were compared regarding their binding properties to amyloid-beta species isolated from human postmortem brain tissue. These differences could have an impact on clinical efficacy and safety when treating AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0214 / #2821

Poster Topic: *Theme A: β-Amyloid Diseases / A02.a. Therapeutic Targets, Mechanisms for Treatment: Abeta, truncated & pGlu-Abeta*

REDUCING THE PRODUCTION OF TOXIC AB PEPTIDES IN ALZHEIMER'S DISEASE BY MUTATING THE APP CHOLESTEROL-BINDING SITE: A NEW THERAPEUTIC STRATEGY?

POSTERS: A02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ABETA, TRUNCATED & PGLU-ABETA

Michael Okafor[1], Laury Dancette[2], Gunnar Brinkmalm[3], Stéphanie Bigou[1], Elena Camporesi[4], Denis Biard[5], Henrik Zetterberg[6,7], Marie-Claude Potier[2,8]
[1]Paris Brain Institut (ICM), Maladie D'alzheimer, Maladie à Prions, Paris, France, [2]Paris Brain Institute (ICM), Maladie D'alzheimer, Maladies à Prions, Paris, France, [3]Department of Psychiatry and Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden, [4]Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [5]CEA, Institut de Biologie François Jacob (IBFJ), Université Paris-Saclay, Laboratoire Sepia, Fontenay-aux-Roses, France, [6]UCL London, Uk Dementia Research Institute, London, United Kingdom, [7]UCL Queen Square Institute of Neurology, Department Of Neurodegenerative Disease, London, United Kingdom, [8]Sorbonne Université, INSERM U1127, CNRS 7225, Paris Brain Institute - Icm, Paris, France

Aims: Amyloid-β (Aβ) peptides of various lengths are produced by sequential proteolysis of the transmembrane amyloid precursor protein (APP) by the β- and the γ-secretases that both operate in the cholesterol-rich membrane bilayer. We previously showed that increase of membrane cholesterol triggers APP endocytosis and the production of toxic Aβ peptides. Furthermore, we found that K to A mutation in the cholesterol-binding site of APP at position 28 in the Aβ sequence leads to the generation of short and non-toxic Aβ peptides (mainly Aβ33) in HEK293T cells, likely by increasing the carboxypeptidase activity of the γ-secretase. Here we wish to investigate the effect of the K28A mutation on APP processing in neuroblastoma cells and in human iPSC-derived neurons, and test whether this mutation can counteract the deleterious effects of the London mutation producing toxic Aβ42 in familial AD.
Methods: Using CRISPR/Cas9 technology and pEBV vector expression, human neuroblastoma cell lines (SH-SY5Y, BE(2)-C and SK-N-AS) and human iPSC clones were engineered
Results: We successfully developed several new human neuroblastoma cell lines by first silencing endogenous APP and concomitantly expressing stably inducible or constitutive APP with or without the K28A mutation. In addition, we generated new hiPSC lines with the K28A mutation starting from iPSC from a patient carrying the London mutation (V717I) and its isogenic control obtained by reversing the V717I mutation using CRISPR/Cas9. We will present data on APP processing in these new cell lines
Conclusions: Collectively these data support the premise of new gene-editing therapy to mitigate the overproduction of toxic Aβ species in the context of AD, similarly to g-secretase modulators but may be more efficiently by reducing the size to Aβ33

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0215 / #1422

Poster Topic: *Theme A: β-Amyloid Diseases / A02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

ANTI-ABETA LIPOSOMAL VACCINE, ACI-24.060, RETAINS MEMORY IN AN AGGRESSIVE MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Emma Fiorini, Chiara Babolin, Catherine Morici, Aurélie Guillaume-Gentil, Fabiana Tione, Harishini Balachandiran, Maxime Ayer, Marie-Gabrielle Beuzelin, Rakel Carpintero, Stefania Rigotti, Andrea Pfeifer, Marie Kosco-Vilbois, Marija Vukicevic
AC Immune SA, Research, Lausanne, Switzerland

Aims: ACI-24.060 is a Phase 2 clinical stage anti-Abeta active immunotherapy that induces sustained antibody responses targeting pathological Abeta species. We have assessed the ability of ACI-24.060 to maintain neuronal health, and thus memory, in the aggressive 5xFAD mouse model of Alzheimer's disease (AD).
Methods: 5xFAD mice were immunized with ACI-24.060 or vehicle, from 1.5 months of age until 10.5 months. Anti-Abeta antibody titers induced by the immunotherapy were assessed by ELISA. To evaluate cognitive performance, learning and memory, ACI-24.060-treated and vehicle-treated 5xFAD mice, and C57BL/6 mice (non-diseased controls), were assessed in the Morris Water Maze (MWM) after a 4-day training period followed by a test trial. The effect of ACI-24.060 on spatial learning was assessed by quantifying escape latency, swim distance, quadrant preference and cognitive score.
Results: In the 5xFAD mouse model, at 10.5 months of age, vehicle-treated mice exhibited substantially impaired learning in the MWM compared to non-diseased animals. ACI-24.060 immunization led to the significant maintenance of learning and memory, reaching similar levels to non-diseased controls. This included learning during the training period (as measured by escape latency and swim distance on the last training day) and the cognitive score over the course of the testing. These significant cognitive improvements were associated with a robust and sustained anti-Abeta IgG response.
Conclusions: The widely used 5xFAD mice that reportedly recapitulates many AD-related phenotypes including amyloid plaques, neuron loss and pronounced amyloidosis, displayed severe cognitive decline before 11 months of age. Treatment with the Abeta targeting vaccine, ACI-24.060, maintained both learning and memory capabilities to the levels of non-diseased animals. These neurological functional results are consistent with the accumulating immunohistochemical data on the activity of ACI-24.060 and strongly support its continued clinical development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0216 / #2110

Poster Topic: *Theme A: β-Amyloid Diseases / A02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

DEVELOPMENT OF A VACCINE TARGETING GALECTIN-3 FOR ALZHEIMER'S DISEASE

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Kazuya Goto[1,2], Wataru Akahata[2], Yuji Fukushima[2], Misako Nakata[2], Akira Kuzuya[1], Ryosuke Takahashi[1], Ryuji Ueno[1,3]
[1]Kyoto University, Department Of Neurology, Kyoto, Japan, [2]Kyoto University, Department Of Neurocognitive Disorders, Kyoto, Japan, [3]Cyn-K, LLC, Neurology, Maryland, United States of America

Aims: Alzheimer's disease (AD) is a major cause of dementia and one of the intractable neurodegenerative diseases. Neuroinflammation is one of the causes of AD, and microglia play an important role in neuroinflammation in the central nervous system. Galectin-3 (Gal-3) is a protein that has the function related to proinflammatory processes and its expression is observed in activated microglia. Recently, cerebrospinal fluid (CSF) Gal-3 levels were reported to be elevated in AD patients. In this study, we assessed CSF Gal-3 levels in AD patients, including those with mild cognitive impairment (MCI) due to AD, and investigated the effect of a vaccine targeting Gal-3 in mice.
Methods: First, we measured CSF Gal-3 of non-AD and AD patients including those with MCI due to AD. Then, we designed a Gal-3 vaccine using virus-like particle (VLP) and administered it intramuscularly to 5xFAD mice at a dose of 10 micrograms three times over a four-week period. Serum samples were collected two weeks and approximately three months after the final injection to measure anti-Gal-3 antibody titers. To investigate the effect of the vaccine on the brain, we conducted western blot analysis of Gal-3.
Results: In our study, we found that CSF Gal-3 in AD patients increased even in the MCI stage compared to non-AD patients. We also observed that the anti-Gal-3 antibody titer of all immunized mice increased both 2 weeks and 3 months after immunization. Furthermore, western blot analysis demonstrated the vaccine reduced Gal-3 levels in the cortex of 5xFAD mice.
Conclusions: Our data suggest that neuroinflammation related to Gal-3 occurs in the early stage of AD and the vaccine we developed could be a potential therapeutic drug for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0217 / #1386

Poster Topic: *Theme A: β-Amyloid Diseases / A02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

USE OF MATHEMATICAL MODELS TO EXPLORE TARGET ANTIBODY LEVELS FOR ANTI-AMYLOID ACTIVE IMMUNOTHERAPIES AS MAINTENANCE THERAPIES.

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Lara Herriott[1], Mark Coles[2], Eamonn Gaffney[1], Nicolas Fournier[3,4], Garance Lucken[3], Olivier Sol[3,4], Julian Gray[3], Marija Vukicevic[4], Marie Kosco-Vilbois[5], Andrea Pfeifer[4], Johannes Streffer[3,4,6], Jonathan Wagg[3,4]
[1]University of Oxford, Mathematical Institute, Oxford, United Kingdom, [2]University of Oxford, Kennedy Institute Of Rheumatology, Oxford, United Kingdom, [3]AC Immune SA, Clinical Development (cdms), Lausanne, Switzerland, [4]AC Immune SA, Research, Lausanne, Switzerland, [5]AC Immune, Research, Lausanne, Switzerland, [6]University of Antwerp, Department Of Biomedical Sciences, Antwerp, Belgium

Aims: Anti-amyloid active immunotherapies are a promising maintenance strategy to preserve and potentially improve clinical benefits driven by initial treatment with amyloid-targeting monoclonal antibodies (mAbs). Lecanemab treatment reduces both amyloid burden and plasma pTau181 levels and increases the plasma ratio of Abeta42/40. However, the antibody levels needed to stabilize biomarkers at post-mAb treatment levels, i.e., in a maintenance clinical setting, may be quite different to those achieved during initial treatment. In this study, mathematical models were developed to predict biomarker responses to anti-amyloid active immunotherapies administered as maintenance therapies with the objective of defining target antibody levels required to maintain key biomarkers at levels achieved following initial mAb treatment.
Methods: A previously published Lecanemab exposure-response model was implemented and a minimal QSP model developed. These models provided a quantitative framework for exploring ongoing biomarker responses to a range of mAbs as well as to active immunotherapy following initial mAb therapy.
Results: Both models predict that the maintenance plasma antibody levels needed to stabilize biomarkers at levels achieved following initial mAb treatment are lower than those achieved with initial mAb therapy. However, as compared to the antibody levels predicted to prevent re-accumulation of amyloid plaque, higher antibody levels are required to prevent a return to baseline of the plasma pTau181 concentration and plasma Aβ42/40 ratio as compared to those predicted to prevent re-accumulation of amyloid plaque.
Conclusions: By leveraging QSP models for mAbs, we have improved understanding of the target antibody levels to be achieved by anti-amyloid active immunotherapies in the maintenance context. In addition, such an approach can be extended beyond exploration of maintenance immunotherapy to investigate responses to anti-amyloid active immunotherapy for other clinical contexts such as primary prevention.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0218 / #260

Poster Topic: *Theme A: β-Amyloid Diseases / A02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

MULTI-MODAL AMYL THERAPEUTICS INHIBIT AGGREGATION AND PROMOTE CLEARANCE OF AMYLOID AGGREGATES FROM NEURODEGENERATIVE DISEASES

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Aditya Iyer, Julie Goemaere, Karine Goraj
Amyl Therapeutics, Research And Development, Seraing, Belgium

Aims: Preliminary results from *in vitro and ex vivo* studies with pan-amyloid therapeutics demonstrate the ability to inhibit aggregation, bind and destabilize amyloid fibrils, and promote clearance by phagocytosis of $A\beta_{1-42}$, Tau, and α-synuclein aggregates.
Methods: We have used fluorescence spectroscopy to assess the inhibitory effect of our therapeutics on the aggregation of $A\beta_{1-42}$, Tau, and α-synuclein. We have applied a combinatorial strategy where surface plasmon resonance (SPR), ELISA, and immunogold labeling have been used to confirm *in vitro* binding. Therapeutic-dependent phagocytosis of amyloid aggregates was evaluated in a THP-1 cell assay, and *ex vivo* target engagement was assessed in human tissues.
Results: Our therapeutics have been generated by fusing a human IgG Fc to a M13 bacteriophage protein, and first-generation therapeutics have been shown to specifically bind and destabilize amyloid fibrils from antibody light chain, $A\beta_{1-42}$, Tau, and α-synuclein (Asp et al.2019). Our first-generation therapeutics also reduced amyloid burden ($A\beta_{1-42}$ and Tau) in mouse models with no toxic side effects (Levenson et al., 2016). We present preliminary data with improved therapeutics showing markedly reduced immunogenicity, enhanced aggregation inhibition, nanomolar binding affinities to amyloid aggregates, and effective clearance of amyloid aggregates by phagocytosis. Additionally, we share data confirming binding to amyloid deposits in tissues from Alzheimer's disease (AD) and Parkinson's disease (PD) patients.
Conclusions: Our therapeutics act to inhibit aggregation, destabilize existing aggregates, and promote the clearance of amyloid aggregates. Together with previous data generated with LC fibrils, these results strengthen our platform technology as a potential therapeutic solution in neurodegenerative diseases like AD and PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0219 / #1837

Poster Topic: *Theme A: β-Amyloid Diseases / A02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

NASAL PROTOLLIN MODULATES PERIPHERAL MONOCYTES THAT PROMOTE INCREASED CLEARANCE OF BRAIN AMYLOID BETA IN APPPS1 MICE

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Panagiota Kolypetri, Patrick Da Silva, Christian Gauthier, Rachael Cecere, Estefania Solana, Lei Liu, Howard Weiner
Brigham and Women's Hospital, Neurology, Boston, United States of America

Aims: Nasal administration of Protollin, a proteosome-based adjuvant, leads to reduction of brain amyloid beta (Abeta) in mice developing Alzheimer's disease (AD). In this study, we investigated the effects of nasal Protollin on peripheral monocytes and their contribution on clearance of Abeta in the brain.
Methods: Ly6C^{high} monocytes from peripheral lymphoid organs and brain of APP/PS1 mice were profiled by RNA sequencing; single-cell (sc) RNA-seq of brain cells was conducted using the 10x Genomics Chromium technology; multi-color flow cytometry and ELISA were used to quantify monocytes and brain Abeta respectively; cognitive deficits were assessed using the Y-maze and Morris water maze tests.
Results: We profiled the transcriptome of Ly6C^{high} monocytes from peripheral lymphoid organs and we detected tissue-specific changes after nasal Protollin. In the brain, we found increased recruitment of Ly6C^{high} monocytes that acquired a Protollin-induced transcriptional signature. We directly addressed the role of Protollin-treated monocytes on AD by adoptive transfer of monocytes from nasally treated mice to APP/PS1 animals. Recipient mice showed improved performance in behavioral tests as well as lower brain Abeta compared to controls. To identify unique monocyte-resident brain cell interactions, we performed scRNA-seq and we discovered novel brain cell subsets expressing genes that promote neuronal growth and function. Currently, we investigate the crosstalk between infiltrating monocytes and the newly identified brain cell subsets as well as their impact on Abeta clearance in Protollin-treated mice.
Conclusions: Our data demonstrate that nasal Protollin 1) induces transcriptional changes in peripheral monocytes that migrate to the brain promoting Abeta clearance and improving cognitive deficits and 2) generates unique brain cell subsets promoting neuronal growth and function. Protollin is a novel immunologic approach and it is currently being tested in human trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0220 / #2248

Poster Topic: *Theme A: β-Amyloid Diseases / A02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

LECANEMAB SUPPORTS PHENOTYPIC CHANGE OF GLIAL CELLS : EVIDENCES IN A VITRO MODEL OF ALZHEIMER'S DISEASE

POSTERS: A02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Laura Rouviere, Sarah Lieger, Alexandre Henriques, Esther Steidl, Philippe Poindron, Noëlle Callizot
Neuro-sys SAS, Neuropharmacology Dpt, Gardanne, France

Aims: Alzheimer's disease (AD) is characterized by the extracellular accumulation of senile plaques composed of beta-amyloid (Aβ) and the intracellular deposition of neurofibrillary tangles composed of hyperphosphorylated tau (Tp). Aβ induces a chronic neuroinflammation that contributes to the neurite network disorganization and finally neuronal death. Lecanemab, a humanized monoclonal antibody (Ab) that recognizes protofibrils/oligomers and prevents Aβ deposition, is the first US approved Ab for AD. Its mode of action especially on inflammatory cells is still vague. In this study, we investigated Lecanemab's effect on microglial cells and astrocytes phenotype after Aβ stress.
Methods: Here primary rat cortical neurons, co-cultured with microglia and astroglial cells were used. After 11 days of culture, cells were injured with Aβ for 24 to 72h. Lecanemab was applied one hour before Aβ injury. After fixation, immunocytochemistry was performed in order to analyze different microglial and astroglial markers. For both cell types, pro and anti-inflammatory markers were assessed.
Results: Application of Aβ induced a proliferation of astrocytes and microglial cells. In addition, a significant increase in M1 microglia was observed associated with increase of TREM2/OX-41, 72h after Aβ application and microglial phagocytosis phenotype. A strong reduction of CD206 (M2 markers) was also detected. For astrocytes, a moderate astrogliosis was observed. Interestingly, Lecanemab treatment was able to increase number of S100A (+) cells (A2 population), associated with a moderate increase of GFAP area. This highlights that Lecanemab can induce a change in the astrocyte phenotype.
Conclusions: Altogether, these results showed that microglia and astrocytes phenotypes and functions were modified in disease context, and Lecanemab was able to modulate the Aβ neuroinflammatory response. These results tried to decipher the complex and unclear mode of action of Lecanemab.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0221 / #1161

Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

SUBSTRATE ECTODOMAIN DEFINES GAMMA-SECRETASE SEQUENTIAL PROTEOLYSIS, AND THEREBY ABETA PRODUCT PROFILES, BY MODULATING PRODUCT RELEASE

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

Matthias Koch[1], Thomas Enzlein[2], Shu Chen[3], Martin Zacharias[3], Carsten Hopf[2], Lucía Chávez-Gutiérrez[1]
[1]VIB, Vib-ku Leuven Center For Brain & Disease Research, Leuven, Belgium, [2]Mannheim University of Applied Sciences, Mass Spectrometry And Optical Spectroscopy, Mannheim, Germany, [3]Technical University of Munich, Physics Department, Garching, Germany

Aims: Sequential proteolysis of the amyloid precursor protein (APP) by γ-secretases (GSECs) defines the proportion of short-to-long amyloid-ß (Aß) peptides that are released into the extracellular/luminal space. This proportion is tightly linked to Alzheimer's disease (AD) pathogenesis. Here, we studied the mechanism(s) controlling the sequential GSEC proteolysis (processivity) and its modulation by small compounds, including GSEC modulators (GSMs) and GSEC inhibitors (GSIs).
Methods: *In vitro* GSEC activity assays were performed to investigate the molecular foundations of enzyme processivity. Thermoactivity assays assessed enzyme-substrate (E-S) stability. GSEC activity and processivity were estimated by western blotting, ELISA and/or mass spectrometry. Analysis of WT/mutant APP_{C99} processing was performed in the presence or absence of pharmacological inhibition or modulation.
Results: We found that polar interactions established by the ectodomain (ECD) of the substrate restrain both the extent and degree of GSEC processivity of APP and Notch. Most importantly, our study shows that the substrate ECD drives product release by destabilizing enzyme-substrate (E-S) interactions; and that increasing hydrophobicity at the APP_{C99} ECD, due to mutation or GSM binding, attenuates this substrate-driven product release mechanism and rescues the effects that AD pathogenic variants exert on Aß profiles. Finally, our study reveals that the paradoxical production of longer Aßs caused by some GSIs (e.g. DAPT and semagacestat) arises from a competitive mechanism, wherein GSI binding to the substrate-binding site either blocks substrate entry or results in the release of partially digested Aß peptides. The APP_{C99} ECD facilitates this process.
Conclusions: These findings assign a pivotal role to the substrate ECD in the sequential proteolysis by GSEC, and suggest it as a sweet spot for the potential design of APP targeting compounds, selectively promoting its processing by GSECs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0222 / #735

Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

DIPHENYLPYRAZOLE COMPOUNDS INHIBIT ABETA PEPTIDE PRODUCTION IN INDUCIBLE SY5Y-C99 CELLS.

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

Adriana Figueroa Garcia[1], Raphaëlle Pardossi-Piquard[2], Luc Buee[1], Patricia Melnyk[1], Frédéric Checler[2], Nicolas Sergeant[1]
[1]University of Lille, Lille Neuroscience & Cognition, Inserm U1172, Lille, France, [2]CNRS, Ipmc, Sophia Antipolis, Valbonne, France

Aims: Amyloid precursor protein (APP) cleavage by the β-secretase produces the β-CTF or C99 that is then endoproteolysed by the γ-secretase to produce the Aβ peptides. Cell expressing the C99 precludes the β-secretase cleavage to study its turnover along with the Aβ peptides. We described a diphenylpyrazole family of compounds that reduces the Aβ production and the soluble β-APP fragment counterpart, suggesting an indirect β-secretase inhibitory mode of action in APP-expressing cells. To better understand the diphenylpyrazole compounds' mode of action, inducible SY5Y-C99 expressing cells were used, and C99 expression and Aβ 1-40/42 and x-40/42 were quantified. We aimed to use structure-activity relationship to decipher the mode of action of the diphenylpyrazole compounds on APP metabolism downstream of the β-secretase cleavage of APP.
Methods: Inducible neuroblastoma SH-SY5Y cells expressing the C99 APP fragment were treated with the diphenylpyrazole compounds in comparison to lead compounds from our previously families of compounds (piperazine and polyaminobiaryl-derived compounds) along with proteasome, lysosomotropic, and γ-secretase inhibitors. C99 expression and metabolism were analyzed by immunoblotting. ELISA measured Aβ 1-40/42 and x-40/42 cell-medium concentration.
Results: Although Aβ 1-40/42 and x-40/42 were diminished by 50 and 75% for all diphenylpyrazoles, respectively, three types of carboxy-terminal fragments profiles distinguish 3 types of activity either comparable to a lysosomotropic class of drugs or proteasome inhibitors.
Conclusions: Structure-activity relationship of the diphenylpyrazole compounds suggests Aβ peptide inhibitors whose mode of action includes activity towards a lysosomotropic or proteasome inhibitory process. Further complementary data will be presented to decipher between these proteostasis mechanisms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0223 / #533

Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

HUMAN GAMMA-SECRETASE FAMILY: DIFFERENTIAL STABILITIES OF ENZYME-SUBSTRATE COMPLEXES EXPLAIN DIFFERENCES IN PROCESSIVITY AND REGULATE RESPONSE TO MODULATORS

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

Katarzyna Zoltowska, Maria Szaruga, Sara Gutiérrez-Fernandez, Sam Lismont, Lucía Chávez-Gutiérrez
VIB, Vib-ku Leuven Center For Brain & Disease Research, Leuven, Belgium

Aims: Gamma-secretases are multifaceted intramembrane proteolytic systems, the dysfunction of which leads to early-onset Alzheimer's disease (AD). They are composed of four subunits: presenilin (PSEN1 or PSEN2, catalytic subunit), nicastrin (NCSTN), presenilin enhancer 2 (PEN2) and anterior pharynx defective 1 (APH1A or APH1B). In humans, PSEN and APH1 heterogeneity gives rise to four complexes with distinctive proteolytic profiles. Here, we investigated the mechanistic basis for differences in kinetic and pharmacological properties of the human gamma-secretase family, with a focus on amyloid beta production.
Methods: Gamma-secretases and their substrates were expressed using baculoviral expression system and purified via affinity chromatography. *In vitro* gamma-secretase activity assays were performed in the presence or absence of pharmacological modulation. Thermoactivity assays informed about enzyme-substrate (E-S) complex stability.
Results: We found that significant differences in E-S complex stabilities, which define enzyme processivity and amyloid beta length, arise from the composition of gamma-secretases, with PSEN having the greatest impact. Notably, PSEN2-type complexes presented lower E-S stabilities, similar to those observed for early-onset AD-linked PSEN1 variants. The differential E-S complex stabilities modulated the processing of substrates, including the amyloid precursor protein. Finally, thermoactivity assays performed in the presence of gamma-secretase modulators (GSMs) demonstrated that the differential E-S stability translates not only into a distinct degree of enzyme processivity but also has an impact on the response to GSMs.
Conclusions: Our analyses demonstrated a marked impact of gamma-secretase complex composition on enzyme processivity and pharmacological modulation by GSMs. These findings are relevant for the design and analysis of drugs selectively targeting particular subtypes of gamma-secretase complexes in therapy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0224 / #773

Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

BACE1 INHIBITOR C3 DELIVERED TO THE HIPPOCAMPUS BY FOCUSED ULTRASOUND AMELIORATES ALZHEIMER'S-RELATED PATHOLOGY IN 5XFAD MICE

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

Grainne Geoghegan[1], Sophie Morse[2], Bibiana Mota[1], Julen Gomez-Elcano[1], Luciano Marinelli[1], James Choi[2], Magdalena Sastre[1]
[1]Imperial College London, Brain Sciences, London, United Kingdom, [2]Imperial College London, Bioengineering, London, United Kingdom

Aims: Beta-site APP cleaving enzyme-1 (BACE1) is the rate-limiting enzyme for amyloid-beta (Aβ) production and has been extensively investigated as a therapeutic target for Alzheimer's disease (AD). However, small molecule BACE1 inhibitors have consistently failed in clinical trials. An alternative is the use of low-dose BACE1 inhibition with a highly specific peptidomimetic compound, such as BACE1 inhibitor C3. However, this compound does not cross the blood-brain barrier (BBB). To overcome this, we used rapid short-pulse focused ultrasound (FUS) to transiently disrupt the BBB, allowing for targeted delivery of C3 to the brain. We hypothesise that C3 delivered by FUS is safe and will reduce amyloid pathology in the 5XFAD mouse model of AD.
Methods: Three-month old male 5XFAD mice were randomly assigned to four groups: untreated control, FUS+vehicle, C3 only and FUS+C3. Mice were treated with 0.6mg/kg C3 delivered by 1MHz FUS in a rapid-short pulse sequence targeted to the left hippocampus once a week for 3 weeks. The effects of the treatment were compared among groups and between ipsilateral and contralateral hemispheres. BACE1 activity, plaque load, glial activation and neuronal density were assessed by western blot, ELISA and immunohistochemistry.
Results: Chronic treatment with FUS+C3 reduced amyloid plaque load in the ipsilateral hippocampus compared to the contralateral hippocampus, but did not affect aggregated amyloid. Chronic treatment with FUS+C3 also significantly decreased β-CTF and Aβ expression when compared to the untreated control in frontal cortex homogenates. There were no differences in microglial activation, astrocyte coverage or neuronal density within groups.
Conclusions: C3 can be safely delivered across the BBB by FUS using a rapid short-pulse sequence. Chronic treatment with FUS+C3 reduced BACE1 activity in the cortex and amyloid plaque load in the targeted hippocampus.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0225 / #1900

Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

RETINOID SIGNALLING REGULATION OF ADAM SECRETASES AND MITOCHONDRIA AS A POSSIBLE AD MOLECULAR THERAPY

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

José João Mendonça Vitória, Diogo Trigo, Odete Da Cruz E Silva
Institute of Biomedicine - iBiMED, Departamento De Ciências Médicas - Dcm, Aveiro, Portugal

Aims: Introduction: Alzheimer's Disease (AD) is characterized by extracellular deposits of Aβ peptide, resulting from amyloid cleavage of APP. This processing is controlled by α-, β- and γ-secretase. Resulting fragment toxicity is a direct outcome of the first cleavage: β-secretase (BACE1) causes amyloid cleavage, while the competing α-secretases (ADAM10 and ADAM17) produce a protective cleavage. AD is also linked to several cellular alterations at the mitochondrial level. These anomalies can contribute to disease progression but may also trigger cellular rescue mechanisms. Objectives: This study assessed the potential of retinoid signalling as a therapeutic strategy for AD, by modulating cellular and molecular characteristics.
Methods: Methods: Differentiated SH-SY5Y cells were treated with diverse Retinoic Acid Receptor (RAR) agonists and antagonists, the oxidative agent Paraquat, and Aβ peptide. Protein alterations were assessed by western blotting. Mitochondrial changes and homeostasis were analysed by live imaging confocal microscopy.
Results: Results: Results showed a decrease in APP β-cleavage with RARα activation, potentially impacting protein levels via phosphorylation mediated modifications. Retinoid signalling appears to rescue oxidative stress induced mitochondrial damage.
Conclusions: Conclusion: These results lay the foundation to a promising therapeutic strategy, impacting several cellular processes towards neuronal health. Acknowledgments & Funding: This project was funded by FCT EXPL/BTM-SAL/0902/2021 (DT), La Caixa Foundation CI21-00276 (DT), CENTRO-01-0145-FEDER-181255 (OCS) and 739572 (OCS).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0226 / #1559

Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

MOLECULAR DYNAMICS ACTIVATION OF GAMMA-SECRETASE FOR PROCESSIVE CLEAVAGE OF AMYLOID PRECURSOR PROTEIN AND NOTCH SUBSTRATES

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

Hung Do[1], Sujan Devkota[2], Shweta Malvankar[2], Michael Wolfe[2], Yinglong Miao[3]
[1]University of Kansas, Department Of Molecular Biosciences, Lawrence, United States of America, [2]University of Kansas, Department Of Medicinal Chemistry, Lawrence, United States of America, [3]University of North Carolina - Chapel Hill, Computational Medicine Program And Department Of Pharmacology, Chapel Hill, United States of America

Aims: γ-Secretase, the "proteasome of the membrane", cleaves within the membrane of 150+ peptide substrates including amyloid precursor protein (APP) and Notch. γ-Secretase carries out endoproteolytic (ε) cleavage and then tripeptide trimming of the substrates. Presenilin-1 (PS1) is the catalytic subunit of γ-secretase and its mutations cause early-onset familial Alzheimer's disease (FAD). Here, we aim to determine molecular mechanisms of γ-secretase activation for processive cleavage of APP and Notch, as well as the effects of FAD mutations.
Methods: We combine all-atom simulations using a novel Gaussian accelerated Molecular Dynamics (GaMD) method and biochemical experiments (including mass spectrometry and western blotting) to investigate processive proteolysis of APP and Notch by γ-secretase, in the presence and absence of FAD mutations.
Results: We have previously reported that aromatic residues such as Phe are not tolerated in the P2' position for γ-secretase cleavage of APP substrate. We now show that this sequence specificity rule applies to Notch1 substrate as well and is therefore likely a general rule for all substrates. GaMD simulations have captured the slow dynamic conformational transitions of γ-secretase and proper cleavages of both the wildtype and mutant Notch1 substrate. In addition, our highly complementary simulations and experiments have revealed that FAD mutations reduced fluctuations the enzyme-substrate complex during the ε cleavage and tripeptide trimming of APP.
Conclusions: We have built the first dynamic models for cleavage of Notch1 and uncovered the effects of FAD mutations in processive proteolysis of APP by γ-secretase through novel GaMD simulations, which were highly consistent with complementary experimental findings. They have provided important mechanistic insights into the effects of mutations in substrate processing of APP and Notch by γ-secretase.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0227 / #1675

Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

INVESTIGATING THE ROLE OF RARE GENETIC VARIANTS IN ANGIOTENSIN-1-CONVERTING ENZYME IN ALZHEIMER'S DISEASE PATHOGENESIS

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

Miranda Salvo[1], Leah Cuddy[1], Dmitry Prokopenko[2], Rudolph Tanzi[2], Robert Vassar[1]
[1]Northwestern University, Neurology, Chicago, United States of America, [2]Mass General Institute for Neurodegenerative Disease, Massachusetts General Hospital, Genetics And Aging Research Unit, Department Of Neurology, Charlestown, United States of America

Aims: Recent genome-wide association studies discovered angiotensin-converting enzyme (*ACE*) as a risk locus for developing late-onset Alzheimer's disease (LOAD). The protein ACE1 is known for its role as a blood pressure regulating enzyme in the renin-angiotensin system; however, it is also present in the brain and has other substrates, including amyloid-β. Hypertension is associated with increased risk for developing AD, and people taking some ACE1-targeting therapeutics have reduced incidence of AD. Recent whole genome sequencing (WGS) of LOAD families revealed rare *ACE* coding variants. Previous work from our lab demonstrated that one such variant, rs4980, caused hippocampal neurodegeneration, which was exacerbated by amyloid pathology in a knock-in mouse model. Additional rare AD-risk and AD-protective variants were discovered by WGS in LOAD family cohorts. This project seeks to characterize these rare variants in a cellular model system in order to understand the mechanisms by which they could alter ACE1 processing, expression, function, and affect cell viability.
Methods: SH-SY5Y neuroblastoma cell lines stably expressing each *ACE* variant were used in the following experiments. Cell lines were differentiated for 5 days in retinoic acid, then subjected to experimental procedures to determine ACE1 expression and function as well as markers of apoptosis.
Results: AD-risk variants increased ACE1 catalytic activity while AD-protective variants altered ACE1 membrane expression and ectodomain shedding. No mutations caused overt cell death, indicating the potential involvement of other cell types in AD pathogenic mechanisms.
Conclusions: Increased ACE1 protein activity correlates with AD Braak staging, verifying our activity results. Furthermore, ACE1 ectodomain shedding from the cell membrane may be a protective characteristic in this culture model. Future directions include investigating pathogenic ACE1 substrates such as $A\beta_{42}$, C3, and angiotensin I.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0228 / #813

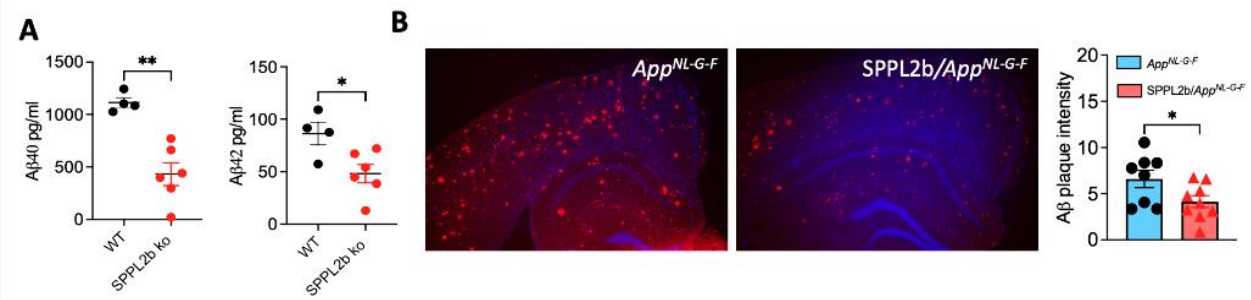
Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

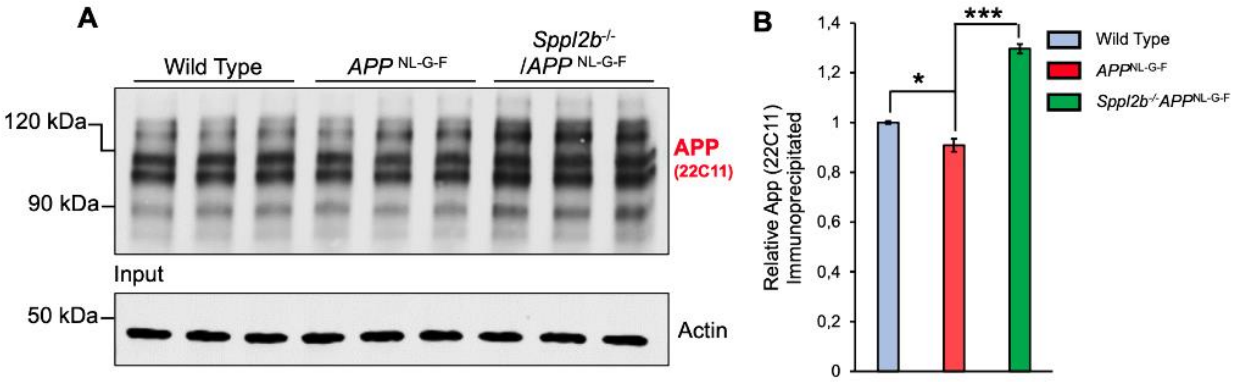
REVEALING A PROMISING THERAPEUTIC TARGET: GENETIC DELETION OF PRESENILIN-LIKE SIGNAL PEPTIDE PEPTIDASE-LIKE 2B HALTS AB-PRODUCTION AND PLAQUE DEPOSITION IN AN ALZHEIMER'S DISEASE MOUSE MODEL.

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

Jack Badman[1], Caterina Grassi[1], Per Nilsson[2], Simone Tambaro[1]
[1]Karolinska Institute, Department Of Neurobiology, Care Sciences And Society, stockholm, Sweden, [2]Karolinska Institutet, Division Of Neurogeriatrics, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden

Aims: Signal Peptide Peptidase-Like 2b (SPPL2b) is a promising brain-specific intramembrane protein involved in the cleavage of Alzheimer's disease (AD)-related proteins, such as BRI2, inflammatory-related proteins like CD74, TNFalpha, and Clec7a, and synaptic function proteins Neuregulin-1 and VAMP 1-4. SPPL2b is expressed specifically in the hippocampus and cortex. The cleavage of TNFalpha by SPPL2b promotes the inflammatory pathway. Conversely, the SPPL2b substrate BRI2 regulates amyloid precursor protein cleavage and Aß production. This work explores the pathophysiological role of SPPL2b in AD pathogenesis and investigates the potential of inhibiting SPPL2b as a novel therapeutic strategy.
Methods: To characterize the role of SPPL2b in the APP cleavage process, we used primary cell cultures from WT and SPPL2b-deficient mice. Furthermore, we assessed the therapeutic potential of inhibiting SPPL2b by employing a new AD mouse model generated through crossbreeding state-of-the-art AppNL-G-F knock-in mice with SPPL2b-deficient mice. Secreted Aβ peptides were quantified using ELISA. Cells and mouse brain samples were analyzed through western blotting, immunoprecipitation, and immunofluorescence.
Results: The results showed a significant increase in BRI2 staining, followed by a substantial reduction in soluble APP, Aβ40, and Aβ42 in the media of SPPL2b KO neurons (Fig.1A). Most importantly, a notable decrease in brain on Aβ42 levels and Aβ plaque deposition was observed at 4 months of age in SPPL2b-deficient/AppNL-G-F mice (Fig.1B). Furthermore, immunoprecipitation of BRI2 from the cortex of those mice revealed an increased interaction between BRI2 and APP
(Fig.2).





Conclusions: The results outlined in this study support a relevant connection between SPPL2b and AD. In a global scenario characterized by the need to identify novel strategies to prevent and counteract AD progression, this study highlights and strengthens the importance of SPPL2b as a novel therapeutic approach for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0229 / #2748

Poster Topic: *Theme A: β-Amyloid Diseases / A02.c. Therapeutic Targets, Mechanisms for Treatment: Secretases, proteases*

SENSITIVITY OF AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE (ADAD) MUTATIONS TO GAMMA SECRETASE MODULATORS IS INFLUENCED BY THE TYPE OF MUTATION AND THE PROPERTIES OF THE GSM

POSTERS: A02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: SECRETASES, PROTEASES

Lothar Lindemann[1], Rosa Maria Rodriguez Sarmiento[2], Johannes Trambauer[3], Holly Garringer[4], Katja Salbaum[5], Liliana Pedro[5], Dennis Crusius[5], Ruben Vidal[4], Rudolph Tanzi[6], Steven Wagner[7], Bernardino Ghetti[4], Dominik Paquet[8], Karlheinz Baumann[1], Harald Steiner[3], Rosanna Tortelli[9], Irene Gerlach[9]
[1]F. Hoffmann-La Roche AG, Neuroscience And Rare Diseases Translational Area, Neuroscience Discovery, Basel, Switzerland, [2]F. Hoffmann-La Roche AG, Pharma Research & Early Development, Therapeutic Modalities, Small Molecule Research, Basel, Switzerland, [3]Biomedical Center (BMC), Division of Metabolic Biochemistry, Faculty Of Medicine, Munich, Germany, [4]Indiana University, Pathology And Laboratory Medicine, Indianapolis, United States of America, [5]Ludwig Maximilium University of Munich, Institute For Stroke And Dementia Research, University Hospital, Munich, Germany, [6]Massachusetts General Hospital/Harvard U, Genetics And Aging Research Unit, Neurology, Charlestown, United States of America, [7]University of California, San Diego, Department Of Neurosciences, La Hoja, United States of America, [8]University Hospital, LMU Munich, Institute For Stroke And Dementia Research, Munich, Germany, [9]F. Hoffmann-La Roche AG, Pharma Research & Early Development, Neuroscience And Rare Diseases Translational Area, Neuroscience Early Development, Basel, Switzerland

Aims: Cerebral amyloid accumulation is an important causal factor of AD pathobiology. Long Aβ fragments such as Aβ42 are the major drivers of amyloid accumulation in the brain. Gamma Secretase Modulators (GSMs) reduce the production of amyloidogenic Aβ42 and Aβ40 while proportionally increasing the non-amyloidogenic shorter fragments Aβ38 and Aβ37. Here we investigated how the activity of GSMs is influenced by ADAD mutations and the type of GSMs studied.
Methods: The ADAD mutations PSEN1 E280A ('Columbian mutation'), PSEN1 L166P, and PSEN2 N141I ('Volga German') were studied for their sensitivity to GSMs in vitro.
Results: The PSEN1 E280A mutation showed equivalent sensitivity to GSMs compared to the WT allele, judged by the GSM's capacity to lower Aβ42 levels, compared to the PSEN2 N141I and PSEN1 L166P mutations. The latter two mutations were less sensitive to an early generation NSAID-type GSM compared to latest generation non-NSAID GSMs.
Conclusions: Responses to GSMs have been described for wild type Gamma Secretase (sporadic AD; healthy volunteers) but can differ in ADAD with mutated Gamma Secretase. We show that the presence of ADAD PSEN1/2 mutations profoundly impact the sensitivity of gamma secretase to GSMs. Both non-NSAID and NSAID GSM can ameliorate the effect of specific ADAD mutations, as judged by their Aβ42 lowering potential. However, the efficacy of NSAID and next generation non-NSAID GSMs is variable depending on the nature of specific PSEN1/2 ADAD mutations. Our studies emphasize the importance of carefully characterizing the pharmacology of GSMs in the presence of specific PSEN1/2 ADAD mutations for assessing the potential therapeutic effects of various GSMs in subjects with ADAD mutations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0230 / #648

Poster Topic: *Theme A: β-Amyloid Diseases / A02.d. Therapeutic Targets, Mechanisms for Treatment: Kinases, other enzymes*

CHEMICAL, BIOCHEMICAL, CELLULAR, AND PHYSIOLOGICAL CHARACTERIZATION OF LEUCETTINIB-21, A DOWN SYNDROME AND ALZHEIMER'S DISEASE DRUG CANDIDATE

POSTERS: A02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

Laurent Meijer, Emmanuel Deau, Gaëlle Hogrel, Mattias Lindberg
Perha Pharmaceuticals, Neurosciences, Roscoff, France

Aims: Memory and learning disorders in **Down syndrome** (**DS**) and **Alzheimer's disease** (**AD**) are associated with an increased activity of **DYRK1A** (dual specificity, tyrosine phosphorylation regulated kinase). In DS, DYRK1A is overexpressed by a 1.5-fold factor (*Dyrk1a* gene on chromosome 21) while, in AD, DYRK1A is cleaved by calpains to a low-molecular weight form with enhanced activity and stability. Genetic and pharmacological inhibition of DYRK1A corrects these cognitive disorders in DS/AD animal models, encouraging the development of a **clinical DYRK1A inhibitor** to treat memory/learning difficulties in patients with AD or DS.
Methods: Inspired by **Leucettamine B**, a marine sponge natural product, we synthesized, optimized and extensively characterized >500 analogues, **Leucettines**, followed by a second-generation family, **Leucettinibs** (>670 analogues) and selected an orally available drug candidate, **Leucettinib-21** with favorable pharmacological properties.
Results: Leucettinib-21 was chosen as a drug candidate following extensive structure/activity studies and multiparametric evaluations. We will present its **physico-chemical properties** (X-ray powder diffraction, differential scanning calorimetry, stability, solubility, crystal structure) and **drug-like profile**. Leucettinib-21's **kinase inhibitory selectivity** (analyzed by radiometric, fluorescence, interaction, thermal shift, residence time assays) reveals DYRK1A as the first target, but also some 'off-targets' which may contribute to the drug's biological effects. Leucettinib-21 was **co-crystallized with CLK1** and **modelled in the DYRK1A structure**. Leucettinib-21 inhibits native, endogenous DYRK1A in cells (demonstrated by direct catalytic activity, and phosphorylation levels of Thr286-cyclin D1 or Thr212-Tau). Leucettinib-21 **corrects memory disorders** in the Down syndrome mouse model Ts65Dn.
Conclusions: Leucettinib-21 is entering safety/tolerance phase 1 clinical trials in Q4-2023.

P0231 / #437

Poster Topic: *Theme A: β-Amyloid Diseases / A02.d. Therapeutic Targets, Mechanisms for Treatment: Kinases, other enzymes*

UNVEILING PHYTOCONSTITUENTS WITH INHIBITORY POTENTIAL AGAINST TYROSINE-PROTEIN KINASE FYN: A COMPREHENSIVE VIRTUAL SCREENING APPROACH TARGETING ALZHEIMER'S DISEASE

POSTERS: A02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

Anas Shamsi[1], Akhtar Atiya[2], Saleha Anwar[3]
[1]Ajman University, Centre Of Medical And Bio-allied Health Sciences Research (cmbhsr), Ajman, United Arab Emirates, [2]King khalid university, Pharmacognosy, Abha, Saudi Arabia, [3]jamia millia islamia, Cirbsc, New Delhi, India

Aims: Tyrosine-protein kinase Fyn (Fyn) is a critical signaling molecule involved in various cellular processes, including neuronal development, synaptic plasticity, and disease pathogenesis. Dysregulation of Fyn kinase has been implicated in various complex diseases, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, as well as different cancer types. Therefore, identifying small molecule inhibitors that can inhibit Fyn activity holds substantial significance in drug discovery. The aim of this study was to identify potential small-molecule inhibitors among bioactive phytoconstituents against tyrosine-protein kinase Fyn.
Methods: Through a comprehensive approach involving molecular docking, drug likeliness filters, and molecular dynamics (MD) simulations, we performed a virtual screening of a natural compound library. This methodology aimed to pinpoint compounds potentially interacting with Fyn kinase and inhibiting its activity.
Results: Our study finds two potential natural compounds: Dehydromillettone and Tanshinone B. These compounds demonstrated substantial affinity and specific interactions towards the Fyn binding pocket. Their conformations exhibited compatibility and stability, indicating the formation of robust protein-ligand complexes. A significant array of non-covalent interactions supported the structural integrity of these complexes.
Conclusions: Dehydromillettone and Tanshinone B emerge as promising candidates, poised for further optimization as Fyn kinase inhibitors with therapeutic applications. In a broader context, this study demonstrates the potential of computational drug discovery, underscoring its utility in identifying compounds with clinical significance. The identified inhibitors hold promise in addressing a spectrum of cancer and neurodegenerative disorders. However, their efficacy and safety necessitate validation through subsequent experimental studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0232 / #1144

Poster Topic: *Theme A: β-Amyloid Diseases / A02.e. Therapeutic Targets, Mechanisms for Treatment: Neurotransmitters & receptor-based*

EVIDENCE FOR DISEASE MODIFYING PROPERTIES OF MEMANTINE WHEN ADMINISTERED PROPHYLACTICALLY TO TRANSGENIC AD AND PURE TAUOPATHY MODEL MICE

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

Antonia Silva[1], Anna Wasserman[1], Dora Wang[1], Taylor Kim[1], Maurits Jansen[2], Jeremy Gatesman[3], Ileana Mauldin[4], Stuart Berr[2], George Bloom[1]
[1]University of Virginia, Dept. Of Biology, Charlottesville, United States of America, [2]University of Virginia, Radiology And Medical Imaging, Charlottesville, United States of America, [3]University of Virginia, Center For Comparative Medicine, Charlottesville, United States of America, [4]University of Virginia, Dept. Of Pathology, Charlottesville, United States of America

Aims: Our laboratory previously reported that memantine potently blocks neuronal cell cycle re-entry, which precedes most neuron death in AD, when provided to Aβ oligomer-treated cultured mouse neurons and Tg2576 AD model mice (https://doi.org/10.1016/j.jalz.2018.05.017). Those results raised the possibility that memantine, which is FDA-approved for treating moderate to severe AD, has previously unrecognized disease-modifying properties that can be harnessed prophylactically for AD and related diseases (ADRDs). To test that possibility, the current study compared effects of treating AD and pure tauopathy mice with memantine, beginning either before cognitive deficits occur (early) versus when they first appear (late).
Methods: J20 (AD), hTau (pure tauopathy) and congenic wild type (WT) mice had *ad libitum* access to memantine in drinking water. Early treatments began at 5 weeks, and late treatments began at 4 and 6 months, respectively, for J20 and hTau mice. All animals were periodically evaluated by Morris water maze (MWM), novel object recognition (NOR), live animal amyloid PET (J20s only) and MRI, and immunohistochemistry. The experiments ended when mice reached 18 months.
Results: Baseline MWM and NOR performances at the beginning were indistinguishable by strain. At 18 months, however, all mice treated early with memantine had improved MWM performances compared to untreated or late treated mice of the same strain. NOR performance at 18 months was similarly improved for early treated J20s. Early, but not late treatment of J20s caused a striking reduction in plaques at 18 months.
Conclusions: When administered prophylactically to AD and pure tauopathy mice, but not when treatment begins at symptom onset, memantine has disease modifying properties, and reduces learning and memory loss associated with normal aging. These results justify testing memantine prophylactically for human ADRDs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0233 / #916

Poster Topic: *Theme A: β-Amyloid Diseases / A02.e. Therapeutic Targets, Mechanisms for Treatment: Neurotransmitters & receptor-based*

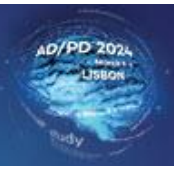
ONESTX-1, A STEROID SULFATASE INHIBITOR, AS A NOVEL PHARMACOLOGICAL APPROACH TO TREAT ALZHEIMER'S DISEASE

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

Manuel J. Muñoz[1,2], Mercedes M. Pérez-Jiménez[1,2], Juan Antonio Fernández Cabrera[3], Almudena Ramos Pozo[1], Ines Sánchez Romero[3], Carlos Gómez Marín[1], José María Hernández Curiel[3], Viñas Andrés Simón[2], Sandra Gavaldá[2], Ángel Cebolla[2], Ángel Carrión Rodríguez[2,3]
[1]Centro Andaluz de Biología del Desarrollo (CABD), J.A., UPO, Molecular Biology And Biochemical Engineering, Sevilla, Spain, [2]OLAVIDE NEURON STX, Company, Sevilla, Spain, [3]University Pablo de Olavide, Physiology, Anatomy And Cellular Biology, Sevilla, Spain

Aims: ONESTX-1/STX64/irosustat is a small molecule that inhibits steroid sulfatase (STS) and showed to be active against Alzheimer and Parkinson in animal models. Oral administration of ONESTX-1 induces increment in the ratio of sulfated vs free steroids in animals and humans. In addition, ONESTX-1 showed a good safety and tolerability profile studied in several clinical trials for previous oncology indications. ONESTX-1 increased the lifespan of *C. elegans*, produced beta-amyloid decrease and memory recovery in Alzheimer mice models (Pérez-Jiménez, 2021). In this work, we studied if memory recovery in old mice could be associated to the activation of the cholinergic activity and other pathways associates to starvation.
Methods: Old mice showing cognitive impairment were used in chronic treatment for 6 months (2 mg/L ONESTX-1 in water from a concentrated stock of 5 mg/mL in DMSO). The passive avoidance test was used to assess memory recovery. Nematodes were treated with 1mM of aldicarb to assay cholinergic activity in wild type or in mutants of putative target genes.
Results: Old mice showed memory recovery in the passive avoidance test with ONESTX-1 or epitestosterone sulfate. Others hallmarks of aging, that appear exacerbated in AD, like acetylcholine deficiency, adult neurogenesis decrease and neuroinflammation seems to be rescued by ONESTX-1 treatment. Using mutant strains in *C. elegans*, we started to elucidate the molecular mechanism triggering this effect.
Conclusions: ONESTX-1 may act at different levels against the progression of Alzheimer's disease according to the preclinical data. The antiaging effect of ONESTX-1 at different levels has been shown to be a novel strategy to fight Alzheimer and Parkinson diseases. One of the downstream actions of ONESTX-1 administration was to induce cholinergic activity, which is impaired in Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0234 / #1122

Poster Topic: *Theme A: β-Amyloid Diseases / A02.e. Therapeutic Targets, Mechanisms for Treatment: Neurotransmitters & receptor-based*

LEVETIRACETAM PREVENTS AB42 PRODUCTION BY MODULATING APP PROCESSING AND DECELERATES SYNAPSE LOSS IN MOUSE MODELS OF AMYLOID PATHOLOGY.

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

Nalini Rao, Jeffrey Savas
Feinberg School of Medicine, Northwestern University, Neurology, Chicago, United States of America

Aims: Impaired proteostasis in a hallmark of Alzheimer's disease (AD) and the inability to degrade $A\beta_{42}$ drives downstream pathologies such as synapse deterioration, plaque formation, and neurofibrillary tangles. While downstream repercussions of hampered proteostasis are documented, we lack an understanding of early AD-pathologies that may serve as therapeutic targets. We previously discovered impaired degradation of synaptic vesicle (SV) proteins in *App*-KI mouse models that importantly occurred before $A\beta_{42}$ accumulation. In this work, we investigated how targeting SVs pharmacologically with FDA-approved anticonvulsant Levetiracetam (Lev) could rescue amyloid pathology.
Methods: To achieve this, we utilized *App*-KI models combined with proteostasis reporter lines, mass spectrometry-based analysis, biochemistry, and *in vitro* parallels to address this question.
Results: First, we found a functional proteostasis impairment at presynaptic sites in *App*-KI mice. Next, isolation of SVs from *App*-KI and human Down Syndrome brains with proteolysis determined the orientation of App in SVs. From this finding, we hypothesized the inability to degrade SVs may result in increased amyloidogenic processing. To target SVs, we utilized Lev as this drug binds SV2a and has been shown to slow cognitive decline in AD patients, however the mechanism of action remains unknown. Utilizing *in vivo* stable-isotope mass spectrometry-based quantification, we discovered that Lev notably prevents production of $A\beta_{42}$ via altering the App processing pathway. Next, using an *in vitro* parallel of *App*-KI mice, we found that this function of Lev is SV2a-dependent and modulates amyloidogenic processing by maintaining App plasma membrane localization. Lastly, we demonstrate that Lev treatment decelerates synapse loss in J20 mice.
Conclusions: Taken together, this work determines the mechanism of action for Lev's therapeutic effect in AD, which represents a robust drug-repurposing candidate as it prevents the early stage of $A\beta_{42}$ production.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0235 / #153

Poster Topic: *Theme A: β-Amyloid Diseases / A02.e. Therapeutic Targets, Mechanisms for Treatment: Neurotransmitters & receptor-based*

DESIGN, SYNTHESIS, IN SILICO AND BIOLOGICAL EVALUATION OF MULTI-TARGETABLE CHALCONE DERIVATIVES BEARING N-ARYL PIPERAZINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

Sushil Kumar Singh, Ashok Kumar, Nilesh Bajad
Indian Institute of Technology (BHU), Department Of Pharmaceutical Engineering & Technology, Varanasi, India

Aims: To develop a drug molecule targeting by two or more mechanisms i.e., a multi-target-directed ligand (MTDL). It is one of the worthwhile approaches in drug discovery against multifactorial diseases like Alzheimer's disease (AD).
Methods: The novel potential MTDLs were designed by scaffold hopping guided strategy and subjected to *in silico* studies and molecular properties analysis. Accordingly, a series of 17 novel multi-targetable chalcone derivatives were synthesized and evaluated for the inhibition of ChEs (eeAChE and eqBuChE), hBACE-1 and blood-brain barrier permeability assay. Furthermore, *in-vivo* behavioural studies were performed on scopolamine-induced amnesia model.
Results: The synthesized lead molecule showed optimal inhibitory activities in micro-molar range against AChE with IC_{50} value of **14.84 ± 1.562** µM and significant BuChE inhibition. It also showed promising blood-brain barrier (BBB) permeability, potential BACE-1 inhibitory activity, and Aβ1-42 aggregation inhibition. The binding mode analysis and protein-ligand stability of the optimal compound with AChE and BACE-1 were revealed with the molecular docking and dynamics simulation studies. The compound showed significant mprovement in memory function in the scopolamine-induced mice model.
Conclusions: Amongst all the tested derivatives, lead-bearing unsubstituted benzylpiperazine fragment and para-bromo substation at chalcone scaffold exhibited potent AChE inhibitory property with significant inhibition of *h*BACE-1. In particular, the findings revealed that the carbon linker between the piperazine and aryl ring-bearing electronegative substituent was essential for the potential activity. Overall results indicated that the multi-targetable chalcone derivatives bearing n-aryl piperazine may be potential novel therapeutic agent for the management of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0236 / #2177

Poster Topic: *Theme A: β-Amyloid Diseases / A02.e. Therapeutic Targets, Mechanisms for Treatment: Neurotransmitters & receptor-based*

SYNERGISTIC EFFECTS OF GALANTAMINE AND COTININE IN A TRANSGENIC RAT MODEL OF AD

POSTERS: A02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

Carla Wahlich, Johanna Habermeyer, Stephan Von Hörsten
University Hospital Erlangen, Department Of Experimental Therapy And Preclinical Experimental Animal Center, Erlangen, Germany

Aims: Since current treatment strategies for AD show limited efficacy and substantial side effects, new and innovative approaches are needed to provide successful therapy within a worldwide aging population. The aim of this study is to pin down synergistic effects of chronic co-treatment using cotinine, a positive allosteric modulator of alpha7-nicotinic acetylcholine receptors plus galantamine, an acetylcholine-esterase inhibitor. Single and combined preclinical therapeutic efficacy of both components is evaluated in hAPP-transgenic rats with endpoints in information processing, emotionality, memory, attention and cognition.
Methods: 6-month-old pre-symptomatic McGill-R-Thy1-APP and wildtype rats receive either galantamine (3 mg/kg/24h) or cotinine (2 mg/kg/24h) individually or combined via drinking water for 13 weeks. General phenotyping evaluating metabolism (activity and calorimetry) and sensorimotor function (startle response) is conducted before and during the treatment phase. Effects of treatment on emotionality, memory (object recognition), cognitive flexibility and attention (operant conditioning) are assessed starting at the eighth week of the treatment phase.
Results: Evaluation of sensorimotor function confirmed genotype differences such as reduced pre-pulse inhibition in transgenic animals in accordance with previous studies in rodents and patients. Co-treatment remarkably increased pre-pulse inhibition suggesting potentiated benefits compared to single compound administration.
Conclusions: Our project aims to tackle AD symptoms by boosting the cholinergic neurotransmission in a dual manner using galantamine and cotinine, both with promising clinical properties. Effects of their co-treatment on pre-pulse inhibition confirm the successful administration and appropriate dosage of the drugs and support the hypothesis of a positive outcome of synergistic cholinergic modulation on AD pathology. Lack of genotype and treatment effects on advanced memory tasks may be due to the relatively young age of the animals and the comparatively long treatment phase (7 weeks) before behavioral testing.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0237 / #606

Poster Topic: *Theme A: β-Amyloid Diseases / A02.f. Therapeutic Targets, Mechanisms for Treatment: ApoE & lipoprotein-based*

NOVEL EPIGENOME-EDITING PLATFORM FOR TREATMENT OF ALZHEIMER'S DISEASE

POSTERS: A02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: APOE & LIPOPROTEIN-BASED

Boris Kantor[1,2], Bernadette Odonovan4[2], Joseph Rittiner[1], Wendy Dong[1], Ornit Chiba-Falek[3]
[1]Duke University, Neurobiology, Durham, United States of America, [2]Duke University, Neurology, DURHAM, United States of America, [3]Duke University, Neurology, Durham, United States of America

Aims: Adeno-associated (AAV) vectors are the therapeutic platform of choice for delivery of genetic cargoes; nevertheless, their small packaging capacity is not suitable for the delivery of large constructs, including most CRISPR/dCas9-effector systems. To circumvent this limitation, here we aimed to develop a compact dCas9-based repressor system packaged within a single, optimized AAV vector. We aimed to evaluate the developed system on its ability to silence *APOE*, the primary genetic risk factor for late onset Alzheimer's disease (LOAD).
Methods: To circumvent small packaging capacity of AAVs, here we applied a robust reporter-based single- virus resolution screening method to devise and select for a compact dCas9-based repressor system packaged within a single, optimized vector. The developed system uses a smaller dCas9 variant derived from *Staphylococcus aureus* (*Sa*). A novel repressor was engineered by fusing the small transcription repression domain (TRD) from MeCP2 with the KRAB repression domain. The final d*Sa*Cas9-KRAB-MeCP2(TRD) construct can be efficiently packaged, along with its associated gRNA, into AAV particles.
Results: The AAV-based system, outlined in this study, supported efficient and long-term and sustainably repressing of the expression of multiple genes-of-interest, both *in vitro* and *in vivo*. Most relevantly, we successfully silenced *APOE*, the primary genetic risk factor for late onset Alzheimer's disease (LOAD).
Conclusions: Here we develop a compact dCas9-based repressor system packaged within a single, optimized AAV vector. This new platform will broaden the CRISPR/dCas9 toolset available for transcriptional manipulation of gene expression in research and therapeutic settings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0238 / #943

Poster Topic: *Theme A: β-Amyloid Diseases / A02.f. Therapeutic Targets, Mechanisms for Treatment: ApoE & lipoprotein-based*

FUNCTIONAL AND MORPHOLOGICAL EFFECTS OF 12 KDA C-TERMINAL APOE FRAGMENTS IN RAT CORTEX CULTURES

POSTERS: A02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: APOE & LIPOPROTEIN-BASED

Christina Nodin[1], Charlotte Mattsson[2], Charlotte Sahlin[2], Christer Möller[2], Johanna Fälting[2], Johan Pihl[1], Paul Karila[1], Susanne Fabre[2]
[1]Cellectricon AB, Cellectricon Ab, Mölndal, Sweden, [2]BioArctic AB, Research & Development, Stockholm, Sweden

Aims: In a previous study, 12 kDa C-terminal ApoE fragments were identified to be increased in Alzheimer's disease (AD) brain as compared to non-demented controls (NDC). To evaluate potential effects of these fragments in AD pathogenesis we used optical electrophysiology and high content imaging (HCA)-based assays to study effects on function and morphology of neurons and astrocytes in neuronal rat cortical cultures.
Methods: Embryonic rat cortical (rCtx) 384-well format cultures were either transduced with Adeno-associated viruses (AAVs) carrying vectors encoding C-terminal ApoE fragments, or fragments were added directly to cells. Neuronal and astrocyte morphology was quantified using HCA. Further, an optical electrophysiology platform was used to investigate effects on neuronal network activity.
Results: Extracellular addition of 12 kDa C-terminal ApoE fragments to rCtx cultures did not result in any effects on either morphological or functional parameters. This was probably caused by an inadequate uptake of the fragments by the cells. However, using AAV-based expression of 12 kDa C-terminal ApoE fragments, successful expression was demonstrated intracellularly in both neurons and astrocytes. As a result of fragment expression, the number of astrocytes and the density of the astrocytic network was decreased, whereas no effects were observed on the neuronal morphology. The astrocytes thus appeared to be more vulnerable to transduction with AAV-ApoE fragments compared to the neurons. Interestingly, spontaneous neuronal activity was affected by expression of ApoE fragments.
Conclusions: An AAV-based approach to achieve intracellular expression of ApoE fragments was established. Expression of ApoE fragments caused a decrease in astrocytic number and cellular network density. Further, neuronal activity was altered in presence of the 12 kDa C-terminal ApoE fragments. Future studies should include appropriate AAV-controls to ensure the specific effects observed.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0239 / #562

Poster Topic: *Theme A: β-Amyloid Diseases / A02.f. Therapeutic Targets, Mechanisms for Treatment: ApoE & lipoprotein-based*

INCREASED LEVEL OF 12 KDA C-TERMINAL APOE FRAGMENTS IN AD BRAIN

POSTERS: A02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: APOE & LIPOPROTEIN-BASED

Charlotte Sahlin[1], Charlotte Mattsson[1], Alex Kasrayan[1], Sofi Andersson[1], Hiroaki Hagiwara[2], Kunihiko Kanatsu[2], Dan Sunnemark[3], Susanne Fabre[1], Charlotte Silfverhielm[1,4], Christer Möller[1], Johanna Fälting[1]
[1]BioArctic AB, Research, Stockholm, Sweden, [2]Eisai Co., Ltd, Eisai Co., Ltd, Tsukuba, Japan, [3]Offspring Biosciences AB, Offspring Biosciences, Södertälje, Sweden, [4]Uppsala University, Department Of Public Health/geriatrics, Uppsala, Sweden

Aims: The epsilon4 (E4) allele of apolipoprotein E (APOE) is a major genetic risk factor for late-onset Alzheimer's disease (AD), yet the pathological mechanism is not fully understood. Compared to ApoE2 and ApoE3, ApoE4 is more vulnerable to undergo proteolytic cleavage generating fragments, some of which have been found to be neurotoxic. We analyzed ApoE fragments in brain extracts from AD and non-demented controls (NDE) and identified fragments that were increased in AD brain. Antibodies selective for the identified fragments were developed.
Methods: ApoE fragments in brain extracts from AD and NDE were analyzed using immunoprecipitation (IP) and Western blot (WB), and ApoE bands were excised from SDS/PAGE gel. Protein sequences were identified using nanoLC-MS/MS. Antibodies towards the N-terminus of the different fragment neo-epitopes were generated using hybridoma technique and fragment selectivity was tested using ELISA. Monoclonal antibodies were assessed for target binding by IP of human AD brain extracts and by immunohistochemistry (IHC) on AD brain sections.
Results: WB analysis of human brain extracts revealed a 12 kDa ApoE band that showed increased intensity in AD brain as compared to NDE. NanoLC-MS/MS analysis of the isolated ApoE band demonstrated fragments cleaved at position L198, A199 and G200, all with an intact C-terminus. Monoclonal antibodies selective for the three ApoE fragments were generated and shown to have >1000-fold selectivity for the fragments versus full length ApoE. IP using the fragment selective antibodies demonstrated specific binding in AD brain extracts. Moreover, IHC showed association of the ApoE fragments to amyloid plaques and cerebral amyloid angiopathy on AD brain sections.
Conclusions: C-terminal ApoE fragments were identified as increased in AD brain. Monoclonal antibodies selective for the three fragment variants were generated and used for further characterization.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0240 / #347

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

TARGETING TNF RECEPTORS IN THE TREATMENT OF ALZHEIMER`S DISEASE

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Irem Bayraktaroglu[1], Natalia Ortí-Casañ[1], Roman Fischer[2], Melanie Eschborn[2], Peter De Deyn[3], Ulrich Eisel[1]
[1]University of Groningen, Department Of Molecular Neurobiology, GRONINGEN, Netherlands, [2]Resano GmbH, Resano Gmbh, Mainz, Germany, [3]University of Groningen, Department Of Neurology And Alzheimer Center, Groningen, Netherlands

Aims: Tumor necrosis factor alpha (TNF-α), a pro-inflammatory cytokine, has been implicated in the pathogenesis of AD. However, anti-TNF therapies failed so far in treating Alzheimer's disease due to the opposing functions of TNF receptors, with TNFR1 associated with neurodegeneration and TNFR2 associated with neuroprotection. Thus, specific targeting TNFR could represent a promising strategy for AD treatment. In this study, we investigate the efficacy of a TNFR1 antagonist and novel TNFR2 agonist in the J20 mouse model of AD.
Methods: Mice will be treated with the TNFR1 antagonist or the novel TNFR2 agonist via intraperitoneal (ip) injections for 6 weeks, twice a week, while the control group will receive phosphate-buffered saline (PBS) injections. At the end of the treatment, behavioral tests will be conducted to assess spatial memory, working memory, and anxiety levels. After the perfusions, FACS analysis will be performed to determine the peripheral effects of the treatment. The brain sections will be immunohistochemically stained for different markers, not only but including Aβ plaques, microglial activation, phagocytic microglia, and inflammasome formation.
Results: Our group has recently shown that a TNFR2 agonist ameliorated neuropathology and improved cognition in an AD mouse model. Moreover, we demonstrated that a TNFR1 antagonist reduces memory deficits in an acute mouse model of neurodegeneration. Thus, in this study, we expect improved cognition, reduced AB plaques, increased microglial activation, and increased phagocytic microglia around the plaques. We also expect to see changes in T-cell response and pro-inflammatory response.
Conclusions: Our study aims to evaluate the efficacy of the TNFR1 antagonist and a novel TNFR2 agonist in mitigating AD neuropathology and improving cognition as well as finding peripheral changes to support the hypothesis that AD is more than a brain disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0241 / #293

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

ENHANCED IN VIVO BLOOD BRAIN BARRIER TRANSCYTOSIS OF A P2X7 RECEPTOR BLOCKING MACROMOLECULAR CARGO USING AN ENGINEERED PH-SENSITIVE MOUSE TRANSFERRIN RECEPTOR BINDING NANOBODY

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

David Brody
Uniformed Services University of the Health Sciences, Neurology, Bethesda, United States of America

Aims: The blood brain barrier (BBB) limits entry of macromolecular diagnostic and therapeutic cargos. BBB transcytosis via receptor mediated transport systems, such as the transferrin receptor, can be used to carry macromolecular cargos with variable efficiency. We hypothesized that pH-dependent unbinding of transport shuttles can be used to improve BBB transport efficiency.
Methods: A mouse transferrin receptor binding nanobody, NIH-mTfR-M1, was engineered to confer greater unbinding at pH 5.5 vs 7.4 by introducing multiple histidine mutations. Multi-nanobody constructs including the mutant $M1_{R56H,\ P96H,\ Y102H}$ and two copies of the P2X7 receptor-blocking 13A7 nanobody were produced to test proof-of-concept macromolecular cargo transport *in vivo* using quantitatively verified capillary depleted brain lysates and *in situ* histology. All animal studies were approved by the NINDS IACUC.
Results: Levels of the heterotrimeric construct $M1_{R56H,\ P96H,\ Y102H}$ -13A7-13A7 in capillary depleted brain lysates peaked at 1 hour and were 60% retained at 8 hours. A control construct with no brain targets was only 15% retained at 8 hours. At 30-60 minutes, the biotinylated nanobody construct was visualized in capillaries using *in situ* histochemistry, whereas at 2-16 hours it was detected in diffuse hippocampal and cortical cellular structures. Levels of the construct reached more than 3.5% injected dose/gram of brain tissue after 30 nmol/kg intravenous injection. However, higher injected concentrations did not result in higher brain levels, compatible with saturation and an apparent substrate inhibitory effect.
Conclusions: The pH-sensitive mouse transferrin receptor binding nanobody may be useful for rapid and efficient modular transport of macromolecular cargos across the BBB in mouse models. Additional development will be required to determine whether this nanobody-based shuttle system will be useful for brain imaging and fast-acting therapeutics to reduce aberrant neuroinflammatory P2X7 signaling.

P0242 / #2402

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

NETWORK PROXIMITY IS PROMISING IN ANTI-INFLAMMATORY DRUGS TO ALZHEIMER'S DISEASE TARGETS

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Jingchun Chen, Joan Cue, Davis Dammann, Jeffrey Cummings
University of Nevada, Las Vegas, Nevada Institute Of Personalzied Medicine, Las Vegas, United States of America

Aims: Disease-modifying therapies (DMTs) for Alzheimer's disease (AD) have a near 100% failure rate in clinical trials. One common cause is the lack of engagement with protein targets relevant to the disease. A promising approach to address this concern is to calculate the network proximity of drug targets to AD-associated targets within the graph network of the human protein-protein interactome (PPI).
Methods: In this preliminary study, we assessed the network proximity of drugs with anti-inflammatory mechanisms of action that are currently in the AD clinical trial pipeline (n=21) to AD risk targets. All candidate drugs and their targets were obtained from the DrugBank database, and AD-associated targets were from a recent GWAS. We calculated the closest proximity of targets for each drug to the AD target module within the human PPI network. We then generated relative distances (z-scores) along with their *p*-values. Finally, we established the drug-disease relationships based on randomly sampled modules with the same number of connections as the original drug-disease modules. Drugs with a negative z-score and $p < 0.05$ are considered to be closer to the target disease than expected by chance, whereas drugs with a positive z-score are farther away.
Results: Our results indicate that Masitinib, as well as a combination of Dasatinib and Quercetin, exhibited significant relative proximity to the AD module ($p < 0.05$).
Conclusions: Of note, the proximity of Masitinib is particularly promising, given that a recent phase 3 trial of the drug demonstrated significant improvement in cognition and daily living compared to the placebo. Further validation including more drugs in proximity calculations with cell-type-specific AD target modules, along with patient electronic health records data and comparator drugs is warranted.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0243 / #2039

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

INHIBITION OF P38ALPHA MAPK RESCUES SYNAPTIC FUNCTION AND BEHAVIORAL PERFORMANCE IN A MOUSE MODEL OF MIXED VASCULAR AND AMYLOID PATHOLOGIES

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Hilaree Frazier, David Braun, Verda Davis, Meggie Coleman, Colin Rogers, Linda Van Eldik
University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America

Aims: Cerebrovascular dysfunction is frequently comorbid with Alzheimer's disease (AD), yet the mechanistic consequences of this mixed pathology remain unclear. Recent work suggests that p38alpha MAPK, a regulator of neuroinflammation, may represent an effective target for AD therapies. For example, MW150, a small molecule p38alpha inhibitor, was shown to improve cognition and decrease cytokines in amyloidogenic mice. However, p38alpha inhibition in the context of mixed vascular and AD pathologies has yet to be thoroughly characterized. We therefore tested if MW150 could reduce neuroinflammation, synaptic dysfunction, and cognitive impairment in a model of mixed amyloid and cerebral small vessel disease (hyperhomocysteinemia [HHcy]).
Methods: To induce HHcy, 5xFAD mice were transferred to a B-vitamin-deficient diet for 8-weeks. WT animals were maintained on control diet. During diet exposure, animals also received intraperitoneal injections of saline vehicle or MW150. Endpoints included behavioral assessments, quantification of cytokines, immunohistochemistry, neuroimaging, and extracellular field recordings.
Results: Mixed dementia (MD) mice had altered cerebrovascular function, increased proinflammatory cytokines and glial cell activation, impaired synaptic transmission, reduced synaptic proteins, and worsened behavioral performance. No effect of MW150 was detected on cytokines, amyloid or vascular pathology, or glial cell activation. Surprisingly, however, the compound did rescue several measures associated with synaptic dysfunction, including population spike thresholds, LTP maintenance, synaptic protein expression, and hippocampal synapse numbers. Behavioral performance on the Morris water maze test was also significantly improved in MD MW150 mice.
Conclusions: These findings support further investigations of p38alpha inhibitors in the clinic, and suggest p38alpha may mediate pathways associated with hippocampal synaptic plasticity. Future work will use a similar technique in other mixed models in order to characterize the translatability of this approach across pathologies (i.e. HHcy and tau).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0244 / #2107

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

TAILORED EXOSOMAL MIRNA-124-3P DELIVERY: A TARGETED THERAPEUTIC APPROACH FOR ALZHEIMER'S DISEASE

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Gonçalo Garcia[1], Artemizia Évora[1], Miriam Corraliza-Gomez[1,2,3], Marta Ianni[1,4], Ana Rubi[1], Ana Teresa Matos[1], Rita Barbosa[1], Ana Vaz[1], Alessandro Polini[5], Dora Brites[1]
[1]Research Institute for Medicines (iMed.ULisboa), Neuronsignal Laboratory, Lisbon, Portugal, [2]School of Medicine, Universidad de Cadiz, Division Of Physiology, Cadiz, Spain, [3]Instituto de Investigacion e Innovacion en Ciencias Biomedicas de la Provincia de Cadiz (INiBICA), Biomedicina, Biotecnología Y Salud Pública, Cadiz, Spain, [4]Universitá Degli Studi di Trieste, Dipartimento Di Scienze Della Vita, Trieste, Italy, [5]CNR NANOTEC - Institute of Nanotechnology, C/o Campus Ecotekne, Lecce, Italy

Aims: Our ANIMATE-FCT project aims at disentangling the clinical value of inflamma-miRNAs and exosomes in Alzheimer's disease (AD). Our previous studies revealed that miR-124-3p modulation reduces APP695 toxicity and tau phosphorylation. Here, we aimed to validate miR-124 as a therapeutic strategy in the neuronal-microglia crosstalk, using 'organ-on-a-chip' (OoC) microfluidic devices and miRNA-engineered neuronal exosomes as a delivery vehicle.
Methods: Exosomes isolated from neuroblastoma SH-SY5Y cells, were enriched with miR-124 (EF124) using ExoFect™. Cellular models included mouse primary microglia, human cell lines, such as SH-SY5Y APP(Swe) cells, CHME-3 microglia, and immortalized human astrocytes, which were cultured in 5:3:2 ratio at OoCs. Exosomes were isolated by differential ultracentrifugation and characterized by NTA and Western Blot. H_2O_2 (10 µM) was used to favor AD oxidative/aging conditions. miRNA/gene expression profiles were determined by RT-qPCR, and proteins by western blot and immunofluorescence.
Results: Both mouse primary microglia and human neuron-astrocyte-microglia microfluidic chips revealed higher EF124 cellular uptake and miR-124 increase, compared with other delivery approaches. In primary microglia, EF124 inhibited Iba1 immunofluorescence, iNOS transcription, and induced arginase-1/TREM2 gene expression. In the AD OoCs, EF124 restored neurite health, improved glial cell morphology, reduced S100B levels, and regulated microglial P2RY12. Transcriptional analysis upon EF124 treatment suggests benefits in neurons (nNOS reduction, PSD95/synaptophysin elevation), microglia (MHC-II reduction, TREM2 elevation), and astrocytes (S100B reduction). miRNA profiling revealed increased miR-124-3p across all the cell types, and of miR-146a-5p in neurons and astrocytes. Upregulated miR-125b-5p and downregulated miR-21-5p/miR-155-5p were exclusive of astrocytes from EF124-treated OoCs tricultures.
Conclusions: In summary, EF124 demonstrates promise to foster neuroregenerative effects through its immunomodulatory capacity under an AD milieu. Scaling up EF124 production using bioreactors will facilitate clinical translation and therapeutic benefits will be confirmed in the 5xFAD mouse model.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0245 / #123

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

OPTIMIZATION AND EVALUATION OF PYRIDINYL VINYL SULFONES AS NRF2 ACTIVATOR FOR THE ANTIOXIDANT AND ANTI-INFLAMMATORY EFFECTS

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Byungeun Kim[1,2], Ki Duk Park[1,2]
[1]Korea Institute of Science and Technology, Center For Brain Disorders, Seoul, Korea, Republic of, [2]University of Science and Technology, Daejeon,, Division Of Bio-medical Science & Technology, Daejeon, Korea, Republic of

Aims: Many studies have reported that chalcone-based compounds exhibit biological activities such as anticancer, antioxidant, anti-inflammatory and neuroprotective effects. Among the published chalcone derivatives, (E)-1-(3-methoxypyridin-2-yl)-3-(2-(trifluoromethyl)phenyl)prop-2-en-1-one (VEDA-1209), which is currently undergoing preclinical study, was selected as a starting compound for the development of new nuclear factor erythroid 2-related factor 2 (Nrf2) activators. Based on our previous knowledge, we attempted to redesign and synthesize VEDA-1209 derivatives by introducing the pyridine ring and sulfone moiety to ameliorate its Nrf2 efficacy and drug-like properties.
Methods: Based on the VEDA-1209 scaffold, we synthesized the optimized analogs by attempting to modify sulfoxide, sulfone, and various functional groups. The synthetic method is divided mainly into producing vinyl sulfoxides and vinyl sulfones. A route for the preparation of final compounds is specified in **Scheme.**
Results: Among the synthesized compounds, (E)-3-chloro-2-(2-((3-methoxypyridin-2-yl)sulfonyl)vinyl) pyridine (10e) was found to have approximately 16-folds higher Nrf2 activating effects than VEDA-1209 (10e: EC50 = 37.9 nM vs VEDA-1209: EC50 = 625 nM) in functional cell-based assay. In addition, 10e effectively improved drug-like properties such as CYP inhibition probability and metabolic stability. Finally, 10e demonstrated excellent antioxidant and anti-inflammatory effects in BV-2 microglial cells and significantly restored spatial memory deficits in lipopolysaccharide (LPS)-induced neuroinflammatory mouse models.
Conclusions: Most of the synthesized compounds showed excellent Nrf2 activation and improved drug-like properties by introducing sulfone core, pyridine rings, and functional groups of VEDA-1209. The compound 10e was selected for further evaluation as it exhibited potent Nrf2 activation and favorable drug-like properties. Furthermore, the 10e remarkably upregulated Nrf2-dependent antioxidant response genes, and suppressed NO production and proinflammatory cytokines in the BV-2 microglial cells. Finally, the 10e ameliorated memory deficit and suppressed the inflammatory response in the LPS-induced mouse model.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0246 / #379

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

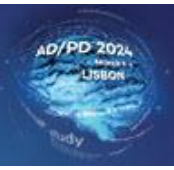
SYSTEMIC ADMINISTRATION OF A TNF RECEPTOR 2 AGONIST IMPROVES NEUROPATHOLOGY AND COGNITIVE FUNCTIONS IN A HUMANIZED ALZHEIMER'S DISEASE MODEL

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Natalia Ortí-Casañ[1], Harald Wajant[2], H. Bea Kuiperij[3], Marcel Verbeek[3], Peter De Deyn[4], Petrus Naude[4], Ulrich Eisel[1]
[1]University of Groningen, Molecular Neurobiology, Gelifes, Groningen, Netherlands, [2]University Hospital Wurzburg, Molecular Internal Medicine, Wurzburg, Germany, [3]Radboud University, Neurology, Nijmegen, Netherlands, [4]University of Groningen, Neurology And Alzheimer Center, Groningen, Netherlands

Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia. Accumulating experimental evidence shows the important role of tumor necrosis factor-α (TNF-α) signaling in AD, but the exact role of TNF-α in AD is still not completely understood. Although TNF-inhibitors are successfully used for treatment of several autoimmune diseases, like rheumatoid arthritis, total inhibition of TNF-α can cause adverse side effects in neurological diseases. This is attributed to the opposing roles of the two receptors of TNF-α. TNF receptor 1 (TNFR1) predominantly mediates inflammatory and pro-apoptotic signaling pathways, whereas TNF receptor 2 (TNFR2) is related to neuroprotection and promotes tissue regeneration. Thus, the specific activation of TNFR2 signaling seems a promising strategy for AD therapy.
Our approach consists on treating an APP overexpressing AD mouse model that contains a chimeric human TNFR2 with a human-specific TNFR2 agonist to investigate its effectiveness in AD-related pathology.
Methods: Treated and control animals were evaluated in behavioral tests and neuropathological changes were investigated.
Results: Our results showed that administration of the TNFR2 agonist resulted in a drastic reduction of Aβ plaques and beta-secretase 1 (BACE-1). Moreover, we observed an increase in microglial activation and phagocytosis, which could be related to a higher clearance rate of Aβ. Finally, at the behavioral level, our treatment showed an improvement in cognitive functions.
Conclusions: These results suggest that activation of TNFR2 might be useful as a potential treatment for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0247 / #1416

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

INVESTIGATION OF PRO-INFLAMMATORY CYTOKINE RELEASE IN A HUMAN MONOCYTE-DERIVED MICROGLIAL MODEL IN RESPONSE TO PURINERGIC AGONISTS AND ANTAGONISTS

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Omar Qureshi[1], Jamie Cowley[2], Ashley Pegg[2], Arshpreet Kaur[2], Leila Sallie[2], Ines Morano[2], Hujo Chan[2], Zhi Li[2], Neale Harrison[2], Mark Bryant[2], Catherine Brady[2], John Gordon[2], Nicholas Barnes[2]
[1]Celentyx, In Vitro Pharmacology, Birmingham, United Kingdom, [2]Celentyx Ltd, In Vitro Pharmacology, Birmingham, United Kingdom

Aims: Neuroinflammation is generally accepted as a major driver of neurodegeneration with genetic evidence linking 'myeloid' associated genes (e.g. TREM2, CD33, ABCA7 and CR1) with AD risk and supporting a role for microglia (and infiltrating monocytes) in mediating pathology. Microglia express several purinergic receptors including P2X7, P2X4, A2A, A3, P2Y4, P2Y6 and P2Y12 receptors which regulate their function.
Methods: We exposed human monocytes to a cocktail of CNS-associated cytokines over 5-10 days to generate a cell type with features of human microglia (iMDM). We then used these iMDM to investigate cytokine release in response to purinergic stimulation.
Results: IL-1b release from LPS-primed iMDM was evoked by the P2X7 agonist BzATP, which was prevented in a concentration-dependent manner by P2X7 antagonists and NLRP3 inhibitors. However, BzATP also had a suppressive effect on TNFa release that was not P2X7-independent. While this suppressive effect on TNFa release could be mimicked by adenosine receptor agonists, use of receptor specific antagonists suggested the BzATP-mediated inhibition was occurring via a distinct pathways. The anti-inflammatory impact of adenosine however was mixed, as when present during iMDM differentiation, adenosine increased release of IL-6. While suramin to an extent was able to reverse the impact of BzATP on TNFa release, individual P2Y antagonists did not have the same impact suggesting a more complex pharmacology that may involve different or heteromeric receptors. Finally while TNFa release in response to LPS was not sensitive to NLRP3 inhibition, in the presence of BzATP, responses exhibited a degree of sensitivity to NLRP3 inhibitors.
Conclusions: These findings suggest purinergic signalling has the potential to regulate neuroinflammation and is likely determined by integrated crosstalk from different purinergic receptors.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0248 / #1682

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

BIPOLAR DISORDER AS DELAYED AND INITIAL MANIFESTATION OF LYME DISEASE: IMPROVEMENT AFTER ANTIBIOTIC TREATMENT

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Iva Sarac[1], Helena Sarac[2], Neven Henigsberg[3], Fran Borovečki[4], Zdravko Krešić[5]
[1]University of Zagreb, School Of Medicine, Zagreb, Croatia, [2]KBC Zagreb, Neurology, Zagreb, Croatia, [3]University of Zagreb, Schoool of Medicine, Psychiatry, Zagreb, Croatia, [4]University of Zagreb, School of Medicine, Neurology, Zagreb, Croatia, [5]General Health Center East, General Practice, Zagreb, Croatia

Aims: Patients with Borrelia burgdorfer (bB) infection are at increased risk of later suffering from psychiatric disorders. So, far, very few cases of patients with history of Bb infection have been described, presenting with psychosis, mood disorders, schizophrenia and schizoaffective disorder bipolar type. This case describes schizoaffective disorder, bipolar type as presenting manifestation of Lyme disease in a patient with a long history of Bb infection.
Methods: A 42-year-old male was initially presented to the Department of Neurology in 2022 due to long-lasting behavioural changes despite psychiatric treatment. His medical history revealed that he had numerous tick bites throughout his life, in 2013 with erythema migrans that was not treated with antibiotics. He has had his first mood symptoms since 2017, since then they have been in constant progression. He was treated with haloperidol, flufenazinchloride, olanzapine. Since 2020 he feels weakness, fatigue and paresthesias. A lyme-disease-serologic tests were positive. He had been treated with a three week course of doxycycline and there were no signs of active Bb infection. However, his bipolar symptoms persisted. Control serologic tests were positive and ceftriaxone was given for 3 weeks.
Results: Several days after ceftriaxone treatment, psychotic symptoms partially improved. His somatic delusions began to improve. On the combination of olanzapine 5 mg in the morning and clonazepam 0.5 mg at bedtime, psychotic symptoms and mood symptoms improved even more. At the time of discharge the patient denied somatic delusions.
Conclusions: This case demonstrated that psychiatric disturbances in Lyme disease may be improved after adequate antibiotic therapy, which is contrary to earlier cases in which psychiatric symptoms persisted or worsened which could be a secondary consequence of inflammation-induced neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0249 / #1470

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

DISCOVERY AND OPTIMIZATION OF NOVEL POTENT BRAIN PENETRANT NLRP3 INHIBITORS

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Tamara Seredenina[1], Jerome Molette[1], Chantal Alliod[1], Roger Moser[1], Alessio Mylonas[1], Véronique Dehlinger[1], Kasia Piorkowska[1], Thomas Jaquier[1], Alexandra Casel-Teav[1], Gloria Pittet[1], Lea Champion[1], Davide Basco[1], Sonia Poli[1], Andrea Pfeifer[2], Marie Kosco-Vilbois[2]
[1]AC Immune, Research, Lausanne, Switzerland, [2]AC Immune SA, Research, Lausanne, Switzerland

Aims: NLRP3 inflammasome activation in microglia is involved in multiple pathological mechanisms of neurodegenerative disorders including Alzheimer's disease (AD). Misfolded proteins, dying neurons, mitochondrial and lysosomal dysfunction all activate NLRP3, promoting a proinflammatory microenvironment and decreasing the efficiency of microglial phagocytosis resulting in further aggregation of misfolded proteins. Genetic NLRP3 deficiency and first-generation NLRP3 inhibitors demonstrated therapeutic benefit in multiple models of neurodegeneration. However, NLRP3 inhibitors with improved brain penetration need to be developed and validated.
Methods: The efficacy of NLRP3 inhibition was evaluated in cell-based assays and in a mouse model of LPS-ATP induced acute peritonitis. Target engagement was confirmed using a MCC950-competition BRET assay. Selectivity over other inflammasomes, ADME properties and safety were evaluated, and pharmacokinetic profile explored in rodents.
Results: Using rational drug design and iterative medicinal chemistry optimization, several distinct chemical scaffolds of small molecule NLRP3 inhibitors were generated. Following NLRP3 activation, IL-1β production by primary human and mouse macrophages, microglia and whole blood, was potently inhibited by selected compounds with efficacy in the low nanomolar range. *In vivo*, this translated into a potent inhibition of NLRP3 in the acute peritonitis model showing IC_{50} = 10 nM. Selected compounds displayed excellent physico-chemical properties, good safety margin in hERG inhibition, no genotoxicity and no off-target binding. Brain penetration was optimized to reach unbound brain-to-plasma partition coefficient (Kp,uu,brain) > 0.3 and ensure efficient NLRP3 inhibition in the brain for 24h at 50 mg/kg.
Conclusions: These novel, potent, selective and brain penetrant NLRP3 inhibitors will enable the preclinical and clinical validation of the therapeutic potential of safely restoring microglial homeostasis in neuroinflammatory and neurodegenerative diseases including AD, alone or in combination with successful Abeta-lowering therapies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0250 / #421

Poster Topic: *Theme A: β-Amyloid Diseases / A02.g. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory*

NOVEL PYROPTOSIS INHIBITORS AND THEIR THERAPEUTIC POTENTIAL

POSTERS: A02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY

Shijun Zhang
Virginia Commonwealth University, Medicinal Chemistry, Richmond, United States of America

Aims: Pyroptosis is a type of inflammasome-dependent cell death, and has been indicated critical roles in neurodegenerative disorders including Alzheimer's disease (AD). However, small molecule pyroptosis inhibitors that target the downstream of inflammasome activation are scarce and only a limited number of compounds that have been used for other indications or purposes were reported to show inhibitory activities on pyroptosis. Therefore, rationally designed pyroptosis inhibitors would be valuable as chemical probes and lead compounds for development of therapeutics. Recently, we have identified a small molecule lead compound as pyroptosis inhibitor and preliminary characterization demonstrated promising protective activities of this lead compound. In this presentation, we will descibe and report 1) Rational design of new analogs to improve potency; 2) mechanistic studies using biophysical and chemical biology methods; 3) systemic characterization of the selected compounds.
Methods: The following methods have been employed: 1. Rational design and chemical synthesis. 2. Binding affinity measurement using MST and fluorescence spectrometer. 3. Chemical biology studies using photoaffinity labeling and protein thermal shift assay. 4. Cellular testing using iBMDMs to examine membrane pore formation, LDH amd IL-1beta release, and cleavage of GSDMD.
Results: A lead compound with novel chemial scaffold was identified. This compound exhibits protection of LPS/nigericin induced pyroptosis with a nanomolar potency. Mechanistic studies suggetsed gasdermin D as a potential target for this lead compound.
Conclusions: Structure-activity relationship studies of a hit compound led to the identification of a new lead compound as pyroptosis inhibitor with nanomolar potency. The observed protective activity of this lead compound is, at least partially, through its binding interactions with gasdermin D and inhibiting its pore formation. The results strongly encourage further development of this scaffold to provide novel pyroptosis inhibitors.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0251 / #1874

Poster Topic: *Theme A: β-Amyloid Diseases / A02.h. Therapeutic Targets, Mechanisms for Treatment: Anti-oxidants*

ALKALOIDS OF THE PYRROCIDIN FAMILY ARE POTENTIAL THERAPEUTIC AGENTS IN ALZHEIMER'S DISEASE

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

Rebeca Lapresa[1,2], Jesus Agulla[1,2], Emilio Fernandez[1,2], Jose M Sanchez-Lopez[3], Antonio Fernandez-Medarde[3], Juan P Bolaños[1,2], Angeles Almeida[1,2]
[1]Instituto de Investigación Biomédica de Salamanca, Hospital Universitario De Salamanca, Universidad De Salamanca, Csic, Salamanca, Spain, [2]Instituto de Biología Funcional y Genómica, Csic, Universidad De Salaman, Salamanca, Spain, [3]Instituto Biomar, Parque Tecnológico De Leon, Leon, Spain

Aims: Alzheimer's disease (AD) is the leading cause of dementia and loss of autonomy in the elderly, with increasing incidence and no cure, indicating the need for novel approaches to AD therapy. Here, we aimed to evaluate the neuroprotective function of two novel alkaloids of the pyrrocidin family, CL0179 and its structural analogue CL0670, against amyloid-β (Aβ) toxicity in mice, both *in vitro* and *in vivo*.
Methods: We used an $A\beta_{25-35}$ oligomers (10 μM) toxicity model in primary neurons to assess neuroprotective and antioxidant activity. Moreover, we used an $A\beta_{25-35}$ (9 nmol) intracerebroventricular (icv) injection model in mice to evaluate neuroinflammation, neurodegeneration and cognitive performance.
Results: In primary neurons, we found that CL0179 and CL0670 compounds prevents Aβ-induced oxidative stress and apoptotic death. In Aβ-injected mice, both CL0179 and CL0670 compounds protected against Aβ-induced gliosis and neurodegeneration. Furthermore, animals treated with these pyrrocidine alkaloids preserved their memory after Aβ icv injection. Finally, using RNA-seq analysis in neurons led to the identification of several molecular hits likely regulated by these alkaloids that may be responsible for their antioxidant and neuroprotective activity.
Conclusions: The pyrrocidine alkaloids CL0179 and CL0670 show marked neuroprotective modulatory brain response against Aβ damage in living mice, strongly suggesting that these novel compounds are promising therapeutic candidates in AD. Funded by The Instituto de Salud Carlos III (PI21/00727 and PMP22/00084, cofunded by the European Union -); Agencia Estatal de Investigacion (PID2019-105699RB-I00; PID2022-138813OB-I00); FEDER; Junta de Castilla y León (CS/151P20; 04/18/LE/0017).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0252 / #430

Poster Topic: *Theme A: β-Amyloid Diseases / A02.h. Therapeutic Targets, Mechanisms for Treatment: Anti-oxidants*

DEVELOPMENT OF NOVEL POLYMER-DRUG CONJUGATES: TOWARDS A MULTI-TARGET TREATMENT FOR ALZHEIMER'S DISEASE

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

Nuruddin Mahadik, Gemma Barron, Paul Kong Thoo Lin, Colin Thompson
Robert Gordon University, School Of Pharmacy And Life Sciences, Aberdeen, United Kingdom

Aims: To design novel antioxidant and anticholinesterase polymer-drug conjugates (PDCs) to treat Alzheimer's Disease (AD).
Methods: An antioxidant drug was conjugated to a cationic polymer (NM15) and an anticholinesterase drug was conjugated to an anionic polymer (N10) and each was characterized by FT-IR and ^{1}H NMR. The antioxidant activity of NM15 was analysed *in vitro* using the ORAC and ABTS assay. The AChE and BuChE activity of N10 was analysed *in vitro* using Ellman's assay. Cell viability and cellular protection from oxidative damage and inflammation were determined in SH-SY5Y and BV-2 cells treated with NM15 *in vitro* using the MTT assay.
Results: Successful conjugation of NM15 and N10 was shown with FT-IR and ^{1}H NMR. NM15 showed significantly enhanced *in vitro* antioxidant activity in ORAC (11333±463 µmolTE/1g) and ABTS (IC_{50}= 19.07±1.1 µg/mL) assay compared to parent antioxidant drug (ORAC 6553±491 µmolTE/1g, ABTS activity IC_{50}= >10 mg/mL) and polymer (ORAC activity could not be determined, ABTS IC_{50}= 44.08±1.56 µg/mL) ($p \leq 0.0001$). Using Ellman's assay, N10 significantly increased AChE (IC_{50}= 0.340±0.01 µg/mL) and BuChE activity (IC_{50}= 1.26±0.1 µg/mL) compared to the parent anticholinesterase drug (AChE IC_{50}=1.67±0.1 µg/mL, BuChE IC_{50}=4.16±0.5 µg/mL) ($p \leq 0.0001$). NM15 was toxic to both cell lines (below 80% cell viability), so a polyelectrolyte complex (PEC) was developed. PEC NM15 significantly protected SH-SY5Y and BV-2 cells from oxidative damage. Results showed 30% and 40% protection against H_2O_2 in SH-SY5Y and BV-2 cells ($P \leq 0.0001$), respectively, as well as 35% protection against Rotenone/Antimycin A in SH-SY5Y ($P \leq 0.0001$) and 25% protection in BV2 cells ($P \leq 0.01$) against Lipopolysaccharide-(LPS) induced inflammation.
Conclusions: This work has demonstrated the possible use of PDCs for the future development of a multi-target treatment option for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0253 / #1030

Poster Topic: *Theme A: β-Amyloid Diseases / A02.i. Therapeutic Targets, Mechanisms for Treatment: Neurotrophic, synaptic plasticity, repair, regenerative medicine*

PRE-AMYLOID COGNITIVE INTERVENTION RESTORES MEMORY IN AGED TGF344-AD RATS, MAINTAINING NETWORKS, ENHANCING PLASTICITY, AND REDUCING MICROGLIA DIFFERENTLY BY SEX.

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

Guadalupe Soria[1], Federico Varriano[1], Elisa López-Bravo[1], Julia Casanova[1], Genís Campoy-Campos[2], Xavier López-Gil[3], Raúl Tudela[4], Emma Muñoz-Moreno[3], Fernado Aguado[5], Cristina Malagelada[2]
[1]University of Barcelona, Laboratory Of Surgical And Experimental Neuroanatomy, Barcelona, Spain, [2]University of Barcelona, Biomedicine, Barcelona, Spain, [3]IDIBAPS, Magnetic Resonance Imaging Core Facility, Barcelona, Spain, [4]CIBER de Bioingeniería, Biomateriales y Nanomedicina, Instituto De Salud Carlos Iii, Barcelona, Spain, [5]University of Barcelona, Department Of Cell Biology, Physiology And Immunology, Barcelona, Spain

Aims: Cognitive reserve plays a crucial role in how individuals cope with age-related or Alzheimer's disease (AD) cognitive decline. Investigating neurobiological pathways involved in cognitive resilience can uncover mechanisms and potential therapeutic targets.
Methods: We investigated early cognitive stimulation's effects (training and regular Delayed Non-matched to Sample task performance from 3 to 18 months) on memory (novel object recognition), functional and structural MRI-based connectomics (Rs-fMRI and DWI), synaptic plasticity markers, and microglia morphology. Our study followed a longitudinal design, including male and female wildtype (WT) rats and the TgF344-AD (TG) AD rat model.
Results: A three-way ANOVA on the recognition index at 19 months showed a cognitive stimulation effect ($p<0.05$). Trained TG males exhibited improved recognition memory compared to untrained rats, with no treatment effect in females. Structural connectomics showed a significant treatment-genotype interaction ($p<0.05$), assessed using a linear mixed model, preserving integration and segregation over time in male trained WT and TG rats vs their untrained counterparts. Intriguingly, functional connectomics analysis indicated a significant treatment effect ($p<0.01$) only in female rats. Western blot analysis revealed enhanced expression of synaptic plasticity markers (PSD95, pGluR1 and pS6), in trained TG animals, primarily in males. Concerning microglia, various morphological features assessed through IF techniques demonstrated a transient neuroinflammatory protection in TG animals at 11 months of age, which was primarily observed only in trained TG males at 19 months of age.
Conclusions: Our study suggests that cognitive stimulation enhances specific synaptic plasticity-related biological pathways and promotes a healthier neuroinflammatory cell population. This leads to sustained neuroplasticity, improved ability to reconfigure large-scale connectivity, and increased resilience against AD-induced memory deficits. This cognitive stimulation may have a greater impact in male than in female.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0254 / #1672

Poster Topic: *Theme A: β-Amyloid Diseases / A02.h. Therapeutic Targets, Mechanisms for Treatment: Anti-oxidants*

BIOANALYSIS OF PYRROLOQUINOLINE QUINONE, A POTENTIAL COGNITIVE ENHANCER IN MICE BRAINS.

POSTERS: A02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-OXIDANTS

Mai Mostafa[1], Reham Abdelkader[2], Rasha Hanafi[1]
[1]German university in Cairo, Pharmaceutical Chemistry, Cairo, Egypt, [2]German university in Cairo, Pharmacology And Toxicology, Cairo, Egypt

Aims: Pyrroloquinoline quinone (PQQ) has recently shown enhancing cognitive functions in animal studies and healthy adults. In attempt to understand the mechanism of action, whether it acts centrally or peripherally, bioanalysis of PQQ in mice brains is performed. Our research question is can PQQ pass the blood-brain barrier (BBB)? the aim of research is qualitative bioanalysis using gas chromatography-tandem mass spectrometry to assess PQQ BBB permeability and its metabolites in mice brains.
Methods: A neuroinflammatory mouse model was treated intraperitoneally (i.p.) with PQQ. PQQ was extracted from mice brains using acetonitrile. PQQ derivatization by silylation where N,O-Bis(trimethylsilyl)trifluoroacetamide was the reagent of choice. GCMSMS method of 15min run time was developed.
Results: BBB shows permeation to PQQ after i.p. administration of PQQ with lipopolysaccharide that mimics Alzheimer's disease induced neuroinflammation. Moreover, the BBB is permeable to PQQ in healthy mice showing intact BBB. Dietary PQQ was identified in mice brains whose standard diet contained soybeans which is rich in PQQ. Based on the preliminary validation, PQQ concentration in mice brains from dietary source as chow diet is 1.59±0.27µg in 250µg brain homogenate while PQQ concentration in treated mice brain with saline and PQQ is 3.89±0.30µg in 250µg brain homogenate (P=0.0006). Pharmacokinetic profile of PQQ in mice brains was performed (Tmax=2hrs).
Conclusions: A novel fast simple GCMS/MS bioanalysis method of BBB permeability of PQQ and its metabolites in mice brains is successfully developed. This is the first study to derivatize PQQ by silylation, extract PQQ from biological samples not only in a single step but also using one solvent following green chemistry guidelines, report PQQ qualifier and quantifier ions and identify PQQ metabolite in mice brains. These findings form novel approach as co-treatment in targeting CNS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0255 / #362

Poster Topic: *Theme A: β-Amyloid Diseases / A02.i. Therapeutic Targets, Mechanisms for Treatment: Neurotrophic, synaptic plasticity, repair, regenerative medicine*

YOUTH-ASSOCIATED BLOOD-BORNE PROTEIN TIMP2 REGULATES AD PATHOLOGY IN MULTIPLE MOUSE MODELS OF BETA-AMYLOIDOSIS

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

Alejandro Grau-Perales, Ana Catarina Ferreira, Brittany Hemmer, Jacob Rosenstadt, Ralphyn Pallikunnath, Suhani Yerapathi, Joseph Castellano
Icahn School of Medicine at Mount Sinai, Neuroscience, New York, United States of America

Aims: Accumulating evidence supports the concept that processes dysregulated in both the aging and AD brain are responsive to signals in the periphery across lifespan. Though we previously showed that the youth-associated blood-borne protein, tissue inhibitor of metalloproteinases-2 (TIMP2), revitalizes hippocampal function in aged mice, the mechanisms have remained unclear. We hypothesize that TIMP2 and other blood-borne factors regulate synaptic plasticity processes and amyloid-beta metabolism in the hippocampus.
Methods: Using behavioral assessments, RNA-sequencing, and super-resolution confocal microscopy in TIMP2 deletion models, including a novel conditional deletion model, we explored how TIMP2 removal regulates adult neurogenesis, dendritic complexity via iontophoretic dye-filling, and hippocampus-dependent behavioral testing. We deleted TIMP2 in several mouse models of AD pathology and examined perturbations in amyloid-beta metabolism and markers of the neurovascular unit, and we addressed rescue using viral-mediated overexpression strategies to examine behavioral improvements.
Results: We found that TIMP2 deletion causes dysfunction in adult neurogenesis and a loss in dendritic complexity with concomitant accumulation of extracellular matrix components. Removing this accumulation via intrahippocampal targeting of ECM components results in rescue, arguing that TIMP2 acts through the extracellular matrix to facilitate synaptic plasticity. Loss of TIMP2 exacerbates gliosis, and pathways related to activation and senescence are significantly altered. Deleting TIMP2 in APP-knockin and 5XFAD mice significantly exacerbates amyloid-beta plaque deposition and corresponding gliosis in several brain regions.
Conclusions: TIMP2 regulates a diverse set of phenotypes across normal hippocampal physiology and in the context of AD pathology, including in processes that depending on flexibility for removal of pathological debris. Together our results argue that age-relevant factors in the systemic environment have long-range roles in shaping hippocampal function, including processes that depend on the dynamics of extracellular matrix homeostasis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0256 / #1757

Poster Topic: *Theme A: β-Amyloid Diseases / A02.i. Therapeutic Targets, Mechanisms for Treatment: Neurotrophic, synaptic plasticity, repair, regenerative medicine*

NEUROPROTECTIVE MECHANISMS OF FOSGONIMETON AGAINST EXCITOTOXICITY IN PRIMARY NEURON CULTURE

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

Sherif Reda[1], Wei Wu[1], Andree-Anne Berthiaume[1], Sharay Setti[2], Robert Taylor[1], Jewel Johnston[1], Kevin Church[2]
[1]Athira Pharma, Inc., Research, Bothell, United States of America, [2]Athira Pharma, Research, Bothell, United States of America

Aims: We have previously shown that fosgonimeton, a small-molecule positive modulator of the neurotrophic hepatocyte growth factor (HGF) system, promotes neuroprotective effects in preclinical models of Alzheimer's disease (AD). We hypothesized that such effects may be driven by activation of HGF-mediated pro-survival signaling mediators, such as AKT. Herein, we characterize signaling effectors downstream of AKT including Bcl-2 (promotes mitochondrial health), GSK3β (mediates tau phosphorylation), and the ribosomal S6 kinase (regulator of cell growth and survival) to provide mechanistic insight into the neuroprotective effects of fosgonimeton against glutamate toxicity.
Methods: Rat primary cortical neurons were challenged with glutamate with or without the active metabolite of fosgonimeton (fosgo-AM), and immunostained for microtubule-associated protein-2, mitochondrial ROS (MitoSox), and phospho-tau (AT100) to determine neuronal survival, neurite network integrity (total neurite length), ROS production, and phospho-tau levels. Western blotting quantified activity status of intracellular signaling effectors such as PI3K, AKT, Bcl-2, and GSK3β. Additionally, we interrogated the requirement of S6 kinase in fosgonimeton neuroprotection assays using pharmacological inhibition.
Results: Fosgo-AM treatment significantly improved neuronal survival, preserved neurite networks, inhibited mitochondrial ROS production, and reduced phospho-tau levels after glutamate injury. Protein analyses indicated that fosgo-AM increased PI3K/AKT activity and upregulated Bcl-2 expression. Fosgo-AM treatment also led to a significant increase in GSK3β phosphorylation, an effect expected to inhibit its ability to phosphorylate tau. Interestingly, the neuroprotective effects of fosgonimeton were abolished under the inhibition of S6 kinase.
Conclusions: Our in vitro data suggest that the neuroprotective effects of fosgonimeton against glutamate toxicity are driven, in part, by signal transduction pathways that promote cell survival and growth and counteract neurodegenerative hallmarks such as mitochondrial dysfunction and tau pathology. Fosgonimeton is currently in clinical trials for mild-to-moderate AD (NCT04488419; NCT04886063).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0257 / #1490

Poster Topic: *Theme A: β-Amyloid Diseases / A02.i. Therapeutic Targets, Mechanisms for Treatment: Neurotrophic, synaptic plasticity, repair, regenerative medicine*

ENGINEERING LIMK1 TO BOOST DENDRITIC SPINE PLASTICITY AND MEMORY IN EXPERIMENTAL MODELS OF ALZHEIMER'S DISEASE

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

Cristian Ripoli[1,2], Raimondo Sollazzo[2], Pietro Renna[2], Francesco Pastore[2], Martina Battistoni[2], Sara Martini[2], Fabiola Paciello[2], Marco Rinaudo[2], Claudio Grassi[1,2]
[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Preclinical Neuroscience, Rome, Italy, [2]Università Cattolica del Sacro Cuore, Department Of Neuroscience,, Rome, Italy

Aims: LIMK1 regulates dendritic spine plasticity by phosphorylating and inhibiting ADF/cofilin proteins, promoting actin polymerization. This, in turn, promotes the enlargement and stabilization of dendritic spines, enhancing the glutamatergic synaptic strength. Dysregulation of LIMK1 has been linked to several neurological disorders, including Alzheimer's disease (AD), in which dendritic spine density is reduced. Developing an extrinsically disordered form of LIMK1 that can be rapidly and specifically activated with a well-tolerated, clinically approved, blood-brain barrier permeant drug, such as rapamycin. Precise LIMK1 modulation could offer a hopeful therapeutic strategy for enhancing glutamatergic synaptic function in AD, addressing diminished dendritic spine density and neuronal connectivity.
Methods: Biochemistry, 2-photon imaging, electrophysiology and behavioral tests in AAV-infected mice were used to investigate the therapeutic potential of the engineered LIMK1 in 3×Tg-AD mice and human iPSC-derived neurons from AD patients.
Results: Chemogenetic LIMK1 activation promoted a direct and inducible control of cofilin phosphorylation, long-term enlargement of dendritic spines and enhancement of glutamatergic synaptic transmission in wild-type animals. Given the reduced expression and phosphorylation of LIMK1 and cofilin, we observed in human AD neurons and in the hippocampi of 3xTg-AD mice, we tested the ability of the engineered LIMK1 to restore the function of these proteins in our experimental models of AD. Activation of engineered LIMK1 effectively promoted cofilin phosphorylation, thus significantly increasing dendritic spine density in hippocampal CA1 pyramidal neurons of 3xTg-AD mice and morphological neurites restoration in human AD neurons. Notably, the activation of engineered LIMK1 *in vivo* improved memory encoding and slowed cognitive decline in 3xTg-AD mice.
Conclusions: Our results indicate that the proposed chemogenetic LIMK1 has the potential to be translated into a therapeutic strategy for reversing cognitive decline in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0258 / #839

Poster Topic: *Theme A: β-Amyloid Diseases / A02.i. Therapeutic Targets, Mechanisms for Treatment: Neurotrophic, synaptic plasticity, repair, regenerative medicine*

INVESTIGATING PROTECTIVE EFFECTS OF NRF2 IN 5XFAD MODEL OF ALZHEIMER'S DISEASE

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

Katherine Sadleir[1], Karen Gomez[1], Armana Patel[1], Makenna Ley[1], Sidhanth Chandra[1], Yunlu Xue[2], Constance Cepko[2], Robert Vassar[1]
[1]Northwestern University, Neurology, Chicago, United States of America, [2]Harvard Medical School, Genetics, Boston, United States of America

Aims: The aim is to test the effects of neuronal overexpression of nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor on pathology in 5XFAD mouse model of Alzheimer's β-amyloid deposition. Nrf2 upregulates expression of antioxidant and detoxification genes and is neuroprotective in retina. In Alzheimer's patients neuronal loss contributes to cognitive impairment. Nrf2 mRNA is decreased in Alzheimer's brains and deletion of the Nrf2 gene increased BACE1 (β-secretase) and Aβ, and worsened cognitive deficits in amyloid mouse models. We hypothesized that neuronal Nrf2 overexpression would reduce BACE1 and amyloid and protect against neuronal loss.
Methods: To overexpress Nrf2 in 5XFAD mouse brains, AAV8 hSyn-Nrf2 and hSyn-GFP or AAV8 hSyn-GFP alone were injected into the ventricles of day-old mouse pups. At 9.5 months of age, the mice were perfused, and half the brain fixed for sectioning and immunofluorescence, the other half dissected into cortex and hippocampus and frozen for mRNA and protein analysis. Immunofluorescence was used to assess plaque load, neuronal loss, neuroinflammation, dystrophic neurites and tau phosphorylation.
Results: Overexpression of Nrf2 reduced BACE1 protein, especially in dystrophic neurites around plaques, but did not decrease neuron loss, neuroinflammation or amyloid deposition. Phospho-tau 181, which accumulates in dystrophic neurites, was also reduced. Bulk mRNA sequencing revealed elevation of Nrf2 targets Hmox1 and Txnrd1 in Nrf2 overexpression mice confirming activation of antioxidant pathways, but in general pathways altered in 5XFAD compared to non-transgenic mice were not corrected by Nrf2 overexpression.
Conclusions: Neuronal overexpression of Nrf2 may provide a method to specifically decrease dystrophic neurites, which could decrease tau pathology seeding and spreading. Future work will elucidate the mechanism by which dystrophic neurites are decreased, and explore Nrf2 overexpression in other cell types such as astrocytes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0259 / #2781

Poster Topic: *Theme A: β-Amyloid Diseases / A02.i. Therapeutic Targets, Mechanisms for Treatment: Neurotrophic, synaptic plasticity, repair, regenerative medicine*

ACD856 IS A BIASED POSITIVE ALLOSTERIC MODULATOR OF TRK-RECEPTORS - ENHANCES NEURITE OUTGROWTH BUT DO NOT AFFECT PAIN SIGNALING

POSTERS: A02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE

Pontus Forsell, Veronica Lidell, Azita Rasti, Gunnar Nordvall, Johan Sandin
AlzeCure Pharma, R&d, Huddinge, Sweden

Aims: The neurotrophins BDNF and NGF have been studied extensively and have important roles in neuronal survival, differentiation, neurogenesis, and synaptic plasticity, making these mechanisms of high interest for therapeutic development within Alzheimer's disease. However, they are also involved in other functions such as pain signaling. This broad range of effects is a result of a complex downstream signaling pathway diversifying their physiological effects. The aim of these studies was to explore if ACD856, a novel positive allosteric modulator of Trk-receptors currently in clinical development for the treatment of Alzheimer's disease, showed any selectivity for different TrkA-signaling pathways.
Methods: Primary mouse cortical neurons were treated with ACD856 and neurite outgrowth, as measured by neurite total length, was studied. Potential effects of ACD856 on pain signaling was assessed using the Hargreaves plantar test assessing thermal allodynia in male Sprague-Dawley rats. The animals had received an intra-plantar injection of NGF in the left hind paw and paw withdrawal latencies were assessed on both ipsilateral and contralateral paws.
Results: In vitro data show that ACD856 can enhance neurite outgrowth in mouse primary cortical neurons. Interestingly, results from the in vivo plantar test in rats showed that ACD856 does not induce heat allodynia, nor does it potentiate NGF-induced heat allodynia.
Conclusions: The results indicate that while ACD856 can enhance neurite outgrowth, it does not induce or aggravate NGF-induced heat allodynia. These findings indicate that the compound acts as a biased Trk-PAM with the advantages of neurotrophic support and cognitive enhancing effects of neurotrophins, but without pain inducing effects. This differential activation pattern of downstream signalling pathways would provide for a significantly improved therapeutic and tolerability profile for this novel class of compounds.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0260 / #691

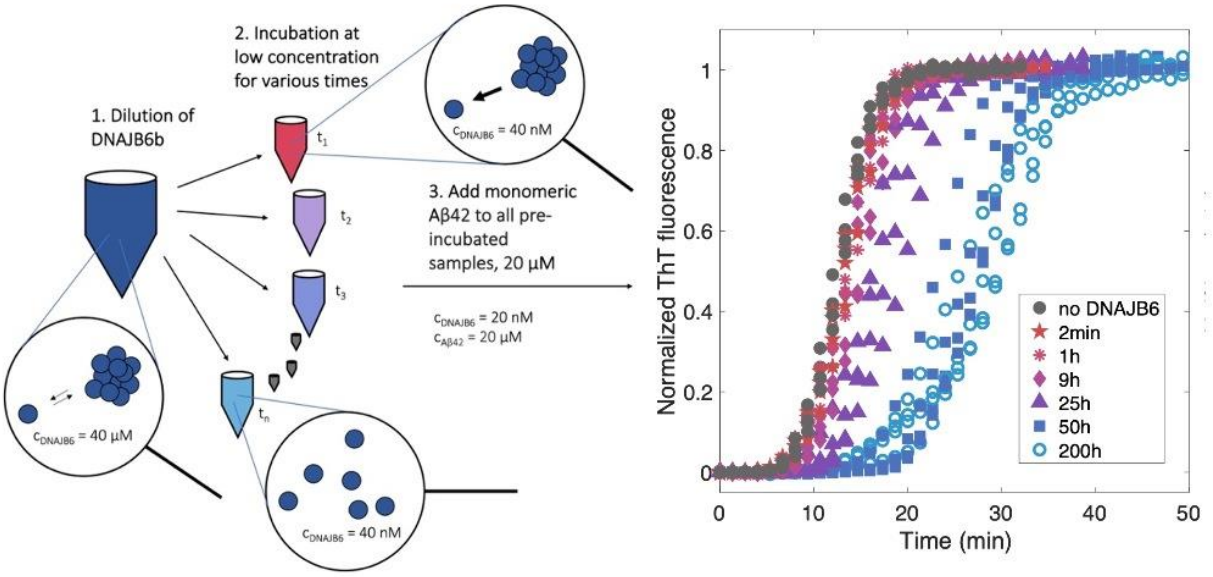
Poster Topic: *Theme A: β-Amyloid Diseases / A02.j. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, misfolding, chaperones*

THE ABILITY OF THE CHAPERONE PROTEIN DNAJB6 TO PREVENT AMYLOID BETA 42 FIBRILLATION DEPENDS ON ITS AGGREGATION STATE

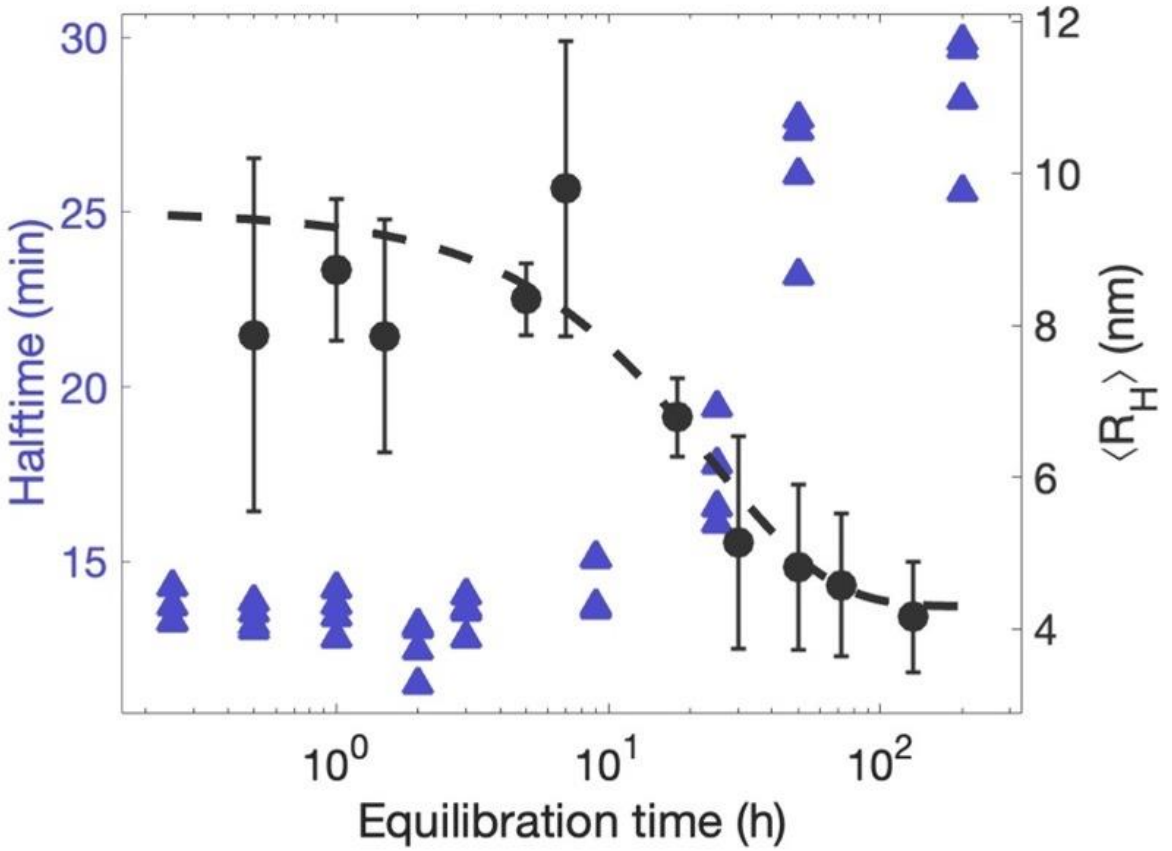
POSTERS: A02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Andreas Carlsson[1], Ulf Olsson[2], Emil Axell[1], Sara Linse[1]
[1]Lund University, Biochemistry And Structural Biology, Lund, Sweden, [2]Lund University, Physical Chemistry, Lund, Sweden

Aims: The human chaperone DNAJB6 increases the solubility of proteins involved in protein aggregation diseases and suppresses the formation of amyloid structures. Thus, DNAJB6 has received increasing attention over the past decade. Understanding the DNAJB6 chaperone mechanism may aid the design of amyloid inhibitors. DNAJB6 is known to self-associate in a concentration dependent manner. Here, we examine how the oligomeric state is related to its amyloid prevention.
Methods: The ability to delay Aβ42 amyloid formation was examined using ThT fluorescence for various equilibration times of DNAJB6 after a step dilution from 40 μM to 40 nM, in quadruplicates. After various times after dilution (room temperature incubation), ranging from 2 min to 8 days, equal volume of monomeric Aβ42 was added to a final concentration of 20 μM, resulting in a DNAJB6 concentration of 20 nM. A plate reader was used to follow the change in ThT signal upon Aβ42 aggregation. The average hydrodynamic radius of DNAJB6 was followed over time (using MDS) after dilution of 6 μM to 100 nM, allowing for comparison between oligomeric size and amyloid prevention.
Results: It was found that DNAJB6 was more efficient in delaying Aβ42 fibrillation if the aggregates were diluted more than 10 h before the addition of Aβ42 monomers, compared to if the addition was made just after the dilution. This time correlates with the dissociation rate of DNAJB6 oligomers into its subunits.



Experimental setup and the resulting fibrillation kinetics of Aβ42, where the colours represent to how long time DNAJB6 was at the diluted concentration before addition of Aβ42 monomers.



*In blue triangles, halftimes of Aβ42 aggregation as function of the equilibration time of DNAJB6 at 40 nM. In black, the change in average hydrodynamic radius after dilution from 6 µM to 100 nM, with plotted standard deviations as error bars. Fitted line f(t) = 4.3nm*e$^{-t/24h}$.*

Conclusions: The data suggest that the high order DNAJB6 oligomers are less prone to delay Aβ42 amyloid formation compared to their subunits.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0261 / #940

Poster Topic: *Theme A: β-Amyloid Diseases / A02.j. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, misfolding, chaperones*

CHAPERONE MULTIMERS SUPPRESS THE GENERATION OF AB42 NEUROTOXIC OLIGOMERS IMPLICATED IN ALZHEIMER´S DISEASE

POSTERS: A02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

António Figueira[1], Joana Saavedra[2], Isabel Cardoso[2], Cláudio Gomes[1]
[1]Faculdade de Ciencias da Universidade de Lisboa, Bioisi – Biosystems & Integrative Sciences Institute, Lisboa, Portugal, [2]Universidade do Porto, I3s–instituto De Investigação E Inovação Em Saúde, Porto, Portugal

Aims: Alzheimer's disease (AD) involves extracellular aggregation of Aβ42 into toxic oligomers and fibrils, whose emergence is regulated by molecular chaperones. These include S100B alarmin, a homodimeric EF-hand protein with intra and extracellular functions which acts as a Ca^{2+}-switched Aβ42 anti-aggregation chaperone. However, S100B occurs also as a homotetramer, with uncharacterized neuroprotective roles. Here, we compared the chaperone activities of both S100B multimers and explored their impact on the formation of Aβ42 oligomers (AβO).
Methods: S100B anti-aggregation activity was evaluated by thioflavin-T (ThT) Aβ42 aggregation assays. Aβ42 conformers targeted by S100B were accessed by computational and structural-biophysical spectroscopies. Aβ42 oligomer distributions were determined through mechanistic analysis of fibril formation and via early detection of Aβ42 species using the X-34 fluorophore.
Results: Aβ42 aggregation kinetics revealed that, unlike the dimer, tetrameric S100B delays Aβ42 aggregation and reduces the amounts of fibrils formed at sub/equimolar ratios, an effect that persists even in the absence of Ca^{2+} binding. Structural analysis revealed that this enhanced catalytic efficiency results from a secondary Ca^{2+}-independent binding site formed upon tetramerization of S100B, with which monomeric and fibrillar Aβ42 interact (Figueira et al JMB 2022). Kinetic and mechanistic analysis revealed that dimeric and tetrameric S100Bpreferentially inhibit Aβ42 fibril surface-catalyzed nucleation, decreasing the reactive influx towards oligomers down to <10%. Such results comply with an independent screening of AβO using a combination of the thioflavin-T and X-34 fluorophores (Figueira et al Front. Neurosci. 2023).
Conclusions: Our study sheds new insights on the functional landscape of S100B chaperone multimers, suggesting its critical role in the regulation of proteopathic Aβ42 aggregation and oligomerization in AD.
Funded by EU-TWIN2PIPSA/GA101079147 and FCT-Portugal BD/06393/2021 (AJF)/UID/MULTI/04046/2020 (BioISI).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0262 / #1441

Poster Topic: *Theme A: β-Amyloid Diseases / A02.k. Therapeutic Targets, Mechanisms for Treatment: TREM2*

TREM2 AGONISM AFFECTS HUMAN MICROGLIA RESPONSE IN THE PRESENCE OF AMYLOID PATHOLOGY IN VIVO

POSTERS: A02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TREM2

Ivana Geric[1], Manuela Polydoro[2], Jin Zheng[2], Tina Bisgaard[2], Leen Wolfs[3,4], Anke Misbaer[1], Arya Nair[3,4], Laura Sans[2], Maria Dalby[2], Joachim Vilstrup[5], Lars Roenn[2], Peter Flagstad[2], Rita Balice-Gordon[2], Bart De Strooper[3,4,6], Niels Plath[2]
[1]Muna Therapeutics, Discovery Biology, Heverlee, Belgium, [2]Muna Therapeutics, Discovery Biology, Copenhagen, Denmark, [3]KU Leuven, Department Of Neurosciences And Leuven Brain Institute, Leuven, Belgium, [4]Flanders Institute for Biotechnology (VIB), Centre For Brain And Disease Research, Leuven, Belgium, [5]Muna Therapeutics, Protein Chemistry And Structural Biology, Aarhus, Denmark, [6]University College London, Dementia Research Institute, London, United Kingdom

Aims: Pharmacological activation of TREM2 represents a novel therapeutic approach to slow Alzheimer´s disease progression, strongly supported by human genetics linking TREM2 to early- and late-onset AD. Lack of TREM2 locks microglia in a homeostatic state in animal models, preventing a switch to a disease-associated state required for phagocytotic clearance of misfolded proteins and cellular debris. Here, we study the impact of TREM2 agonism on the receptor signaling complex and downstream signaling cascades leading to microglia activation.
Methods: TREM2 agonist induced receptor complex dynamics were assessed in vitro in HEK, THP-a and hIPSC derived microglia cells by nanoBiT, western blot and alphaLISA assays. To study TREM2 agonism on human microglia in vivo, xenografted mice were treated systemically with increasing doses of selective, potent and brain penetrant TREM2 agonists in the presence of amyloid pathology. Subsequently, human microglia were isolated and analyzed by qPCR and single-cell RNA sequencing.
Results: Small molecule mediated TREM2 activation leads to TREM2/DAP12 receptor complex formation required for downstream signaling. In vivo, human TREM2 is expressed by pathology associated microglia and induced by amyloid plaques. Systemic treatment with TREM2 agonists leads to differential gene expression patterns in xenografted human microglia only in the presence of amyloid pathology. Effects were observed at compound exposure levels in the brain consistent with in vitro agonist potency.
Conclusions: TREM2 activation by small molecule agonists leads to the rapid formation of a receptor complex required for downstream signaling. In vivo, TREM2 agonism modulates gene networks in human microglia selectively in the presence of amyloid pathology. Human microglia xenografted into rodent pathology models is therefore a valuable approach to study the effects of pharmacological TREM2 activation in the context of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0263 / #2432

Poster Topic: *Theme A: β-Amyloid Diseases / A02.k. Therapeutic Targets, Mechanisms for Treatment: TREM2*

FSH AS A RISK FACTOR FOR ELEVATED TREM 2 IN THE SERUM OF PATIENS WITH PREMATURE OVARIAN FAILURE

POSTERS: A02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TREM2

Milena Eric Jovicic[1], Svetlana Jovicic Pavlovic[1,2], Natalija Pavlovic[3,4], Svetlana Vujovic[4]
[1]Institute for virusology, vaccine and sera torlak, Department For Laboratory Diagnostic, belgrade, Serbia, [2]UNIVERSITY CENTRE OF SERBIA, Clinic For Neprology, Belgrade, Serbia, [3]UNIVERSITY CLINICAL CENTRE OF SERBIA, National Center For Infetility And Ebdocrinology Of Gender, Clinic For Endocrinology, Diabetes And Diseases Of Metabolisam, Belgrade, Serbia, [4]UNIVERSITY CLINICAL CENTRE OF SERBIA, National Center For Infetility And Ebdocrinology Of Gender, Clinic For Endocrinology, Diabetes And Diseases Of Metabolisam, belgrade, Serbia

Aims: Women are at greater risk than men for developing Alzheimers disease during lifetime.The aim of our study is to determination the realarionship between FSH and TREM 2 in the serum of patienssuffering from premature ovarian failure
Methods: In the serum of affected patiens, FSH and TREM 2 were determinated using the Elisa techique.
Results: The resalts of our study conducted on 78 patiens suffering from POF and 75 controls showed that there is a positive corelation the values of FSH and TREM2 inthe serum.
Conclusions: From this, we can concluded that FSH and TREM 2 can be a target for future therapeutic research.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0264 / #1865

Poster Topic: *Theme A: β-Amyloid Diseases / A02.j. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, misfolding, chaperones*

FLUORINATED NANOCARRIERS TO TARGET THE BRAIN AND TREAT NEUROLOGICAL DISEASES

POSTERS: A02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Joana Loureiro[1], Meghna Dabur[1], Stephanie Andrade[1], Maria João Ramalho[1], Maria Carmo Pereira[2]
[1]Faculdade de Engenharia da Universidade do Porto, Lepabe, Porto, Portugal, [2]University of Porto, Lepabe, Porto, Portugal

Aims: Blood-brain barrier (BBB) crossing commonly hinders currently available treatments for brain diseases; almost all attempts to produce new drugs have failed in clinical trials. Strategies based on nanotechnology have been deployed as drug carriers and have successfully surmounted the challenges inherent in BBB crossing. On the other hand, fluorinated compounds have been found to have therapeutic characteristics and exhibit hydrophobicity, lipophilicity, and high metabolic stability. A new strategy combining nanotechnology and fluorinated molecules is addressed to acquire the physiochemical properties for overcoming the BBB passage.
Methods: Different types of nanoparticles (lipid- and polymer-based) were produced, having fluorine molecules and brain-targeting molecules on their surface. The fluorination of poly (lactic-co-glycolic acid) (PLGA), a long chain fatty acid (Palmitic acid) and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[carboxy(polyethylene glycol)-2000] (sodium salt) (DSPE-PEG2000-COOH) was achieved using a fluorinating source (trifluoro-ethylamine). The fluorination of the compounds was confirmed by nuclear magnetic resonance spectroscopy for both proton and fluorine. The conjugation of transferrin (a targeting molecule with affinity with transferrin receptors overexpressed in the BBB) to the surface of the formed nanoparticles was quantified using Bradford dye assay.
Results: Fluorinated liposomes and PLGA nanoformulations appeared to have low polydispersity and sizes below 200 nm, which is the size required to cross the BBB. No significant variations in physicochemical properties were identified in the nanocarriers containing fluorine nor in the formulations modified with transferrin.
Conclusions: The developed fluorinated nanocarriers have shown potential to be used in the treatment of brain diseases, such as Alzheimer`s disease. Rather than the ability to transport therapeutic molecules, the produced nanoparticles present anti-amyloidogenic properties.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0265 / #1655

Poster Topic: *Theme A: β-Amyloid Diseases / A02.k. Therapeutic Targets, Mechanisms for Treatment: TREM2*

SINGLE-CELL STUDY OF MICROGLIA TRANSCRIPTIONAL STATE HETEROGENEITY ACROSS HUMAN AND IPSC-DERIVED MODELS

POSTERS: A02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TREM2

Anjali Garg[1], Brenna Novotny[1], Ricardo Albanus[1], Logan Brase[2], Celeste Karch[1], John Morris[3], Richard Perrin[4], Greg Sutherland[5], Bruno Benitez[6], Oscar Harari[1]
[1]Washington University Saint Louis, Psychiatry, St. Louis, United States of America, [2]Washington University in St. Louis, Psychiatry, St. Louis, United States of America, [3]Washington University in St. Louis, Hope Center For Neurological Disorders, St. Louis, United States of America, [4]Washington University at Saint Louis, The Charles F. And Joanne Knight Alzheimer Disease Research Center, St. Louis, United States of America, [5]University of Sydney, Medicine And Health, New South Wales, Australia, [6]Beth Israel Deaconess, Harvard Medical School, Center For Life Sciences,, MA, United States of America

Aims: Single-cell study of microglia transcriptional state heterogeneity across human and iPSC-derived models
Methods: We leveraged single-nuclei transcriptomic profiles (snRNA-seq) of human microglia (parietal cortex from 67 donors from the Knight ADRC and DIAN brain banks; N=15,726; Dataset1), iPSC-MLC CRISPRi/a-based genetic screens in human iPSC-derived microglia (N= 15,350; Dataset2), and WT and R47H TREM2 xenografted microglia (xMGs), isolated from chimeric AD mice (N= 25,407; Dataset3) to build a comprehensive atlas of microglia heterogeneity, that captures transcriptional states fairly well represented in each dataset. We employed Seurat v4 to integrate the data, and scArches to build classifiers. We leveraged this new reference to classify and annotate novel microglia in additional cohorts, species and experiments.
Results: We identified homeostatic, activated, interferon (IFN), and IL1B clusters across datasets present in all data we had integrated. In addition, we identified MHCII. We observed that some of the clusters of original states were combined into single clusters. For example, CXCL10-IFN and INF. Furthermore, we build a multiclassifier to label novel microglia generated from hundreds of samples, and data from various experimental models. The cross-validation analyses indicate that the overall accuracy of the classifier (scArches) is 0.85, although it changes for the distinct datasets. For human microglia in Dataset1 the accuracy was 0.79, while for iPSC-MLC was 0.73 and 0.96 for Dataset 3. Our results indicate that this multi-model reference can capture subtle differences better that study-centric analyses.
Conclusions: We are repurposing microglia transcriptomic single-cell data to build a cross-species and experimental iPSC-MLC to bridge across cohorts, species, and experiments. Our results, indicate that this new resource allows to simultaneously interrogate gene expression across different experiments and transcriptional states, and providing the foundation to integrate additional single-cell molecular data.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0266 / #1289

Poster Topic: *Theme A: β-Amyloid Diseases / A02.k. Therapeutic Targets, Mechanisms for Treatment: TREM2*

SPLICEOGENIC VARIANTS IN TREM2 AND THEIR INTERPLAY WITH NEURODEGENERATION-RELEVANT SPLICING FACTORS

POSTERS: A02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TREM2

Olena Korvatska[1], Maria Lukes[2], Kostantin Kiianitsa[1], Wendy Raskind[2]
[1]University of Washington, Department Of Psychiatry And Behavioral Sciences, Seattle, United States of America, [2]University of Washington, Department Of Medicine, Division Of Medical Genetics, Seattle, United States of America

Aims: RNA splicing defects caused by mis-localized RNA binding proteins and splicing factors (SF/RBP), exemplified by TAR DNA-binding protein 43 (TARDBP/TDP-43) and fused in sarcoma protein (FUS), are important contributors to the neurodegenerative process in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Currently known mis-spliced targets are predominantly neuronally expressed genes, and little is known about the pathogenicity of splicing defects in other brain cell types. TREM2 is a microglia-expressed immune receptor that modulates risk of Alzheimer's disease (AD) and causes early-onset dementia, such as Nasu-Hakola disorder and behavior variant of frontotemporal dementia (FTD), through several mechanisms including aberrant splicing. We recently discovered that several pathogenic missense TREM2 variants thought to affect protein code only also affected its splicing. To extend this observation, we comprehensively screened additional disease-relevant *TREM2* variants for splicing defects. We also tested whether SF/RBP involved in ALS and FTLD regulate *TREM2* splicing and whether they potentiate the effect of spliceogenic *TREM2* variants.
Methods: We selected SF/RBPs known to be causative/associated with neurodegenerative diseases and to be expressed in human microglia. Predicted splicing defects of TREM2 variants were scored by SpliceAI. We experimentally confirmed these effects in human microglia cell line HMC3 using a full-length TREM2 reporter co-transfected with either an overexpressing construct or siRNA to a correspondent SF/RBP
Results: We confirmed an effect on TREM2 isoform balance for multiple predicted spliceogenic variants in intron 1 and exon 2. We also found that several RBP/SF potentiate the effect of spliceogenic genetic variants on exon skipping.
Conclusions: TREM2 is a subject of complex regulation via an interplay of multiple trans-acting splicing factors with cis-regulatory genetic variants. Certain SF/RBPs perturbed in ALS and FTLD may affect microglia function via TREM2 mis-splicing.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0267 / #262

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

PRECLINICAL NEURONAL MODELS TO SCREEN THE EFFECTIVENESS OF DRUGS DIRECTED TO SLOW DOWN ALZHEIMER'S AND PARKINSON'S DISEASE PROGRESSION

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Jolien Beeken, Anaïs Luykx, Teun Van Nunen, Yanick Fanton
InnoSer, Neurology Research Group, Diepenbeek, Belgium

Aims: Alzheimer's (AD) and Parkinson's (PD) disease drug development is held back due to the lack of in vitro reproducible models that represent human complexity and can be used to screen disease-modifying therapeutics relatively inexpensively, efficiently, and fast. Most therapies for neurodegenerative diseases (NDD) currently focus on relieving symptoms rather than preventing disease progression. New and more powerful therapeutic approaches targeting disease pathology are needed to address the acceleration and severity of NDD. The goal of InnoSer is to validate in vitro disease-induced cell models of mono SH-SY5Y and HMC3 cell cultures and co-culture models to screen disease-modifying drugs for NDDs prior to screening in vivo.
Methods: Microglial (HMC3) and differentiated neuronal-like cells (SH-SY5Y) were treated with pre-formed Amyloid beta (Aβ) or alpha-Synuclein (αSyn) fibrils to mimic AD and PD pathophysiology. The HMC3 cells' phagocytic capacity was investigated by treatment with pHrodo labelled pre-formed fibrils and detected by an IncuCyte S3 Live-Cell Analysis System, while cell viability was assessed using the MTT kit.
Results: Following Aβ or αSyn fibril treatment, HMC3 cells' phagocytic capacity was significantly increased indicating the internalization of the fibrils. Simultaneous treatment with Aβ and Aducanumab significantly increased HMC3 cells' phagocytic capacity compared to fibril treatment alone. Glutamate, the most common neurotransmitter that generates glutamate-induced excitotoxicity in AD and PD, appears neurotoxic for SH-SY5Y and HMC3 cells in high concentrations as cell viability was significantly decreased after glutamate treatment. After 24 hours of incubation with Aβ, the HMC3 and SH-SY5Y cells' viability was significantly decreased.
Conclusions: This NDD model of pre-formed fibril treatment on HMC3 and SH-SY5Y cells will serve as a cheaper, easier, and faster alternative model to screen AD and PD disease-modifying drugs before screening in vivo.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0268 / #558

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

THERAPEUTIC POTENTIAL OF HUMAN MICROGLIAL TRANSPLANTATION IN A CHIMERIC MODEL OF CSF1R-RELATED ADULT-ONSET LEUKOENCEPHALOPATHY WITH AXONAL SPHEROIDS AND PIGMENTED GLIA (ALSP)

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Jean Paul Chadarevian[1], Jonathan Hasselmann[2], Adrian Escobar[3], Alina Lahian[1], Joia Kai Capocchi[2], Tau Lim[3], Christina Tu[2], Sepideh Kiani Shabestari[1], Lauren Le[2], Jasmine Nguyen[2], William Carlen-Jones[2], David Hume[4], Clare Pridans[5], James Bennett[6], Zbigniew Wszolek[7], Robert Spitale[8], Hayk Davtyan[2], Mathew Blurton-Jones[1]
[1]University of California Irvine, Department Of Neurobiology And Behavior, Irvine, United States of America, [2]University of California Irvine, Institute For Memory Impairments & Neurological Disorders, Irvine, United States of America, [3]University of California Irvine, Stem Cell Research Center, Irvine, United States of America, [4]University of Queensland, Mater Research Institute, Brisbane, Australia, [5]University of Edinburgh, Center For Inflammation Research, Edinburgh, United Kingdom, [6]Seattle Children's Hospital, Seattle Children's Research Institute, Seattle, United States of America, [7]Mayo Clinic, Department Of Neurology, Jacksonville, United States of America, [8]University of California Irvine, Department Of Pharmaceutical Sciences, Irvine, United States of America

Aims: ALSP is a rare, autosomal dominant primary microgliopathy caused by heterozygous mutations in colony stimulating factor1 receptor (CSF1R). CSF1R signaling is necessary for microglial differentiation and survival. As a result, patient brains have fewer microglia that exhibit a chronically activated proinflammatory phenotype. ALSP patient brains also exhibit an array of neuropathologies including axonal spheroids, reactive astrocytosis, lipid accumulation, white matter atrophy, and myelin disruption. Recent analysis of two homozygous mutant CSF1R cases revealed a complete absence of microglia and more extensive calcification, accompanied by extreme intellectual disability and prenatal mortality.
Methods: To explore the therapeutic potential of human microglial transplantation, we generated a xenotolerant mouse model that harbors a deletion of the *fms*-intronic regulatory element (FIRE) of CSF1R leading to an absence of microglia. At 2months of age the resulting 'hFIRE' mice were transplanted with PBS or human iPSC-derived microglia progenitors. 6.5 months later, mice were sacrificed, and brains harvested for RNA-sequencing, immunohistochemistry and biochemical analysis. To increase translational relevance, ALSP patient-derived L786S-Het iPSCs were CRISPR-corrected, and iPSC-microglia transplanted into 4-month-old hFIRE mice.
Results: By 8.5months of age, hFIRE mice exhibit large numbers of axonal spheroids, robust astrogliosis, brain calcification, lipid accumulation, and white matter abnormalities. Remarkably, transplantation of iMG restores microglial transcript levels and prevents ALSP-related neuropathologies, including the onset of disease-associated oligodendrocytes(DOLs). In addition, CRISPRcorrection rescues proliferative deficiency and increases homeostatic marker expression in xenotransplanted L786L-corrected iMG. Surprisingly, transplantation of CRISPR-corrected iMG, but not uncorrected L786S-Het iMG, into 4-month-old mice significantly reduces pre-existing spheroid, astrogliosis, and calcification within just 6 weeks.
Conclusions: Taken together, these results indicate hFIRE mice model the diverse neuropathologies of ALSP patients and provide initial evidence iPSC-microglia could be further developed as a promising new therapeutic strategy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0269 / #1028

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

CELLULAR RESILIENCE TO ALZHEIMER'S PATHOLOGY

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Wei-Ting Chen[1], Maria Dalby[2], Ashley Lu[1], Katleen Craessaerts[3], Luuk De Vries[4], Marisa Vanheusden[1], Diego Sainz[1], Araks Martirosyan[1], Benjamin Pavie[5], Nikky Corthout[5], Veerle Van Lieshout[3], Anke Misbaer[1], Henne Holstege[6], Inge Huitinga[4,7], Mark Fiers[3], Rita Balice-Gordon[2], Niels Plath[2], Bart De Strooper[3,8]
[1]Muna Therapeutics, Discovery Biology, Heverlee, Belgium, [2]Muna Therapeutics, Discovery Biology, Copenhagen, Denmark, [3]KU Leuven & VIB, Center For Brain & Disease Research, Leuven, Belgium, [4]Royal Netherlands Academy of Arts and Sciences, Netherlands Institute For Neuroscience, Amsterdam, Netherlands, [5]VIB-KU Leuven, Vib Bio Imaging Core, Leuven, Belgium, [6]Amsterdam UMC - Location VUmc, Amsterdam Neuroscience, Department Of Human Genetics, Amsterdam, Netherlands, [7]Netherlands Institute for Neuroscience, Netherlands Brain Bank, Amsterdam, Netherlands, [8]University College London, Dementia Research Institute, London, United Kingdom

Aims: Alzheimer´s disease pathology is characterized by the formation of amyloid beta positive plaques and phospho-tau containing neurofibrillary tangles leading to neurodegeneration and cognitive decline. Around 30% of amyloid plaque positive elderly, however, remain cognitively healthy. We hypothesize that cellular mechanisms downstream of amyloid stress underlie cellular resilience to amyloid pathology, preventing tau phosphorylation, neurodegeneration and dementia.
Methods: Human postmortem brain samples (n=50, dorsolateral prefrontal cortex) were collected from individuals characterized by amyloid pathology with (AD+Dem) or without (AD-Dem) cognitive deficits. Samples were analyzed by Visium spatial transcriptomics, histology for amyloid beta and pTau, and single nuclei transcriptomics. Findings were validated using Xenium to reveal the cellular resolution of transcripts of interest and their spatial relationship to pathology *in situ*.
Results: We identified 54 cellular subpopulations and several gene co-expression networks that were differentially responsive to amyloid beta and pTau pathology in the presence or absence of dementia. In AD+Dem samples, pTau positive neuritic plaques were surrounded by cells including microglia with prominent inflammatory gene networks, while in AD-Dem samples these cells were localized around amyloid plaques with no or minimal tau pathology. Differential gene expression networks in cells near amyloid plaques in the presence and absence of tau pathology included those involved in protein folding, mitochondria health, cell death and microtubule-based transport. These mechanisms may play important roles in cellular resilience to amyloid-induced tau pathology.
Conclusions: Spatial transcriptomics from human brain tissue is a powerful approach to identify cellular mechanisms of resilience towards neuropathology. These mechanisms represent a rich source for the identification of novel therapeutic targets for the treatment of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0270 / #1594

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

GENERATION OF YOLK-SAC-LIKE MYELOID PROGENITORS MODELS MICROGLIA ONTOGENY

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Nicola Fattorelli[1,2], Anna Martinez-Muriana[1,2], Leen Wolfs[1,2], Maxim Van Hoek[3,4], Jessie Premereur[3,4], Heidi Denton[3,4], Emanuela Pasciuto[1,2], Alma Mohebiany[3,4], Bart De Strooper[1,2,5], Renzo Mancuso[3,4]
[1]VIB-KU Leuven, Center For Brain & Disease Research, Leuven, Belgium, [2]KU Leuven, Department Of Neurosciences And Leuven Brain Institute, Leuven, Belgium, [3]VIB Center for Molecular Neurology, Microglia And Inflammation In Neurological Disorders (mind) Lab, Antwerpen, Belgium, [4]University of Antwerp, Department Of Biomedical Sciences, Antwerp, Belgium, [5]University College London, Dementia Research Institute, London, United Kingdom

Aims: Myeloid cells are innate immune effectors involved in the surveillance and maintenance of tissue homeostasis. Although displaying phenotypic and functional heterogeneity, myeloid cells share a common ontogeny in the yolk sac during early stages of development. Previous studies have profiled human myelopoiesis *in vivo*. However, wide access to human embryonic tissue is limited. Hence, development of in vitro protocols mimicking this biological process is key to model myeloid cells physiology and disease. Here, we aimed at generating yolk sac-like myeloid progenitor cells *in vitro* and validating their multipotency to generate different tissue-resident macrophages, such as microglia.
Methods: We used single-cell transcriptomics and proteomics approaches to explore the heterogeneity of human pluripotent stem cell-derived myelopoiesis. Then we used immunophenotyping and cell sorting to characterize and isolate different cell populations, and xenotransplantation of human stem-cell-derived myeloid progenitors to test differentiation capacity *in vivo*.
Results: We confirmed the generation of inducible yolk sac myeloid progenitors (iYSMPs) *in vitro*, whose transcriptional profile overlapped with myeloid progenitor cells described in published human embryonic datasets. Using pseudotime, we inferred that iYSMPs were able to differentiate into macrophages, neutrophils and erythrocytes lineages, mimicking human ontogeny. We found that the production of iYSMPs was restricted to a specific time window of the differentiation process, after which they transitioned towards myeloid lineages. Finally, we were able to functionally validate iYSMPs multipotency *in vivo* by xenografting different mouse tissues, where thanks to environment-specific cues they generated microglia and brain macrophages in the brain, and Kupffer cells in the liver.
Conclusions: Overall, we provide evidence of the generation of human iYSMPs, which coupled to genetic manipulations and multi-omics approaches could address a variety of questions concerning physiology, development and pathology of human myeloid cells.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0271 / #836

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

NICOTINIC ACID RECEPTOR HCAR2 AFFECTS MICROGLIA RESPONSE AND AMYLOID PATHOLOGY AT EARLY- AND LATE-STAGE DISEASE

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Miguel Moutinho[1], Israel Coronel[1], Samantha Geis[2], Martin Benito[2], Paul Fallen[1], Abigail Wallace[1], Shweta Puntambekar[2], Adrian Oblak[3], Gary Landreth[1]
[1]Stark Neurosciences Research Institute, Indiana University, School of Medicine, Anatomy, Cell Biology And Physiology, Indianapolis, United States of America, [2]Indiana University School of Medicine, Stark Neuroscience, Indianapolis, United States of America, [3]Stark Neurosciences Research Institute, Indiana University, School of Medicine, Department Of Radiology & Imaging Sciences, Indianapolis, United States of America

Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disease and a leading cause of dementia worldwide. Although we have recently showed that the niacin receptor HCAR2 stimulates a protective microglia phenotype in an amyloid mouse model at a stage of rapid amyloid accumulation and neuronal dysfunction, it is unclear whether HCAR2 plays a role at different stages of disease. Our aim is to study the function of HCAR2 at early and late stages of amyloid pathology
Methods: We analyzed amyloid pathology and microglia response in 2-month- and 8-month -old 5xFAD mice lacking the HCAR2 receptor, corresponding to early and late stage of disease respectively. To examine if activation of HCAR2 exerted beneficial effects, 2-month-old 5xFAD mice were provided with high doses of nicotinic acid through food pellets for 4 months and 8-month-old mice were treated with an FDA-approved formulation of nicotinic acid (Niaspan®) by daily oral *gavage* for 30 days. Brain tissue of treated mice was processed for biochemical and imaging analysis.
Results: Our preliminary results show that the lack of HCAR2 exacerbates amyloid pathology in 2 and 8-month-old 5xFAD accompanied by deficits in microglia mobilization to plaque-rich areas. Interestingly, the number of microglia is reduced in 2-month animals which is accompanied by a reduction in proliferation. Both the provision of a nicotinic acid-enriched diet to 2-month-old 5xFAD animals and the treatment of 8-month-old 5xFAD mice with Niaspan® attenuated amyloid burden.
Conclusions: These preliminary data demonstrate that HCAR2 impacts amyloid pathology and microglia response throughout the course of amyloid pathology, highlighting an important role of this receptor in disease and its potential as a therapeutic target. Our findings with nicotinic acid-treated mice further support the therapeutic potential of HCAR2 in Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0272 / #1351

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

FROM PATHOGENESIS TO TREATMENT: DISCOVERING TARGETS FOR DRUG DEVELOPMENT WITH PATIENT-DERIVED MICROGLIA

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Hazel Quek[1], Carla Cuní-López[1], Romal Stewart[1], Michelle Lupton[2], Tara Roberts[3], Colin Masters[4], Vincenzo La Bella[5], Anthony White[1]
[1]Mental Health and Neuroscience, QIMR Berghofer Medical Research Institute, Cellular And Molecular Neurodegeneration, Brisbane, Australia, [2]Mental Health and Neuroscience, QIMR Berghofer Medical Research, Genetic Epidemiology, Brisbane, Australia, [3]Ingham Institute for Applied Medical Research and School of Medicine, School Of Medicine, Sydney, Australia, [4]The University of Melbourne, Florey Institute Of Neuroscience And Mental Health, Parkville, Australia, [5]ALS Clinical Research Centre and Laboratory of Neurochemistry, University of Palermo, Department Of Neurology And Psychiatry, Palermo, Italy

Aims: Neurodegenerative disorders, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), pose a significant challenge due to the absence of effective treatments. Recent findings highlight the pivotal role of neuroinflammation, primarily orchestrated by microglia, the resident immune cells of the brain, in the pathogenesis of these diseases. Consequently, targeting microglia has emerged as a promising therapeutic avenue. Nonetheless, existing microglial models inadequately capture the intricate and multifaceted contributions of microglia within the complex milieu of brain tissue, thereby impeding drug development success.
Methods: To address this limitation, we adapted an established protocol to generate human-induced microglia cells (MDMi) derived from peripheral blood mononuclear cells as an alternative approach to using microglia derived directly from human brain tissues. Our prior work with MDMi has elucidated dynamic and functional differences between microglia derived from ALS and age-match healthy individuals. Importantly, we show that the MDMi platform mirrors the natural biological and clinical heterogeneity in patients, allowing a personalised therapeutic regime instead of a one-size-fits-all strategy, which has yielded limited success.
Results: Our study now extends to AD MDMi where RNAseq has identified Paired immunoglobin-like Type 2 receptor (PILRB) and chitotriosidase-1 (CHIT-1) as crucial genes upregulated in AD but not in aged-matched MDMi. Interestingly, the upregulation of PILRB expression in AD was coupled with altered subcellular localisation to the plasma membrane from the mitochondria compared to age-matched individuals. PILRB translocation in AD was further exacerbated when treated with amyloid-beta (1-42) peptide compared to age-matched MDMi. Unpublished data also showed impaired microglial morphology and phagocytosis in AD MDMi, which confirmed a significant role of microglia implicated in AD.
Conclusions: Overall, utilising MDMi can identify biomarkers for developing microglial-targeted therapies to improve AD treatment outcomes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0273 / #1772

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

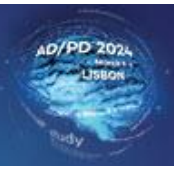
TARGETING IMMUNE CHECKPOINT TIM3 REGULATES MICROGLIAL FUNCTION AND AMELIORATES ALZHEIMER'S DISEASE PATHOLOGY

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Zhuoran Yin[1], Kimitoshi Kimura[1], Ayshwarya Subramanian[1], Yufan Wu[1], Danyang He[1], Karen Dixon[1], Udbhav Chitta[1], Xiaoming Zhang[1], Ahad Khalilnezhad[1], Thomas Pertel[1], Ruihan Tang[1], Samuel Myers[2], Aastha Aastha[1], Masashi Nomura[3], Vasundhara Singh[2], Lei Liu[1], Conner Lambden[1], Kilian Kleemann[1], Neha Gupta[1], Yiran Cheng[1], Sebastian Silveira[1], Huiyuan Zhang[1], Aamir Suhail[1], Toni Delorey[2], Orit Rosenblatt-Rosen[2], Dennis Selkoe[1], Aviv Regev[2], Mario Suvà[2], Oleg Butovsky[1], Vijay Kuchroo[1]
[1]Brigham and Women's Hospital, Neurology, Boston, United States of America, [2]Broad Institute of MIT and Harvard, Broad Institute Of Mit And Harvard, Cambridge, United States of America, [3]Massachusetts General Hospital, Pathology, Boston, United States of America

Aims: Microglia, the resident brain immune cells, play a critical role in brain homeostasis and disease progression. Our previous studies show that microglia acquire the neurodegenerative phenotype (MGnD) in Alzheimer's disease (AD), which is beneficial for limiting disease progression. *Havcr2*, encoding immune checkpoint molecule Tim3, has recently been identified as a risk gene for late-onset AD. However, its role in microglia, which is important given its role in inducing T cell exhaustion, remains unknown. Our study aims to understand the function of microglia-specific Tim3 in AD.
Methods: We specifically targeted microglia-specific Tim3 in transgenic AD mice. We used RNAseq and immunohistochemistry (n = 6-8) to investigate the gene expression profile and AD pathology. Additionally, we utilized single-cell RNAseq to identify microglial clusters. We performed forced alternation tests to evaluate cognition (n = 15-22). Moreover, we conducted IP-MS (immunoprecipitatioin-mass spectrometry) screening and confirmatory IP-WB (IP-western blot) analysis to identify the intracellular binding patterns for Tim3.
Results: We demonstrate that the deletion of Tim3 in microglia induces an MGnD activation state in developing brains with enhanced phagocytosis ability. Genetically targeting microglial Tim3 in 5xFAD mice reduces Aβ plaque load, decreases dystrophic neurites, attenuates plaque-associated synaptic degradation, and improves cognition. Furthermore, we show that Tim3 binds to Smad2, a key molecule in TGFβ signaling. Motif enrichment analysis identifies Smad2 as a core transcription factor regulating the transcriptome of Tim3-deficient microglia. Detailed analysis shows that the C terminus of Tim3 is necessary for their binding and enhanced phosphorylation of Smad2.
Conclusions: Our study demonstrates a novel Tim3-mediated regulatory mechanism of MGnD and underscores the beneficial role of targeting Tim3 in restricting neurodegenerative pathology in AD mouse models. This highlights Tim3 as a promising target for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0274 / #2296

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

COMPARISON OF HUMAN PRIMARY MICROGLIA AND HUMAN IPSC DERIVED MICROGLIA CELLS AS IN VITRO MODELS FOR MICROGLIA ACTIVATION

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Matteo Zanella[1], Malika Bsibsi[1], Kimberly Lo[1], Berke Gurkan[1], Cheng-Chih Hsiao[2], Lieke Geerts[1], Malathi Raman Srivastava[3], Camilla Fairbairn[3], Stefan Kostense[1], Jeroen Degroot[1], David Fisher[4], Marijn Vlaming[1]
[1]Charles River Laboratory, Early Discovery, Leiden, Netherlands, [2]Netherlands Brain Bank, ., Amsterdam, Netherlands, [3]bit.bio, Babraham Research Campus, Cambridge, United Kingdom, [4]Charles River Laboratory, Early Discovery, Saffron Walden, United Kingdom

Aims: Microglia are resident immune cells in the central nervous system (CNS) and play an essential role in neuroinflammation and neurodegenerative disease. Microglia can be isolated from both control and diseased post-mortem human brain tissue. However, the limitation on brain collection and yield of isolated cells restricts the ability to perform screening studies. Induced pluripotent stem cells (iPSCs)-derived microglia, may provide a suitable alternative for large-scale compound validation. Yet, to effectively use iPSC-derived microglia, one must characterize the extent to which these cells faithfully represent biological processes in brain tissue.
Methods: Here, we compared morphological and functional properties of primary human microglia cells and iPSC-derived microglia.
Results: Exposure of primary and iPSC-derived microglia to LPS resulted in increased cytokine secretion in a concentration and time dependent manner. Cytokine secretion was strongly inhibited by dexamethasone. Priming of primary and iPSC-derived microglia with LPS and treatment with nigericin, a potent inflammasome activator, resulted in robust secretion of IL-1β and IL-18. Furthermore, nigericin induced IL-1β and IL-18 release was inhibited by the inflammasome inhibitor MCC950 in both cell types. Similarly to in house isolated microglia, iPSC-derived microglia showed a strong expression of specific microglia markers and cytokine release upon LPS- and nigericin-treatment. Finally, the *in vitro* phagocytosis by uptake of pHrodo™ BioParticles, labeled human myelin, α-synuclein and β-amyloid fibrils was monitored over time by high-content imaging. Time-dependent uptake was observed and was sensitive to disruption of the actin-cytoskeleton with cytochalasin D.
Conclusions: Taken together, we successfully demonstrated that primary and iPSC-derived microglia respond similarly to different stimuli. Therefore, these cell types could serve as a reliable tool for evaluating the efficacy of prospective drugs for neurological diseases associated with microglia activation, such as Alzheimer's and Parkinson's Disease.

P0275 / #463

Poster Topic: *Theme A: β-Amyloid Diseases / A02.m. Therapeutic Targets, Mechanisms for Treatment: Microglia*

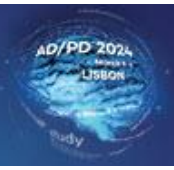
EVALUATING THE TREATMENT OUTCOMES OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN PATIENTS WITH MODERATE-TO-SEVERE ALZHEIMER'S DISEASE

POSTERS: A02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Shouzi Zhang
Beijing Geriatric Hospital, Department Of Psychiatry,, Beijing, China

Aims: The repetitive transcranial magnetic stimulation (rTMS) shows great potential in the treatment of Alzheimer's disease (AD). However, its treatment efficacy for AD patients in moderate to severe stage is relatively evaluated. In this study, we further evaluate the treatment efficacy of rTMS in moderate-to-severe phase of AD.
Methods: we proposed a randomized, sham-controlled, clinical trial of rTMS among 35 moderate-to-severe AD patients. A high frequency (10 Hz) stimulation of the left dorsal lateral prefrontal cortex (DLPFC), 60-session long treatment lasting for 3 months procedure was adopted in the trial. Each participant completed a battery of neuropsychological tests at baseline and post-treatment for evaluation of the rTMS therapeutic effect. Twelve of them completed baseline resting-state functional magnetic resonance imaging (fMRI) for exploration of the underlying neural contribution to individual difference in treatment outcomes.
Results: The result showed that the rTMS treatment significantly improved cognitive performance on the severe impairment battery (SIB), reduced psychiatric symptoms on the neuropsychiatric inventory (NPI), and improved the clinician's global impression of change (CIBIC-Plus). Furthermore, the result preliminarily proposed resting-state multivariate functional connectivity in the (para) hippocampal region as well as two clusters in the frontal and occipital cortices as a pre-treatment neuroimaging marker for predicting individual differences in treatment outcomes.
Conclusions: The finding could brought some enlightenment and reference for the rTMS treatment of moderate and severe AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0276 / #1447

Poster Topic: *Theme A: β-Amyloid Diseases / A02.n. Therapeutic Targets, Mechanisms for Treatment: Astroglia*

NETSSEQ REVEALS DEEP MOLECULAR INSIGHTS INTO ASTROCYTE BIOLOGY AND IDENTIFIES NOVEL THERAPEUTIC TARGETS FOR ALZHEIMER'S DISEASE

POSTERS: A02.N. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ASTROGLIA

Xiao Xu, Clare Bender, Jenna Harvey, Bernadino Ossola, Daniel Barker, Justin Powell, David Cadwalladr, Toni Cheung, Jason Lawrence, Steven Sheardown, Gabriela Crane, Keith Page, Mark Carlton, Nicola Brice, Lee Dawson
Cerevance, Neuroscience, Cambridge, United Kingdom

Aims: An integrated understanding of specific cell types in neurodegenerative disease is essential for developing novel therapeutics. Using Cerevance's proprietary Nuclear Enriched Transcript Sort Sequencing (NETSseq) platform on post-mortem human brain tissue, individual cell types in control and disease donors have been profiled, thereby enabling the identification of novel drug targets.
Methods: Using NETSseq on tissue across multiple brain structures from Alzheimer's disease (AD) and control donors, we have generated deep RNA-seq transcriptomic profiles (expression of >12,000 genes per sample) and ATAC-seq epigenetic profiles for multiple glial and neuronal cell types. These data have enabled us to stratify donors across the disease continuum, to identify cell-type specific genes that change across this continuum, and to identify gene signatures associated with different glial activation states.
Results: NETSseq data demonstrate clear glial expression of genes that are known genetic risk factors for AD. In astrocytes, we observe gene signatures and chromatin changes associated with regional differences, disease progression, and multiple disease-associated activation states. Many pathways are altered in disease, including those involved in glutamate homeostasis. We found that the inwardly rectifying K+ channel Kir4.1/KCNJ10 is specifically expressed in astrocytes, changes expression during AD progression and astrocyte activation, and when modulated, affects glutamate uptake, suggesting KCNJ10 is an example of a novel target for preventing neuronal hyperexcitability in AD.
Conclusions: Highly reproducible molecular profiles from specific cell types have been generated using NETSseq. The identification of numerous astrocyte-specific genes that change across the AD disease continuum, suggests that astrocyte dysfunction may contribute to disease progression. These data are being used to pinpoint and prioritize novel targets for drug discovery, potentially offering promising prospects for the development of transformative therapies for AD and other diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0277 / #1089

Poster Topic: *Theme A: β-Amyloid Diseases / A02.o. Therapeutic Targets, Mechanisms for Treatment: Gene therapy and gene editing*

CENTRAL NERVOUS SYSTEM-DIRECTED ADENO-ASSOCIATED VIRUS (AAV) INDUCED EXPRESSION OF A PROTECTIVE APOE VARIANT IN CYNOMOLGUS MONKEYS

POSTERS: A02.O. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

Melvin Evers, Madhurima Chatterjee, Meriem Bourajjaj, Amila Zuko, Angga Kusuma, Ines Lopes Pereira, Sara Gimeno Peris, Greg Dobrynin, Liesbeth Heijink, Ying Poi Liu
uniQure biopharma B.V., Research And Development, Amsterdam, Netherlands

Aims: Polymorphism in the apolipoprotein E (*APOE*) gene is a major genetic risk determinant of late-onset Alzheimer's Disease (AD), with the *APOE*ε4* allele conferring an increased risk and the *APOE*ε2* allele conferring decreased risk relative to the common *APOE*ε3* allele. The objective of this study is to evaluate expression of *APOE* in the brain tissue and cerebrospinal fluid (CSF) of cynomolgus monkeys (*Macaca fascicularis*) following a single administration of an adeno-associated virus (AAV) encoding a protective *APOE* transgene through intra-CSF injections.
Methods: We measured AAV vector DNA and *APOE* mRNA levels in the brain tissue of monkeys. Additionally, we measured the expressed human ApoE protein in CSF, brain tissue and plasma of these monkeys.
Results: After a single intra-CSF administration of AAVs, we successfully expressed human *APOE* in cynomolgus monkeys. We detected vector DNA copies and *APOE* mRNA molecules as well as human ApoE protein in different brain areas and CSF.
Conclusions: Our study demonstrates CNS-specific expression of a protective variant of human *APOE* in cynomolgus monkeys implicating potential of a one-time administered gene therapy by overexpressing a protective APOE variant as a treatment for autosomal dominant AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0278 / #1587

Poster Topic: *Theme A: β-Amyloid Diseases / A02.o. Therapeutic Targets, Mechanisms for Treatment: Gene therapy and gene editing*

THERAPEUTIC EFFECTS OF MIR-937-3P OF NEURAL-INDUCED HUMAN ADIPOSE TISSUE-DERIVED STEM CELLS ON A-BETA ALZHEIMER'S DISEASE MODEL

POSTERS: A02.O. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

Sujeong Jang, Jiyun Choi, Han-Seong Jeong
Chonnam National University Medical School, Physiology, Hwasun-gun, Korea, Republic of

Aims: Alzheimer's disease (AD), which is the most common type of dementia causes 60~70% of dementia cases, has continuous impairment of cognitive and behavioral function. Until now, there is no cure except symptomatic treatment such as cholinesterase inhibitors. In this study, we investigated whether the therapeutic and neuroprotective effects of human adipose tissue-derived MSC (hADSC) miRNAs on the Aβ-induced Alzheimer's disease model in neuroblastoma cells by investigating the apoptosis pathway.
Methods: We isolated and differentiated hADSCs into neuronal cells, and then performed the microarray to analyze the miRNA candidates by comparing the expression between hADSCs and neural-induced hADSCs (NI-hADSCs). Following KEGG and GO analysis, miR-937-3p can action of axonal guidance, nervous system development, and synaptic transmission. Neuroblastoma cells were induced as an Alzheimer's disease with Aβ and then treated with miR-937-3p. To figure out the therapeutic and neuroprotective effects of miR-937-3p, we investigated the signaling pathway using immunocytochemistry (ICC), FACS, western blotting analysis, qPCR, and protein array.
Results: We found that the cells treated with miR-937-3p showed neurite outgrowth and morphological changes into mature neurons with increased neuronal markers via ICC. Aβ-induced apoptosis was decreased with miR937-3p via FACS analysis by Annexin V and PI staining. Treatment of miR-937-3p increased Bcl-2 and Mcl-1 expression and decreased Bax, cleaved-caspase-3, -7, and -9. In addition, the neuronal markers (NFH, NeuN, MAP2, Tuj1) and oligodendrocyte markers (OLIG2, CNPase) were increased with miR937-3p compared to Aβ group. After miR937-3p treatment, Wnt5α was increased, and downstream pathways were activated. Interestingly, both Wnt/Ca^{2+} and Wnt/PCP pathways activated and regulated PKC, Cdc42, RhoA, Rac1/2/3, and p-JNK.
Conclusions: Therefore, miR-937-3p induces the differentiation of cells into mature neurons and reduces the apoptotic death by activating the Wnt/Ca^{2+} and Wnt/PCP pathways and inhibiting apoptosis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0279 / #1236

Poster Topic: *Theme A: β-Amyloid Diseases / A02.o. Therapeutic Targets, Mechanisms for Treatment: Gene therapy and gene editing*

MIR-132 GENE THERAPY FOR ALZHEIMER'S DISEASE IN NON-HUMAN PRIMATES

POSTERS: A02.O. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

Boutheyna Khelaifia[1], Brittney Armitage-Brown[2], Dana Mika[2], Claudia Goupil[1], Douglas Munoz[2], Sébastien Hébert[1]
[1]Université Laval - Centre de Recherche du CHU de Québec, Neurosciences, Québec, Canada, [2]Queen's University, Department Of Medecine, Kingston, Canada

Aims: Accumulating evidence suggests that multi-target drugs will be required to completely restore neuronal dysfunction and cognitive loss in AD. This could be feasible using microRNAs (miRNAs) by simultaneously targeting key disease genes and phenotypes. Neuronal miR-132 is the most strongly downregulated during AD progression and has been shown to rescue disease phenotypes (Amyloid, Tau, cognition) in mice and cells. The study aims to advance the preclinical development of a miR-132 mimic (miR-132m) for AD gene replacement therapy. Specifically, we performed pharmacokinetics and biosafety studies following miR-132m delivered to the central nervous system (CNS) of non-human primates.
Methods: We first used naive cynomolgus monkeys injected with fluorescent miR-132m into the cisterna magna. CSF and blood samples were collected, and the animals were euthanized 72 hours after injection. CNS tissues were dissected. Quantification of miR-132m and miRNAs associated with neuro-inflammation and degeneration was performed by qRT-PCR. Next, a biosafety study was conducted in monkeys treated with an unmodified miR-132m through continuous intrathecal infusion for 30 days. Blood tests were conducted during this treatment.
Results: We observed a significant increase of miR-132m levels in the CSF up to 8h post-injection, in serum up to 1h post-injection, and in various tissues post-mortem, including the entorhinal cortex, midbrain, pons, cerebellum, and spinal cord. In contrast, the other tested miRNAs remained stable. Finally, no signs of toxicity were observed after the continuous infusion of miR-132m into the CSF.
Conclusions: These results suggest that the direct injection of miR-132m into the CSF is effective and well-tolerated by the organism. Further studies are underway to assess the cellular distribution and genes targeted by miR-132m in the CNS. These findings will be used in developing Phase I clinical trials in humans.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0280 / #2179

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

NOVEL RIVASTIGMINE DERIVATIVES AS PROMISING MULTI-TARGET COMPOUNDS FOR POTENTIAL TREATMENT OF ALZHEIMER'S DISEASE

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

M. Amélia Santos[1], Inês Dias[1], Leo Bon[1], Marlène Emmanuel[1], Paul Vogt[1], Daniel Chavarria[2], Fernanda Borges[2], Catarina Guerreiro-Oliveira[3], Sandra Morais Cardoso[4], Sílvia Chaves[1]
[1]Instituto Superior Técnico, Universidade de Lisboa, Centro De Quimica Estrutural, Lisboa, Portugal, [2]University of Porto, Department Of Chemistry And Biochemistry, Porto, Portugal, [3]University of Coimbra, Cnc-center For Neuroscience And Cell Biology, Coimbra, Portugal, [4]Instituto Superior Técnico, Cnc-center For Neuroscience And Cell Biology, Coimbra, Portugal

Aims: The main goal is to develop new drugs to combat the multi-faceted Alzheimer's disease (AD), with no cure so far. Pursuing the drug design strategy of extra-functionalization of drugs already approved for AD, a series of polyfunctional hybrids were developed and assayed as multitarget-directed ligands. Thus, Rivastigmine (RIV) templates, (for cholinesterase, ChE, inhibition) were hybridized with other moieties to provide the conjugates with extra pharmacological responses to tackle several important hallmarks of AD.
Methods: The RIV hybrids were firstly designed on the basis of computational simulations and then selected compounds were prepared by usual methods of organic synthesis. Using standard spectroscopic techniques (UV-Vis absorption and fluorescence), the new compounds were evaluated in aqueous solution for their biological activity, namely the inhibition of important enzymes (as AChE, BChE and MAO), inhibition of Aβ aggregation and capacity for radical scavenging. Effects of these compounds in cell viability and neuroprotection were also assessed in neuroblastoma cell lines after $A\beta_{1-42}$ and ROS induced toxicity.
Results: The results obtained, namely for the inhibition of enzymatic activity and Aβ aggregation, the radical scavenging capacity and also cell viability, are rationalized on the basis of structural variations, specifically the type of the extra-functional moieties linked to the rivastigmine template, their substituent groups (mainly *O*- or *N*-electron donors) and also the length of the linker between the two main moieties. Discussion is also made in comparison our previous results with other RIV conjugates previously studied by us [D. Vicente-Zurdo, *et all*, *Biomed.* **2022**, *10*, 1510].
Conclusions: The new hybrids show good activity for the inhibition of ChEs (AChE and BChE), MAO and $A\beta_{1-42}$ self-aggregation, and also neuroprotection, thus appearing as potential pleiotropic drugs against Alzheimer´s disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0281 / #1555

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

HEARING IMPAIRMENT EXACERBATES COGNITIVE DYSFUNCTION AND ACCELERATES THE PROGRESSION OF ALZHEIMER'S DISEASE BY INCREASING INFLAMMATION IN THE BRAIN

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Hyong Ho Cho[1], Byeong C. Kim[2], Min-Kyung Song[3]
[1]Chonnam National University Medical School, Otolaryngology, Gwangju, Korea, Republic of, [2]Chonnam National University Medical School & Hospital, Neurology, Gwangju, Korea, Republic of, [3]Gwangju City Hospital, Neurology, Gwangju, Korea, Republic of

Aims: Hearing loss as the most significant risk factor for developing Alzheimer's disease. However, the precise mechanisms that connect hearing impairment and Alzheimer's disease are still unclear. The study aimed to investigate the impact of drug-induced hearing loss (DIHL) on cognitive function, memory retention, and protein expression closely related to the progression of Alzheimer's disease in 5XFAD and Tg2576 mice.
Methods: The DIHL animal models were established by injecting kanamycin and furosemide into mice aged 3.5 to 4 weeks. Cognitive function and long-term potentiation (LTP) were measured to investigate the potential correlation between hearing loss and Alzheimer's disease. Immunohistochemistry and immunoblotting were utilized to assess the accumulation and expression of beta-amyloid, p-tau, Iba-1, and GFAP. The protein expression levels of the mammalian target of rapamycin (mTOR) signaling pathway and its downstream pathways, as well as pro-inflammatory cytokines, were analyzed.
Results: DIHL exacerbated cognitive dysfunction and resulted in a significant increase in the accumulation of beta-amyloid and hyperphosphorylated tau in the hippocampus and cortex of mice with Alzheimer's disease, when compared to the control group. The levels of protein expression for neuroinflammatory markers, such as Iba1 and GFAP, as well as pro-inflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), were found to be elevated. Additionally, DIHL increased the protein expression of phosphorylated mTOR and the phosphorylation of p70 ribosomal S6 protein kinase 1 (S6K1) and S6 pathways. Furthermore, restoring hearing loss reversed the impaired LTP in both wild-type and Alzheimer's disease mice.
Conclusions: Hearing loss exacerbates cognitive dysfunction, impairs memory retention, and significantly increases the accumulation of beta-amyloid and hyperphosphorylated tau protein aggregates in the brain. Activation of the mTOR pathway, astrocytes, and microglia can also occur that exacerbate the progression of Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0282 / #1962

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

NETWORK-INFORMED UNBIASED GLOBAL PROTEOMICS STRATEGY TO DISCOVER BIOMARKERS FOR E2511, A NOVEL TRKA MODULATOR

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Satya Saxena[1], Yuanqing Ye[2], Luigi Giorgi[2], Viswanath Devanarayan[3], Allan Levey[4], Duc Duong[4], Kiran Pandey[5], Nicholas Seyfried[4], Michael Irizarry[6], Kanta Horie[1], Pallavi Sachdev[1]
[1]Eisai Inc, Translational Medicine, Nutley, United States of America, [2]Eisai Inc., Neurology, Nutley, United States of America, [3]Eisai, Inc, Real World Evidence And Medical Value, Global Medical Affairs At The Neurology Business Group, Nutley, United States of America, [4]Emory University School of Medicine, Center For Neurodegenerative Disease, Atlanta, United States of America, [5]Emtherapro, Inc., R&d, Atlanta, United States of America, [6]Eisai, Inc, Neurology Business Group, Nutley, United States of America

Aims: Here, we describe the utility of an orthogonal network-informed unbiased tandem-mass tag spectrometry (TMT-MS)-based global proteomics strategy to further support the effect of E2511 treatment on CSF proteins that overlap with brain modules linked to axonal and synaptic activity.
Methods: A total of 32 healthy subjects from E2511-A001-005, a Phase 1 randomized, double-blind, placebo-controlled, multiple ascending (MAD) study, were randomly assigned to receive either placebo or once daily doses of 10, 20, 40 and 80 mg E2511 for 14 days. In this study, pre (day -2)- and post (day 13)-treatment CSF samples from placebo and highest dose level cohort (80 mg) were analyzed using TMT-MS. CSF proteome from the placebo and 80 mg cohorts were mapped to 44 brain-derived co-expression modules from the proteomes of over 500 control, asymptomatic AD and AD brains[2].
Results: Compared to previous results, TMT-MS global proteomics achieved cumulative CSF proteome depth of 2,040 proteins. We identified 91 differentially altered proteins (unadjusted $p < 0.05$) when comparing CSF proteomes of placebo and 80 mg E2511-treated subjects. 40/91 proteins altered by E2511 treatment mapped to 20 brain-derived co-expression modules linked to AD. Treatment had a significant effect on CSF proteins that overlap with brain modules linked to axonal and synaptic activity (M1, M4, M19, M22-9 proteins), protein folding (M14-4 proteins), cell-extra cellular matrix interaction (M11, M27- 6 proteins), and matrisome (M42- 2 proteins).
Conclusions: Human brain network-informed proteomic-profiling of CSF provided a powerful and unique tool to identify hubs within protein co-expression modules related to E2511 MoA. This biomarker discovery strategy helped to corroborate the mechanism of action (MoA) and target engagement of E2511 in regulating axonal and synaptic biology. Further studies to confirm E2511 proof-of-mechanism and support dose-selection are planned.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0283 / #2885

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

NOVEL-GENERATION CU(II) SELECTIVE PEPTIDE SHUTTLES CAPABLE OF PREVENTING CU-AMYLOID BETA-INDUCED TOXICITY AND MICROGLIAL ACTIVATION

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Michael Okafor[1,2], David Schmitt[1], Stéphane Ory[2], Stéphane Gasman[2], Peter Faller[1], Nicolas Vitale[2]
[1]Institut de Chimie (UMR 7177), Université de Strasbourg-CNRS, Laboratory Of Biometals And Biological Chemistry, Strasbourg, France, [2]Institut des Neurosciences Cellulaires et Intégratives (INCI), CNRS, Université de Strasbourg,, Intracellular Membrane Trafficking In The Nervous And Neuroendocrine Systems, Strasbourg, France

Aims: Alzheimer's disease (AD) remains the most common neurodegenerative disease with hallmarks including the apparition, in specific parts of the brain, of intracellular neurofibrillary tangles and extracellular amyloid plaques. The latter results from an abnormal metabolism of Amyloid-beta precursor protein (APP) leading to the accumulation of Aβ in plaques or lack of clearance therein. *Ex vivo* analysis of AD patients' brains show abnormally elevated concentration of Cu, Zn and Fe in these plaques. Further studies demonstrated a reduced Cu level in the entire brain and more specifically in regions heavily affected in AD. This decrease is accompanied by a decline in neuronal Cu levels and by an increase in extracellular labile Cu promoting reactive oxygen species (ROS) generation. To correct this Cu dyshomeostasis in the brain of AD patients, we designed and synthesized novel Cu(II)-selective peptide shuttles, with the goal of equilibrating normal neuronal cell Cu homeostasis in the context of AD
Methods: The physicochemical properties of these Cu(II)-selective peptide shuttles were validated using Uv-vis spectroscopy, Fluorescence spectrometer and Mass spectrometry. Their biological properties were also characterized using the PC12 cell neuronal model and organotypic hippocampal slices (OHSCs) model.
Results: Our novel Cu(II) selective peptide shuttles possess high affinity and stability towards Cu(II) and are capable of selectively retrieving Cu(II) from extracellular Aβ, and importing Cu into cells. We also demonstrated the capacity of these new Cu-shuttles to protect OHSCs from Cu- Aβ-induced insult and their ability to rescue microglial activation and proliferation in these brain slices
Conclusions: These new Cu(II)-selective peptides have proven to be good candidates for Cu shuttles capable of preventing Cu induced toxicity in the context of AD and could be important tools in tracking the mechanistic of Cu trafficking

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0284 / #356

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

ANTI-PHOSPHO-TAU SERINE 396/404 SCFV ANTIBODIES ELIMINATE HYPERPHOSPHORYLATED TAU BY INDUCING AUTOPHAGY VIA ENDOPLASMIC-RETICULUM STRESS PATHWAY IN ALZHEIMER'S DISEASE CELL MODEL

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Soi Moi Chye
International Medical University, Division Of Applied Biomedical Science And Biotechnology, Bukit Jalil, Malaysia

Aims: In this study, anti-phospho-Tau serine 396/404 single chain variable fragment (scFv) antibody was generated by using Ph.D-12 phage display library. The effectiveness of scFv antibodies to eliminate hyperphosphorylated tau and mechanism invovlvement was investigate in Alzheimer's disease cell model.
Methods: Anti-phospho-Tau serine 396/404 single chain variable fragment (scFv) antibody was generated by using Ph.D-12 phage display library. SH-SY5Y cells were transfected with Tau-441 2N4R and treated with okadaic acid to serve as Alzheimer's disease cell model. Methyl Thiazolyl Tetrazolium (MTT) assay was used to evaluate the effectivenes of scFv antibodies to protect hyperphorylated tau induced cell death. The molecular mechanism invovement was measured by Western blot.
Results: Three scFv antibodies, FPLNSEENPFEL, FPLNSEENPLEL and FPLNSEENAFEL were identified. Based on MTT results, the cell viabilities of treated okadaic acid alone was 58.06%. However, after treated with FPLNSEENPFEL or FPLNSEENPLEL or FPLNSEENAFE, the cell viability increased to 79.38, 83.28%, 74.69%, respectively. For Western blot analysis, the pSer396 protein expression was increased 1.51-fold for okadaic acid treatment only if compare with control. However, after treated with FPLNSEENPFEL or FPLNSEENPLEL or FPLNSEENAFE, the pSer396 protein expression decreased to 0.79-fold, 1.09-fold and 0.72-fold, respectively. Moreover, PHF-1 protein expression was 2.69-fold for okadaic acid treatment only if compare with control. However, after treated with FPLNSEENPFEL or FPLNSEENPLEL or FPLNSEENAFE, the PHF-1 protein expression decreased to 0.74-fold, 0.76-fold, 0.92-fold, respectively. Moreover, protein expression level of selected proteins (IRE-1-α, Calnexin, PERK, Atg12, Beclin-1 and eIF-2α) which involved in ER-stress pathway were decreased by treating T-SH-SY5Y cells with scFv antibodies if compared with treated with oxalic acid alone.
Conclusions: In conclusion, three scFv antibodies are able to reduce cytotoxicity of hyperphosphorylated Tau proteinvia ER-stress signalling pathway. in Alzheimer's disease cell model.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0285 / #2276

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

IMPROVED CLINICAL PERFORMANCE OF PLASMA MICRORNA-BASED DIAGNOSTICS USING THE APO-EASY® IVD KIT FOR EARLY ALZHEIMER DIAGNOSIS.

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Seval Kul[1], Gabriel Sanchez[2], Stéphanie Boutillier[2], Lucas Pham-Van[1], Rodwell Mkhwananzi[2], Bruno Dubois[3], Hüseyin Firat[2]
[1]FIRALIS AMONETA, Amoneta, HUNIGUE, France, [2]Firalis, Amoneta, Huningue, France, [3]Pierre et Marie Curie University, Alzheimer Research Center Im2a, Paris, France

Aims: Improved clinical performance of plasma microRNA-based diagnostics using the APO-Easy® IVD kit for early Alzheimer diagnosis.
Methods: Total RNA from 600µl of Plasma-EDTA samples were extracted for miRNA quantification using qPCR. In parallel, a Real Time PCR test has been developed for the detection of APOE genotypes (variants of rs429358 and rs7412). This new kit, named APO-Easy® underwent rigorous analytical and clinical validation against the current gold standards, both Sanger sequencing and NGS. The Clinical diagnostic performance of both miRNA and APOE genotyping have been assessed in 1000 samples from two cohorts; ADDIA (NCT03030586) collected at 13 European clinical centres
Results: We employed five distinct predictive models, employing a five-fold cross-validation approach with 20 replicates. When employing the three microRNAs, the mean area under the curve (AUC) in the training set, as determined by the lasso model, stood at 0.71 (95% CI=0.68-0.72), with corresponding test set sensitivity and specificity values of 0.57 and 0.87, respectively. Notably, the introduction of APO-Easy® qPCR testing led to a significant enhancement in the AUC of the training set, elevating it to 0.84 (95% CI=0.82-0.86). Consequently, the test set sensitivity and specificity saw substantial improvements, reaching values of 0.71 and 0.87, respectively. Additionally, the APO-Easy® kit have been fully analytically and clinically validated for IVDR and FDA approval using 800 samples from ADDIA, and 200 samples from ADKIT cohorts with 100% accuracy versus both Sanger sequencing and NGS.
Conclusions: Three microRNAs, coupled with the APO-E genotyping using the APO-Easy® kit, represents an effective blood-based diagnostics for early-stage AD diagnosis and its differentiation from other non-AD dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0286 / #2434

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

NEOCOPRIDE, A NOVEL DISEASE-MODIFYING DRUG CANDIDATE TO TREAT ALZHEIMER DISEASE

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Patrick Dallemagne[1,2,3], Alexandre Henriques[4], Maria-Letizia Campanari[4], Romain Legrand[1], Noëlle Callizot[4], Christophe Rochais[1,2,3]
[1]Caen Normandie University, Ufr Santé, Caen, France, [2]Centre d'Etudes et de Recherche sur le Médicament de Normandie, Ufr Santé, Caen, France, [3]RonomA, R&d, Saint Etienne du Rouvray, France, [4]Neuro-Sys, -, Gardanne, France

Aims: Alzheimer disease (AD) represents a major medical problem where mono-therapeutic interventions demonstrated only a limited efficacy so far. Neocopride is a novel pleotropic molecule which targets both acetylcholinesterase and 5-HT_4 receptor. The present poster describes for the first time the results of the biological evaluation of Neocopride.
Methods: Neocopride was tested in an in vitro model of AD on rat primary hippocampal neurons injured with Aβ at concentrations between 5 pM to 100 nM. The efficacy of the compounds was compared to the one of donepezil (1 µM), as reference compound. Then, an in vivo AD model was used by Intra-hippocampal injections of a solution containing AβO in aged mice to test daily administration of Neocopride at 3 mg/kg per os. This model induces short- and long-term memory deficits. The cognitive dysfunctions are associated and well correlated with the neuronal loss and the activation of microglial cells. Donepzil at 1mg/kg by intraperitoneal was used as reference substance
Results: In vitro, Neocopride improved neuronal survival at 1 nM and 5 nM. At these doses it also increased the length of neurites per neurons and decreased the hyperphosphorylation of Tau. Interestingly, Neocopride successfully increased the number of synapses (50 pM to 5 nM). In mice, Neocopride was found to significantly restore short and long-term memory impairment induced by Aβ1-42. Neocopride improved also neuronal survival and neuroinflammation by decreasing microglial activation and astrogliosis. Moreover, protein level of PSD95 were assessed and revealed that Neocopride was able to restore synapses to a level similar to control mice.
Conclusions: Altogether, these results show that Neocopride displayed synergistic beneficial effects and could be a promising drug candidate for Alzheimer's disease. Neocopride is currently involved in a regulatory preclinical study.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0287 / #848

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

EVALUATION OF THE NEUROPROTECTIVE EFFECTS OF THE BIOINSPIRED PEPTIDE NEUROVESPINE IN A PARKINSON'S DISEASE MODEL

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Francisca Marques, Gabriel Campos, Márcia Renata Mortari
Institute of Biological Science, Department Of Physiology, Brasília, Brazil

Aims: To assess the anti-parkinsonian efficacy of the bioinspired peptide Neurovespine in a Parkinson's Disease model induced by unilateral intrastriatal injection of the neurotoxin 6-OHDA. This will be achieved by quantifying lesion severity in the experimental animals through direct counting of dopaminergic neurons in the Substantia Nigra using immunofluorescence labeling.
Methods: A 22-day experimental protocol was established, starting from the induction of the 6-OHDA lesion and continuing until the termination of the experiment when the animals were euthanized. Neurovespine (1mg/kg, 4mg/kg, or 7mg/kg) was administered i.p. 30 minutes before the lesion and after the lesion at 24h, 48h, and 72h. For each animal, three sections of the substantia nigra were selected for analysis. Immunohistochemical analysis was performed to evaluate the presence and condition of neurons in the substantia nigra. Anti-tyrosine hydroxylase (TH) immunolabeling was utilized for this purpose.
Results: In the analysis of the remaining TH-positive (THr) neurons in the substantia nigra, a significant difference was observed between the means of the 4 mg/kg Neurovespine treatment group and the Injured control group. This finding suggests a neuroprotective effect of the peptide on dopaminergic neurons at this dosage. Statistical significance was determined using [the Mann-Whitney test followed by the Dunn test] with a p-value threshold of [$p<0.05$].
Conclusions: The data presented in this study demonstrate that the administration of Neurovespine peptide at a dosage of 4 mg/kg effectively preserved dopaminergic neurons in the Substantia Nigra. These findings highlight the potential of Neurovespine as a valuable tool for Parkinson's Disease research and suggest its potential as a model drug for the development of novel neuroactive compounds. Funding: CAPES, CNPq e FAPDF.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0288 / #2232

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

CENTRAL AND PERIPHERAL TARGETS OF KETOGENIC DIETARY INTERVENTIONS IN PRECLINICAL MODELS OF ALZHEIMER'S DISEASE

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Paule Mbra[1,2], Laura Hamilton[1], Gaël Moquin-Beaudry[2], Federico Pratesi[2], Myriam Aubin[1], Chenicka-Lyn Mangahas[1], Marian Mayhue[1], Anne Aumont[1], Martine Tétreault[1], Mariano Avino[1], Eric Massé[1], Karl Fernandes[1,2]
[1]Université de Sherbrooke, Faculty Of Medicine And Health Science, Sherbrooke, Canada, [2]Research Center on Aging, CIUSSS-Estrie CHUS, Gerosciences, Sherbrooke, Canada

Aims: Alzheimer's Disease (AD) remains a major global health concern, requiring innovative therapeutic strategies. Increasing evidence support benefits of ketogenic dietary interventions on cognition. In this study, we investigate the central and peripheral targets of such diets in AD mouse models.
Methods: 3xTg-AD and 5xFAD mice and their control strain/genotype mice were fed a standard carbohydrate-rich diet (Control diet, 70% carbohydrate, 20% fat, 10% protein), an identical diet supplemented with ketogenic medium-chain triglycerides (MCT, a ketogenic substrate), or challenged with an extreme ketogenic diet (CFHF, carbohydrate-free high fat diet). Cognitive assessments were conducted using the Morris water maze, while the underlying cellular mechanisms were investigated through Golgi staining and bulk RNA-sequencing of the hippocampus. Peripheral metabolism was monitored by variety of longitudinal measures (blood sampling, EchoMRI, indirect calorimetry), followed by bulk RNA-sequencing of the liver and 16S rRNA-sequencing of fecal matter.
Results: AD mice on the MCT and CFHF ketogenic interventions showed improved learning performances after 1 month. After 6 months on the MCT and KD ketogenic interventions, the hippocampus of AD mice retained increases in the number of dendritic spines and correction of 41% (with MCT) and 56% (with CFHF) of differentially expressed genes. The analysis of peripheral metabolism revealed a distinct vulnerability of AD mice to hyperleptinemia and body weight gain when submitted to CFHF, whereas MCT showed evidence of improving peripheral energy metabolism. Interestingly, AD mice showed hundreds of deregulated genes in the liver and microbiome alterations, and these were also differentially affected by the MCT and CFHF diets.
Conclusions: This study highlights the cognitive benefits of ketogenic diets in AD models and reveals similarities and differences between MCT and CFHF interventions. It underscores the intricate relationship between diet, genes, metabolism, and microbiome.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0289 / #120

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

MAGNETIC TARGETED DELIVERY OF THE SPIONS-LABELED MESENCHYMAL STEM CELLS DERIVED FROM HUMAN WHARTON'S JELLY IN ALZHEIMER'S RAT MODELS

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Mehdi Mehdizadeh[1], Farshid Qiyami Hour[2], Amir Johari Moghadam[3], Ali Shakeri-Zadeh[4], Mehrdad Bakhtiyari[1], Ronak Shabani[1]
[1]Iran University of Medical Sciences, Department Of Anatomy, Tehran -, Iran, [2]University of Manitoba, Department Of Human Anatomy And Cell Science, Manitoba, Canada, [3]Iran University of Medical Sciences, Department Of Neuroscience, Tehran, Iran, [4]Johns Hopkins University, School Of Medicine, Baltimore, United States of America

Aims: Alzheimer's disease (AD) as a progressive neurodegenerative disorder is one of the leading causes of death globally. Among all treatment approaches, mesenchymal stem cells (MSCs)-based therapy is a promising modality for neurological disorders including the AD. This study aimed to magnetically deliver human Wharton's jelly-derived MSCs (WJ-MSCs) toward the hippocampal area within the AD rat's brain and determine the effects of them in cognitive improvement.
Methods: Rats were randomly divided into five groups as follow: vehicle-treated control, AD model (injection of 8 μg/kg of amyloid β 1–42), IV-NTC (treated with IV-injected Non-Targeted Cells), IV-TC (treated with IV-injected Targeted Cells), and ICV-NTC (treated with Intracerebroventricular-injected Non-Targeted Cells). WJ-MSCs were labeled with dextran-coated superparamagnetic iron oxide nanoparticles (dex-SPIONs, 50 μg/ml), by bio-mimicry method.
Results: SPIONs-labeled MSCs were highly prussian blue positive with an intracellular iron concentration of 2.9 ± 0.08 pg/cell, which were successfully targeted into the hippocampus of AD rats by a halbach magnet array as magnetic targeted cell delivery (MTCD) technique. Presence of SPIONs-labeled cells in hippocampal area was proved by magnetic resonance imaging (MRI) in which signal intensity was reduced by increasing the number of these cells. Behavioral examinations showed that WJ-MSCs caused memory and cognitive improvement. Also, histological assessments showed functional improvement of hippocampal cells by expression of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE).
Conclusions: Overall, this study indicates MTCD approach as an alternative in MSC-based regenerative medicine because it approximately has the same results as invasive directly ICV-injection method has.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0290 / #1579

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

COMPUTATIONAL ANALYSIS OF LONGITUDINAL ELECTROENCEPHALOGRAMS OF TREATMENT OUTCOME IN ALZHEIMER 'S DISEASE USING HIERARCHICAL DYNAMIC CAUSAL MODELING.

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Tak Youn[1], Hae-Jeong Park[2]
[1]Dongguk University International Hospital, Psychiatry, Goyang, Korea, Republic of, [2]yonsei University, Nuclear Medicine, Seoul, Korea, Republic of

Aims: Both acetylcholinesterase(AChE) inhibitor and non-competitive antagonist of N-methyl-D-aspartate(NMDA) receptor are approved for the clinical treatment of Alzheimer's disease(AD). To understand the long-term effects of neuropharmacological intervention on neurobiological properties at different hierarchical levels, we explored long-term changes in neurobiological parameters of an NMDA canonical microcircuit model(CMM-NMDA) in the default mode network using dynamic causal modeling of longitudinal EEG in patients with AD.
Methods: Resting-state EEG was recorded from a total of 69 AD patients when starting medication after diagnosis of AD. We divided the patients into two groups, good and poor respondent groups according to clinical evaluation after treatment and dosage changes of AD medication with MMSE score change. We analyzed brain EEG connectivity among the 246 cortical regions defined by the Brainnetome atlas using the fieldtrip toolbox by evaluating spectral coherence for five frequency bands (delta, theta, alpha, beta, and gamma). We then analyzed each EEG connectivity between groups using ANCOVA with age, sex, and the initial MMSE scores as covariates.
Results: Our study found that the difference in brain EEG connectivity, especially intrahemispheric regional connectivity in gamma frequency bands, is increased at multiple regions of right hemisphere and DLFPC and hippocampal areas, DLFPC and caudate nucleus, middle frontal and inferior parietal areas in poor respondent group($p<0.00001$).
Conclusions: This study shows increased gamma bands EEG connectivity between right anterior and posterior areas in poor respondent group. Elevated gamma band power was observed in AD when compared to MCI and control subjects was reported in a previous study. Our results suggest the potential of the gamma EEG connectivity of initial EEG when starting treatment as a biomarker to predict long-term medical treatment for AD medication.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0291 / #1016

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

LICOCHALCONE-A IN ALZHEIMER'S DISEASE: NEUROPROTECTION AND BLOOD-BRAIN BARRIER PERMEABILITY

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Dalia Nour[1], Rasha Hanafi[2], Reham Abdelkader[1]
[1]German University in Cairo, Pharmacology And Toxicology, cairo, Egypt, [2]German University in Cairo, Pharmaceutical Chemistry, cairo, Egypt

Aims: There is growing interest in the neuroprotective effects of flavonoids however, their effectiveness hinges on their ability to cross the blood-brain barrier (BBB). This raises questions about whether their protective effects are purely systemic. We were able to show that Licochalcone-A (LCA), a natural flavonoid, acts as a potential neuroprotective agent and cognitive enhancer. Therefore, we aimed to investigate the potential of LCA in Alzheimer's disease (AD) by assessing its ability to cross BBB in an *in vivo* AD mouse model.
Methods: Gas chromatography–tandem mass spectrometry (GC-MS/MS) technique was applied to characterize and detect LCA in brain samples of LPS-neuroinflammatory mouse model. Mice received intraperitoneal (i.p.) injections of 250 µg/kg LPS for seven consecutive days, along with 20 mg/kg LCA starting on the fourth day. Sample extraction was performed using liquid-liquid extraction and acid hydrolysis followed by N,O-bis(trimethylsilyl)trifluoroacetamide derivatization. With Icaritin as an internal standard, method validation and quantification in the biological samples were performed.
Results: A rapid, sensitive, and selective GC–MSMS method was developed (LOD= 0.15 µg/ml, LOQ= 0.5 µg/ml) with a total run time of 15 min. Good linearity (R^2>0.994) was observed within the concentration range of 0.5–20 µg/ml. The quantifier and the qualifier MRM transitions were established for LCA. Using the developed method, LCA was detected in the mice brain samples at its specific retention time with an estimated amount of 1.8 ±0.56 mg/ 300 mg brain.
Conclusions: This is the first study to report that LCA crosses the BBB exhibiting its neuroprotective effects inside the central nervous system (CNS). These findings open new avenues to further investigate its underlying signaling pathways in CNS. The developed procedure can be easily expanded to confirm the permeability of other flavonoids.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0292 / #510

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

BIODEGRADABLE NANOPARTICULATE FORMULATIONS OF LEUPROLIDE ACETATE TO COMBAT ALZHEIMER'S DISEASE THROUGH INTRANASAL DELIVERY

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Tosha Pandya[1], Abhay Dharamsi[2]
[1]INDRASHIL UNIVERSITY, School Of Pharmacy, RAJPUR,Mehsana highway, India, [2]PARUL INSTITUTE OF PHARMACY, Pharmaceutics, VADODARA, India

Aims: This research work aimed to develop a nanoparticulate delivery system that can deliver LA directly to the brain through the intranasal route. Nanoparticles made of PLGA and Chitosan efficiently entrap peptide drugs and can deliver drugs directly to the brain by passing through the olfactory lobe.
Methods: PLGA nanoparticles were developed using nanoprecipitation and Chitosan nanoparticles encapsulating leuprolide acetate were prepared using the ionic gelation method. Optimization was done using response surface methodology.The optimized nanoparticles were evaluated by DSC study, TEM analysis, *in vitro* drug release study, ex vivo diffusion study, histopathology study, and accelerated stability study. They were also evaluated for *in vivo* kinetic and dynamic study to see the anti-Alzheimer potential of nanoparticles.
Results: The optimized PLGA nanoparticles had particle size of 182.6 ± 1.5 nm, PDI (0.3), %EE (77.3 ± 0.6), and Zeta Potential (-5.6 mv ± 0.2), whereas the optimized chitosan nanoparticles of leuprolide acetate exhibited particle size of 254.3 ± 10.74 nm, %EE of 85.59 ± 0.76 %, and zeta potential of +18.00 ± 0.23 mv. The in vitro drug release from optimized nanoparticles indicated sustained release. The Ex vivo diffusion study indicated an apparent permeability coefficient for the drug-containing nanoparticles higher than for plain drug solution. Sheep nasal toxicity and accelerated stability study proved the intranasal safety and stability of the developed formulation. The in vivo drug uptake study indicated a greater brain drug concentration from Chitosan nanoparticles than from PLGA NPs and plain drug solution. The anti-Alzheimer potential was also evident from the Y maze study and histopathology of Alzheimer-induced rat brain treated with drug-loaded nanoparticles.
Conclusions: Thus, the biodegradable nanoparticulate formulations of leuprolide acetate was found to have great potential for Alzheimer's disease management.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0293 / #1315

Poster Topic: *Theme A: β-Amyloid Diseases / A02.p. Therapeutic Targets, Mechanisms for Treatment: ASO and RNAi*

AN RNAI THERAPEUTIC TARGETING APP REDUCED BETA-CTF AND CORRECTED ENDOSOMAL ABNORMALITIES IN MULTIPLE HUMAN ALZHEIMER'S DISEASE IPSC LINES

POSTERS: A02.P. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ASO AND RNAI

Lan Dang, Matthew Stricos, Nishitha Kodali, Diana Cha, Olufemi Adeduji, Kevin Fitzgerald, Kirk Brown
Alnylam Pharmaceuticals, Biology, Cambridge, United States of America

Aims: Endosomal-lysosomal abnormalities are hallmark of Alzheimer's disease (AD). Endolysosomal dysfunction contributes to abnormal amyloid precursor protein (APP) clearance; concurrently, peptides resulting from dysregulated APP metabolism can also impair endolysosomal function, creating a cycle of endolysosomal dysfunction and APP metabolism dysregulation. An RNAi therapeutic targeting *APP* mRNA is intended to reduce APP production. To explore the impact of APP lowering on endolysosomal dysfunction, we evaluated the effect of an siRNA targeting *APP* mRNA on downstream APP cleavage products, including beta-secretase-derived APP C-terminal fragment (beta-CTF), and on endosomal defects in multiple human AD induced pluripotent stem cell (iPSC) lines.
Methods: Early-onset AD patient-derived iPSCs carrying pathogenic mutations in PSEN1 and CRISPR/Cas9-edited iPSCs carrying APP homozygous Swedish mutation (swe/swe) lines were differentiated to neurons and astrocyte cocultures, transfected with siRNA targeting *APP* mRNA or control siRNA on Day 7. Beta-CTF, soluble APP-alpha, soluble APP-beta protein analysis by Meso Scale Discovery enzyme-linked immunosorbent assay, and high content imaging for Rab5+ early endosome and Rab7+ late endosome size were performed on Day 30.
Results: An RNAi therapeutic targeting *APP* mRNA significantly reduced *APP* mRNA and levels of downstream APP cleavage products in human AD patient-derived iPSC lines with pathogenic mutations in PSEN1. Reducing APP expression reduced early endosomal enlargement defects. Immunohistochemistry showed high accumulation of intracellular beta-CTF in both APP and PSEN1 mutation lines, which was significantly reduced in cells treated with *APP* siRNA.
Conclusions: By lowering both intracellular and extracellular drivers of AD pathology, an RNAi therapeutic targeting *APP* may potentially alter the cascade of pathological events that result in neurodegeneration. The Phase 1 first-in-human study of ALN-APP, an investigational RNAi therapeutic targeting *APP* mRNA, is ongoing in patients with early-onset AD (NCT05231785).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0294 / #633

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

NEW LOW-DOSE CURCUMIN DERIVATIVES WITH THERAPEUTIC POTENTIAL IN ALZHEIMER'S DISEASE

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Beatriz Rodrigues[1], Eduarda Ventura[1], Patricia Moreira[2], Rosa Resende[2], Armanda Santos[1,2], Cláudia Pereira[2,3], Maria Teresa Rosete[1,2], Maria Paula Robalo[4,5], Ana Silva[2], Sónia Silva[1,6]
[1]University de Coimbra, Faculty Of Pharmacy, Coimbra, Portugal, [2]University of Coimbra, Center For Neuroscience And Cell Biology, Coimbra, Portugal, [3]University of Coimbra, Faculty Of Medicine, Coimbra, Portugal, [4]instituto Politécnico de Lisboa, Instituto Superior De Engenharia De Lisboa, Lisboa, Portugal, [5]Instituto Superior Técnico, Centro De Química Estrutural, Lisboa, Portugal, [6]University of Coimbra, Coimbra Institute For Clinical And Biomedical Research, Coimbra, Portugal

Aims: Objectives: Curcumin has been suggested as a promising treatment for Alzheimer's disease (AD) since it inhibits the formation and extension of Aβ aggregates and destabilizes pre-formed ones. However, curcumin's low bioavailability limits its therapeutic use. Two curcumin derivatives were synthesized to improve low-dose efficacy.
Methods: Methods: The anti-inflammatory, antioxidant, and anti-amyloidogenic effects of curcumin derivatives were evaluated *in vitro* using BV-2 cells exposed to lipopolysaccharide as a neuroinflammation cell model and N2a-APPswe cells as an AD model. *In vivo* evaluation was accomplished using APPswe/PSEN1dE9 mice and their wild-type counterpart. One-year-old animals were orally administered with derivative 27 (50 mg/kg/day) or vehicle for 28 days.
Results: Results: Both molecules significantly reduced nitric oxide (NO) production and the protein levels of inducible NO synthase, Pro-interleukin-1β and, for derivative 27, also cyclooxygenase-2 protein levels in lipopolysaccharide-exposed BV-2 cells. Moreover, Derivative 27 activated Nrf2, and significantly increased Nrf2 and heme-oxygenase-1 mean fluorescence intensity, in N2a-APPswe cells. *In vivo*, Derivative 27 significantly decreased Pro-interleukin-1β and amyloid protein precursor protein levels in the hippocampus and Aβ levels in the hippocampus and plasma.
Conclusions: Conclusion: These data suggest that both curcumin derivatives at low doses seem to be more effective than curcumin, in mitigating some of AD hallmarks.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0295 / #197

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

NONCLINICAL AND CLINICAL DEVELOPMENT OF PPI-1011, AN ORAL PLASMALOGEN PRECURSOR, AS A TREATMENT FOR ALZHEIMER'S DISEASE

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Tara Smith[1], Kaeli Knudsen[1], Shawn Ritchie[2]
[1]Med-Life Discoveries LP, Therapeutics, Saskatoon, Canada, [2]Med-Life Discoveries LP, Therapeutics, SASKATOON, Canada

Aims: Plasmalogen deficiency is strongly correlated with the onset and progression of Alzheimer's disease (AD). This, combined with the role of plasmalogens in many neuronal functions, has led to the hypothesis that plasmalogen deficiency underlies the development of AD. Plasmalogen augmentation has therefore been hypothesized as a novel therapeutic strategy for AD and other conditions of plasmalogen deficiency. PPI-1011 is a novel synthetic plasmalogen precursor that we have advanced into the clinic and is the first plasmalogen-system targeted therapy undergoing formal regulatory approval. This poster summarizes the nonclinical and Phase 1 safety data generated to date.
Methods: Nonclinical safety studies included 28-day GLP-studies in primates and rats, AMES and micronucleus genotoxicity, and a hERG. C14-labeled ADME studies in rats were performed to characterize pharmacokinetics, mass balance, excretion, and distribution. Currently, a Phase 1 study is on-going to evaluate the safety, tolerability, and pharmacokinetics of both single and 14-day repeat dosing of PPI-1011 in healthy adult volunteers.
Results: Orally administrated PPI-1011 was well tolerated up to 400 mg/kg/day in primates and 500 mg/kg/day in rats. Neither genotoxicity nor cardiotoxicity was observed. In rats, the pharmacokinetics were characterized by strong bioavailability, with over 50% of the compound absorbed. Plasma levels peaked between 6-12 hours, with a $t_{1/2}$ of 40 hours. Quantitative whole-body autoradiography demonstrated uptake across all tissues, including the brain. The 14-day repeat dose portion of the Phase 1 study is on-going, but single administrations of PPI-1011 were well-tolerated up to 100 mg/kg.
Conclusions: PPI-1011 is well-tolerated in both animals and humans, representing a novel treatment modality to address the plasmalogen deficiency observed in AD. A Phase 2 clinical protocol is under development to evaluate the effects of PPI-1011 on cognitive decline in AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0296 / #1788

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

IN SILICO INVESTIGATION OF THE ABILITY OF OCTOVESPIN TO ACT AS MULTITARGETS AGAINST ALZHEIMER'S AND PARKINSON'S DISEASE

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Yuri Só[1], Caio Costa[2], Luana Cristina Camargo[3], Ricardo Gargano[1], Márcia Renata Mortari[3]
[1]Universidade de Brasília, Physics, Brasília, Brazil, [2]University of Brasilia, Physics, Brasilia, Brazil, [3]Institute of Biological Science, Department Of Physiology, Brasília, Brazil

Aims: Natural compounds are important sources of substances with medicinal potential to treat neurological disorders, such as Alzheimer's disease (AD) and Parkinson's disease (PD), which are emerging health problems in the 21st century. Existing medications for AD and PD have limited efficacy and side effects, so it is important to investigate new potential compounds and drugs that are less harmful and more effective. This study investigates two compounds: Octovespin, a peptide modified from a peptide isolated from *Polybia occidentalis* wasp venom, and Fraternine-10, a peptide isolated from the venom of the wasp *Parachartergus fraternus*. Those peptides had promising results in AD and PD mice models, although the its action mechanism have not been investigated. To evaluate the molecular effect of Octovespin and fraternine-10, we conducted *in silico* studies, starting with molecular docking against five common targets for AD (ACE, BACE1, GSK-3, TACE, and AChE) and four targets for PD (A2A-AR, ASN, COMT, MAO-B).
Methods: We compared our findings with four standard drugs for AD (Donepezil, Galantamine, Rivastigmine, and Tacrine) and PD (Dopamine, Rasagiline, Safinamide, and Selegiline) using AutoDock 4.1. We also performed molecular dynamics (MD) simulations with the docking complexes to analyze the dynamic behaviors and binding free energy at 100 ns time scale. In addition, we investigated frontier molecular orbitals and density-functional theory (DFT) from computational quantum mechanics.
Results: Overall, the potential binding affinity from molecular docking and MD-simulation suggest that Octovespin and fraternine-10 could be a suitable therapeutic lead for AD and PD treatment, since these compounds present high or equivalent values of binding affinity.
Conclusions: Our results can help us understand the characteristics and capabilities of natural compounds like Octovespin and Fraternine-10 to interact with common targets of AD and PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0297 / #636

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

A GLIMMER OF SUSTAINED HOPE: RETROSPECTIVE CLINICAL OBSERVATIONS ON TRANSCRANIAL PULSE STIMULATION IN ALZHEIMER'S CARE

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Catherine Widmann, Barbara Kofler, Sarah Bernsen, Monika Sommer, Luisa Kaluza, Sergio Castro-Gomez, Ullrich Wüllner
University of Bonn Medical Center, Neurodegenerative Diseases And Geriatric Psychiatry, Bonn, Germany

Aims:

or alternative treatments for Alzheimer's Disease (AD), this retrospective analysis focuses on Transcranial Pulse Stimulation (TPS), an eme
nary objective is to assess the preliminary efficacy of TPS in enhancing cognitive outcomes across multiple domains in a cohort of 28 patien
.

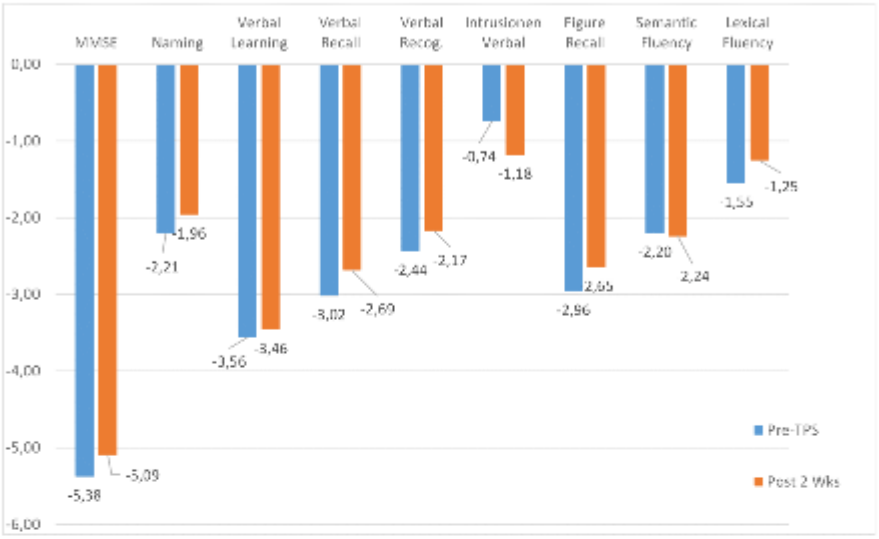
Methods:

ales, 11 males; average age 73.6 ± 8.6 years) underwent a standardized TPS protocol comprising six sessions over two weeks and again a
al cognitive status (MMSE), language, and executive function—were conducted pre- and post-TPS and at two-week and 6-month follow-up
loyed to analyze the data, adjusting for age, sex, and education.

Results: Findings indicated short-term stability in all tested cognitive domains (e.g., verbal memory, language, executive function). In a limited 6-month follow-up (n=5), significant improvements were noted in general cognition, verbal learning, and semantic fluency, albeit limited by the small sample size. Over 80% of patients, either remained stable or showed cognitive improvement two weeks post-TPS, a trend sustained at 6-month follow-

Figure 1.

CERAD z-Scores 2 weeks post TPS versus pre-TPS



Note. Data from 28 AD patients: 17 female (60.7%); mean age 73.6 ± 8.6 years.

ups.

Table 1.

Tests Paired means 2 Wks Post TPS and 6 Mo FU

Parameter Comparisons	Mean Diff.	SE	95% CI		T	Sig.	Hedges Corr. Point Estimate	Effect Size
			LL	UL				
MMSE	1.56	0.52	0.12	3.00	3.01	**0.04**	**1.22**	**large effect size**
Naming	0.34	0.35	-0.63	1.31	0.98	0.38	0.39	
Verbal Learning	1.78	0.59	-0.12	3.67	2.98	**0.06**	**1.30**	**large effect size**
Verbal Recall	0.93	0.43	-0.46	2.31	2.13	0.12	0.92	
Intrusions	1.20	0.99	-1.94	4.34	1.22	0.31	0.53	
Verbal Recog.	-0.33	0.19	-0.93	0.28	-1.72	0.18	-0.75	
Figure Recall	0.24	0.24	-0.43	0.91	1.00	0.37	0.40	
Semantic Fluency	0.76	0.22	0.15	1.37	3.45	**0.03**	**1.39**	**large effect size**
Lexical Fluency	0.24	0.21	-0.35	0.83	1.14	0.32	0.46	

Note. Preliminary 6-month data (n = 5) compared to 2 weeks Post TPS. Hedges' correction is generally considered a more accurate point estimate for effect sizes than Cohen's d since it applies a correction factor to account for bias in small samples. Hedges' corrected point estimates in a paired t-test, commonly used benchmarks for effect sizes are as follows: Small effect: g=0.2, Medium effect: g=0.5, Large effect: g=0.8.

Conclusions: This retrospective analysis supports TPS as a tolerable, potentially efficacious non-pharmacological intervention for AD. Stable cognitive performance was noted in a two-week follow-up. Preliminary data suggest TPS may have clinical

utility in AD management and warrant further longitudinal studies. Earlier work, such as Beisteiner et al. (2020), queried TPS's ability to alter cognitive trajectory in AD. The TPS mechanism may involve central nervous system stimulation or unexplored lymphatic effects. Given challenges in anti-amyloid antibody trials, our findings at two-week and 6-month follow-ups highlight the need for expanded TPS studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0298 / #2929

Poster Topic: *Theme A: β-Amyloid Diseases / A02.q. Therapeutic Targets, Mechanisms for Treatment: Other*

THE MITOCHONDRIAL ENZYME ABAD AS A POTENTIAL THERAPEUTIC TARGET – INHIBITION OF AMYLOID-BETA-ABAD INTERACTION USING BRAIN-TARGETED NANOPARTICLES

POSTERS: A02.Q. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Yomna Youssef[1], Salma Tammam[2], Sanjay Mathur[3], Shaista Ilyas[3], Basma Elshenawy[2], Alaa Gad[2], Reham Abdelkader[4]
[1]German International University, Clinical Neurophysiology, Cairo, Egypt, [2]German University in Cairo, Pharmaceutical Technology, Cairo, Egypt, [3]Faculty of Mathematics and Natural Sciences, University of Cologne, Inorganic And Materials Chemistry, Cologne, Germany, [4]German university in Cairo, Pharmacology And Toxicology, Cairo, Egypt

Aims: The interaction between amyloid-beta and the mitochondrial enzyme amyloid-beta-binding alcohol dehydrogenase (ABAD) elicits many detrimental events, including the excessive generation of reactive oxygen species leading to mitochondrial dysfunction and apoptosis of neuronal cells. In this work, hindrance of the amyloid-beta-ABAD interaction is attempted by developing brain-targeted chitosan nanoparticles (CS-NPs) and loading them with a decoy peptide (DP) that can inhibit ABAD and eliminate amyloid-beta-induced toxicity, modulating the pathogenesis of Alzheimer's disease.
Methods: CS-NPs of two sizes; small (S-CS-NPs) with a hydrodynamic diameter (HD) of 59 ± 6 nm and large (L-CS-NPs) with a HD of 89 ± 6 nm were formulated to study the effect of NP size on the efficiency of delivering the DP across the blood-brain barrier (BBB). The DP was loaded into NPs, and the ability of NPs to bypass the BBB and allocate to the brain in neuroinflammatory mouse models was evaluated by conducting biodistribution studies. Cognitive functions were tested by performing the Y-maze test, and amyloid-beta, estradiol, adenosine triphosphate (ATP) and activity of the antioxidant enzyme superoxide dismutase (SOD) were quantified in the brains of the mice by ELISA.
Results: *In vivo* studies demonstrated the ability of S-CS-NPs, but not L-CS-NPs, to accumulate in the brains of mice in which neuroinflammation was induced, but not healthy ones. Upon intravenous administration of free DP and DP-loaded S-CS-NPs, only animals receiving DP-loaded S-CS-NPs displayed an improvement in cognition. A decrease in their amyloid-beta concentrations was observed and their levels of estradiol, ATP and activity of SOD were normalized indicating preservation of the ABAD normal function.
Conclusions: DP-loaded S-CS-NPs can deliver DP to the brain in animals with neuroinflammation enhancing their cognitive functions due to the possible impediment of amyloid-beta-ABAD interaction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0299 / #337

Poster Topic: *Theme A: β-Amyloid Diseases / A03.a. Drug Development, Clinical Trials: Immunotherapy*

DEVELOPMENT OF ANTI-HMGB1 ANTIBODY FOR DEMENTIAS

POSTERS: A03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

Hitoshi Okazawa
Change Cure, Ceo, Yokohama, Japan

Aims: Initiated from our previous comprehensive phosphoproteome analyses of cerebral cortex tissues from four mouse AD models and postmortem human AD patients (Tagawa et al, Hum Mol Genet 2015), we found that HMGB1, a DAMP molecule released from necrosis, triggers secondary neurite degeneration (Fujita et al, Sci Rep 2016) and neuronal necrosis of surrounding neurons. In addition, we confirmed that TRIAD necrosis (Hoshino et al, JCB 2006), the subtype of necrosis via DNA damage occurring in AD, initiates in cortical neurons of frontotemporal lobar degeneration across multiple gene mutations from the early pathological stage. The TRIAD necrosis phenotype resembles two reports published in Nature Neuroscience (Lee JH et al, Nature Neurosci 2022) and Nature (Yuan P et al, Nature 2022) that followed our observation (Tanaka et al, Nature Commun 2020). TRIAD phenotypes are also confirmed in postmortem brains of human AD and FTLD patients (Tanaka et al, Nature Commun 2020; Homma et al, Life Sci Alliance 2021; Tanaka et al, Commun Biol 2021). Based on these notions, we are currently developing human anti-HMGB1 monoclonal antibody as a new drug against FTLD, AD and other neurodegenerations.
Methods: for phosphoproteoma analysis, biochemical analysis, behavioral tests, pathological analysis, human pathologies and so on were described in our previous publications in details (Tagawa et al, Hum Mol Genet 2015; Tanaka et al, Nature Commun 2020; Homma et al, Life Sci Alliance 2021; Tanaka et al, Commun Biol 2021).
Results: We confirmed therapeutic effects on four types of cognitive function test, morphological changes in immunohistochemistry, and biochemical changes in western blot and so on. We also obtained results of non-clinical GLP tests.
Conclusions: In the presentation at ADPD2024, we will report our proceeding in human clinical trial.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0300 / #2136

Poster Topic: *Theme A: β-Amyloid Diseases / A03.a. Drug Development, Clinical Trials: Immunotherapy*

DESIGN OF A RANDOMIZED PHASE 2B, PLACEBO-CONTROLLED TRIAL ASSESSING SAFETY AND EFFICACY OF AD04 IN EARLY ALZHEIMER'S DISEASE ("ADVANCE")

POSTERS: A03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

Benjamin Haaland[1,2], Sam Dickson[3], Joshua Christensen[3], Agustín Fernández-Fernández[4], Timo Grimmer[5], Oliver Peters[6], Suzanne Hendrix[7], Achim Schneeberger[8]
[1]Pentara Corporation, Statistics, Salt Lake City, United States of America, [2]Pentara Corporation, Statistical Consulting, Millcreek, United States of America, [3]Pentara Corporation, Statistics, Millcreek, United States of America, [4]University of Oviedo, Institute Of Oncology Of Asturias (iuopa), Oviedo, Spain, [5]Technical University Munich, Center For Cognitive Disorders, Munich, Germany, [6]Department of Psychiatry, Charité-universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, [7]Pentara Corporation, Ceo, Millcreek, United States of America, [8]Advantage Therapeutics, Cmo, Miami, United States of America

Aims: Therapeutic options for patients with Alzheimer's disease (AD) are limited. The AFF006 randomized controlled trial (RCT) compared two doses of AD04 with three formulations of AD02, and demonstrated benefits of 2mg AD04 in post-hoc analyses. We present the study design of a follow-up RCT - ADVANCE - presenting evidence from AFF006 and estimated success probability for ADVANCE.
Methods: The findings for the 2mg AD04 analysis are post-hoc and may have been a false positive result. A statistical analysis was performed to account for selecting the best study arm compared to the remaining arms (multiplicity issue). Instead of performing a traditional power calculation, ADVANCE was designed using a conservative assurance analysis which factors in the uncertainty introduced by using treatment effect estimates and SDs from the small sample size of AFF006. The probability of success was estimated incorporating an attenuated treatment effect, and the potential impact of more frequent dosing in ADVANCE.
Results: ADVANCE plans to enroll 122 patients with early AD, MMSE 22-30, randomized 1:1 to 2mg AD04 or placebo monthly. Early AD includes patients with either an AD-type CSF signature (abeta and tau), or evidence of hippocampal atrophy based on a Schelten's score, with clinical confirmation based on FCSRT≤40 or Free Recall≤17. The primary endpoint will be time savings estimated based on adapted ADAS-cog, ADCS-ADL and CDR-sb scores. The multiplicity-adjusted p-value for the AFF006 study was p=0.02. Assurance calculations estimate a success probability of 85% for ADVANCE's primary endpoint.
Conclusions: The ADVANCE RCT is evaluating a novel immune-stimulating intervention for patients with early AD, based on evidence from AFF006 (phase 2). The study has a high estimated probability of success.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0301 / #2856

Poster Topic: *Theme A: β-Amyloid Diseases / A03.a. Drug Development, Clinical Trials: Immunotherapy*

PHARMACOKINETIC COMPARABILITY STUDY OF ADUCANUMAB (BIIB037) ADMINISTERED SUBCUTANEOUSLY VERSUS INTRAVENOUSLY IN HEALTHY VOLUNTEERS

POSTERS: A03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

Philip Montenigro, Gioacchino G. Curiale, Jackson Burton, Gab-Jin Park, Jennifer Murphy, Jing Xie, John O'Gorman, Gersham Dent, Kate Dawson
Biogen Inc., Medical Affairs, Cambridge, United States of America

Aims: Aducanumab (BIIB037) has accelerated approval for patients with early Alzheimer's disease (AD) via intravenous (IV) infusion. Study 221HV104 (NCT05216887) evaluated the pharmacokinetic (PK) comparability and safety and tolerability of aducanumab administered by subcutaneous (SC) injection versus IV infusion, potentially offering a more convenient and accessible route of administration.
Methods: An open-label, parallel-arm study compared a single weight-based 10 mg/kg IV dose of aducanumab with two 700 mg SC doses of aducanumab administered 2 weeks apart. 124 healthy volunteers were randomized and dosed with study treatment, with 120 participants included in the PK Analysis Set.
Results: Aducanumab AUC_{inf} in participants treated with aducanumab 10 mg/kg IV and participants treated with two aducanumab 700 mg SC doses were comparable, with a geometric LS mean ratio of 93.9% (0.939, 90% CI [0.863, 1.022]). Aducanumab was well tolerated in healthy volunteers after a single 10 mg/kg IV dose or two 700 mg SC doses. The overall incidence of adverse events (AEs) was 50.8% in the IV arm and 30.2% in the SC arm**.** Headache was the most common AE in both arms. One serious AE (enterocolitis) in the SC arm was assessed as severe, related to treatment, led to treatment discontinuation, and resolved. All other AEs reported during the study were classified as mild or moderate and resolved or were resolving. No deaths occurred during the study. Three participants (4.8%) in the SC arm developed treatment-emergent anti-aducanumab antibodies.
Conclusions: Aducanumab administered as two 700 mg SC doses demonstrates a high degree of PK comparability to aducanumab administered as a single weight-based 10 mg/kg IV dose and is well tolerated in healthy volunteers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0302 / #2196

Poster Topic: *Theme A: β-Amyloid Diseases / A03.b. Drug Development, Clinical Trials: Amyloid clearance*

APOLLOE4 PHASE 3 TRIAL OF ORAL ANTI-AMYLOID AGENT ALZ-801/VALILTRAMIPROSATE IN APOE4/4 EARLY ALZHEIMER'S PATIENTS: STUDY DESIGN AND BASELINE CHARACTERISTICS

POSTERS: A03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

Earvin Liang[1], Susan Abushakra[1], Rosalind Mclaine[1], David Watson[2], Merce Boada Rovira[3], Karim Bennys[4], Niels Prins[5], Daphne Troost[6], Anton Porsteinsson[7], Marwan Sabbagh[8], Susan Flint[1], Winnie Pak[1], John Hey[1], Martin Tolar[9]
[1]Alzheon, Medical, Framingham, United States of America, [2]Alzheimer's Research and Treatment Center, Alzheimer's Research And Treatment Center, Wellington, United States of America, [3]Ace Alzheimer Center Barcelona, Ace Alzheimer Center Barcelona, Barcelona, Spain, [4]University Hospital Montpellier, Center For Alzheimer's Disease, Montpellier, France, [5]Brain Research Center, Ceo, Amsterdam, Netherlands, [6]Brain Research Center, Brain Research Center, Amsterdam, Netherlands, [7]University of Rochester, Department Of Psychiatry, Rochester, United States of America, [8]St. Joseph's Hospital and Medical Center, Barrow Neurological Institute, Phoenix, United States of America, [9]Alzheon, Ceo, Framingham, United States of America

Aims: ALZ-801/valiltramiprosate, an oral inhibitor of amyloid oligomer formation, showed meaningful efficacy, hippocampal protection, and favorable safety in APOE4 carrier Alzheimer's disease (AD) patients (Abushakra 2016, Kocis 2017, Hey 2018). APOE4/4 homozygotes who have high burden of amyloid pathology showed strongest benefits (Abushakra 2017), with no amyloid related imaging abnormalities (ARIA) that are seen with anti-amyloid antibodies. A 78-week pivotal Phase 3 trial is ongoing to assess cognitive, functional, and volumetric MRI effects of ALZ-801 265mg BID in APOE4/4 homozygotes with Early AD.
Methods: APOLLOE4 (NCT04770220), a Phase 3, double-blind, placebo-controlled multicenter-study enrolled APOE4/4 Early AD subjects ages 50-80 years, MMSE ≥22, CDR-G=0.5/1. Screening/baseline MRIs allowed microhemorrhages (MH) >4 and siderosis; vasogenic edema (ARIA-E) was exclusionary. Stable cholinesterase inhibitors were allowed, anti-coagulants were excluded. Study is powered to detect ~2.5 placebo-adjusted ADAS-cog13 effect at 78 weeks, the primary endpoint; hippocampal volume, and functional outcomes are main secondary outcomes.
Results: This pivotal study enrolled 325 subjects, 51% female, mean age 69 years, 65%/35% MCI/Mild AD, 82% Caucasian, 35% on cholinesterase inhibitors, baseline MMSE=26, ADAS-cog13=24, CDR-SB=3.0, and CDR global=0.6. Of the 313 subjects with baseline 1.5/3T MRIs, 32% and 9% had any MH or >4 MH, 9% had siderosis, 90% had mild or moderate white matter-disease. With enrollment completed, results are expected in 3Q 2024. The study's independent safety monitoring board oversees safety. No increased ARIA-E risk has been detected to date in the blinded Phase 3 and open-label Phase 2 study.
Conclusions: ALZ-801, an oral potentially disease-modifying agent, shows favorable safety and tolerability in ongoing APOE4 carrier studies, including homozygotes at highest risk for ARIA, and may become a safe, convenient alternative to anti-amyloid antibodies in APOE4 carrier AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0303 / #802

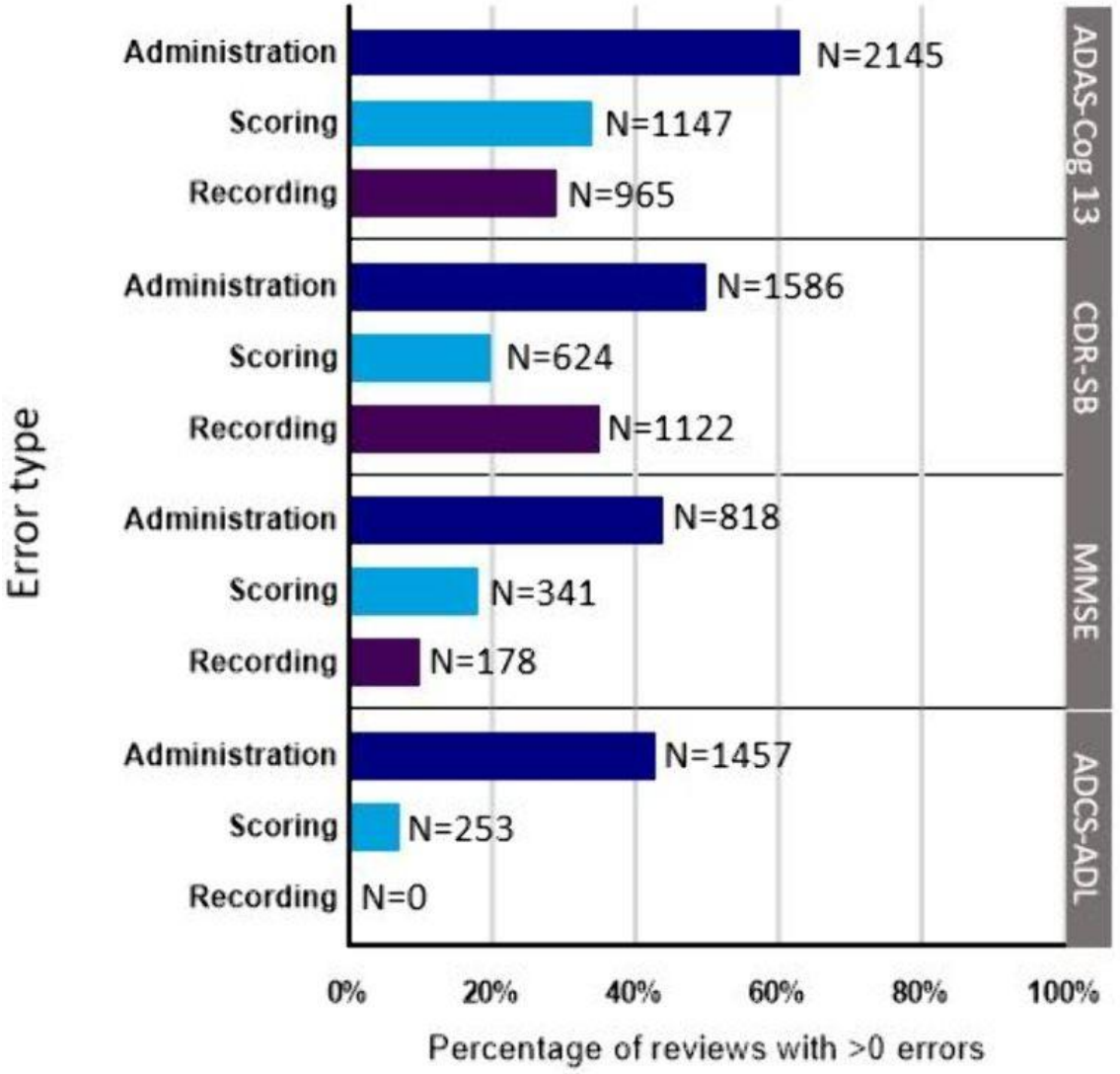
Poster Topic: *Theme A: β-Amyloid Diseases / A03.b. Drug Development, Clinical Trials: Amyloid clearance*

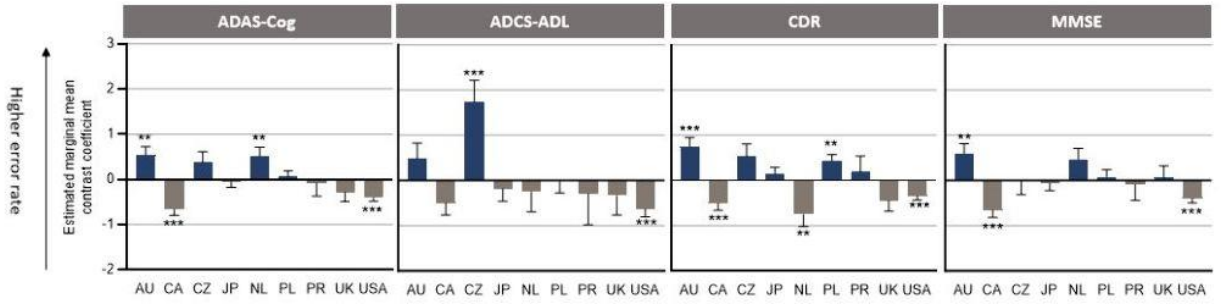
CENTRAL MONITORING OF RATER PERFORMANCE AND CHARACTERISTICS OF EFFICACY ASSESSMENTS IN THE TRAILBLAZER-ALZ 2 STUDY

POSTERS: A03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

Giulia Tronchin[1], Lisle Kingery[2], Robyn Leventhal[3], Edward Bartolic[3], Svenja Wacker[3], Jordan Barbone[3], Alette Wessels[1]
[1]Eli Lilly and Company, Neuroscience, Indianapolis, United States of America, [2]Work carried out while an employee of Cogstate, Ltd., New Haven, United States of America, [3]Cogstate, Ltd., New Haven, United States of America

Aims: Raters are qualified and trained in scale administration, but errors can occur in administration, recording, and scoring on outcome scales used in Alzheimer's disease (AD) clinical trials. In TRAILBLAZER-ALZ 2, Rater Performance Central Monitoring (RPCM) was employed to identify and reduce rater errors. RPCM facilitates ongoing feedback on administration and scoring practices to enhance standardization within and across raters, while improving overall quality of study data. The objectives were to describe the RPCM methodology and rater performance on efficacy assessments in TRAILBLAZER-ALZ 2.
Methods: RPCM was performed for AD Assessment Scale- Cognitive subscale 13-item, Clinical Dementia Rating, AD Cooperative Study- Activities of Daily Living Scale, and Mini-Mental State Examination. RPCM was conducted in a standardized manner by neuropsychologists, who reviewed and reported on raters' administration, recording, scoring, and interview skill competencies via a Scale Review Form (SRF). Assessment worksheets and audio recordings were reviewed, feedback was shared with raters and errors were corrected throughout the duration of the trial by email and/or teleconference. Estimated marginal contrasts for country differences were extracted from Poisson mixed models fitted to predict error rate (total number of errors recorded per SRF by country). Models were independently fit for each assessment. Each model included raters as random effect, offset by the log number of reviews completed per rater.
Results: Data available for analyses were from 809 raters across eight countries. Error prevalence was quantified for each efficacy assessment (Figure 1). Error detection rate differences for countries were reported by review type and scale (Figure
2).





Conclusions: RPCM in TRAILBLAZER-ALZ 2 identified and corrected errors in scale administration procedures and improved overall data integrity. Country specific differences observed will help in tailoring monitoring programs towards optimizing rater performance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0304 / #1684

Poster Topic: *Theme A: β-Amyloid Diseases / A03.b. Drug Development, Clinical Trials: Amyloid clearance*

TARGET ENGAGEMENT IN INTERCEPT-AD: DEVELOPMENT OF A NOVEL ASSAY MEASURING ACU193-AMYLOID BETA OLIGOMER COMPLEXES IN HUMAN CSF

POSTERS: A03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

Erika Cline[1], Elizabeth Johnson[1], Oladayo Oladiran[2], Jennifer Gillies[2], Derrick Johnson[3], Nathan Mcowen[3], Caitlin Hansen[2], Jacob Wohlstadter[2], Eric Siemers[4], Hugo Vanderstichele[5], Robert Dean[6], Jasna Jerecic[1]
[1]Acumen Pharmaceuticals, Inc., Bioanalytical Methods, Charlottesville, United States of America, [2]Meso Scale Diagnostics, LLC, Assay Development, Rockville, United States of America, [3]B2S Life Sciences, Assay Development, Franklin, United States of America, [4]Acumen Pharmaceuticals, Inc., Medical, Charlottesville, United States of America, [5]Biomarkable, Biomarkable, Gent, Belgium, [6]Indiana University School of Medicine, Department Of Pathology And Laboratory Medicine, Indianapolis, United States of America

Aims: We sought to develop an assay to measure target engagement of ACU193, a monoclonal antibody selective for soluble amyloid beta oligomers (AβOs), in the Phase 1 trial INTERCEPT-AD. So far, antibodies targeting Aβ protofibrils or fibrils have relied on plaque reduction as an indication of target engagement. Due to the AβO selectivity of ACU193, we used a different approach of measuring the ACU193-AβO complex in cerebrospinal fluid (CSF).
Methods: The assay was developed on the ultrasensitive MSD S-PLEX platform. Multiple antibody pairs comprising anti-idiotypic antibodies for ACU193 capture and anti-Aβ antibodies for AβO detection were screened for sensitivity, specificity, and selectivity to the ACU193-AβO complex in AD and non-AD CSF. A semi-quantitative reference standard was developed comprising a pre-formed complex, with AβOs titrated and ACU193 at a constant concentration. Assay recovery and reproducibility were evaluated.
Results: Screening antibody pairs in ACU193-spiked CSF enabled selection of the reference standard and detection antibody that optimized quantitation of endogenous AβOs. The ACU193-specificity of the anti-idiotypic capture antibody and the AβO-selectivity of the detection antibody yielded an assay with low background in untreated AD and non-AD CSF, with quantifiable signal dependent on the presence of ACU193 in CSF. Non-competition and competition assays demonstrated specificity and selectivity of the assay for AβOs over monomeric Aβ. The assay recovery and intra- and inter-run reproducibility met assay design specifications.
Conclusions: Development efforts highlight the importance of using AβO reference standards and anti-Aβ detection antibodies optimally suited for quantifying endogenous CSF AβOs. The resulting MSD S-PLEX assay was specific and selective for the ACU193-AβO complex in CSF. Application of the assay to INTERCEPT-AD CSF samples showed dose-dependent target engagement of ACU193 approaching Emax at highest doses administered.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0305 / #2904

Poster Topic: *Theme A: β-Amyloid Diseases / A03.b. Drug Development, Clinical Trials: Amyloid clearance*

PLASMA PROTEOMIC ANALYSIS FROM ALZHEIMER'S PATIENTS IN SPARC CLINICAL TRIAL TO IDENTIFY PHARMACODYNAMIC BIOMARKERS OF THE S2R MODULATOR CT1812

POSTERS: A03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

Britney Lizama[1], Duc Duong[2], Kiran Pandey[3], Valentina Di Caro[1], Adam Mecca[4], Ryan O'Dell[4], Christopher Van Dyck[4], Michael Grundman[5], Anthony Caggiano[1], Nicholas Seyfried[2], Mary Hamby[1]
[1]Cognition Therapeutics, Inc., Research, Pittsburgh, United States of America, [2]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [3]Emtherapro, Inc., R&d, Atlanta, United States of America, [4]Yale School of Medicine, Alzheimer's Disease Research Unit, New Haven, United States of America, [5]Global R&D Partner, -, San Diego, United States of America

Aims: An unbiased assessment of plasma proteomes from patients completing the randomized, double-blind, placebo-controlled 6-month trial SPARC (NCT03493282) was performed to identify plasma pharmacodynamic biomarkers of CT1812, and for comparative analyses with a previous analysis identifying CSF pharmacodynamic biomarkers of CT1812.
Methods: Tandem-mass tag mass spectrometry proteomics was performed on baseline, 1-month, and 6-month plasma from 17 treatment-compliant SPARC participants testing two doses (100 mg, 300 mg; oral, once daily) of CT1812 compared to placebo in patients with mild-to-moderate AD. Treatment effects were assessed through differential abundance analyses (pooled drug vs placebo; $p \leq 0.1$) followed by pathway analyses (MetaCore, STRING). Plasma proteomes were compared across timepoints and to CSF proteomes, to identify plasma and CSF biomarkers commonly altered by CT1812. SPARC plasma proteomes were compared to that from the interim SHINE cohort (SHINE-A) to identify congruent plasma biomarkers across trials.
Results: Across plasma samples, 2738 proteins were detected. At 1 mo, 155 ($p \leq 0.1$) proteins were differentially abundant (CT1812 vs placebo). At 6 mo, 68 ($p \leq 0.1$) proteins were differentially abundant. Pathway analysis was performed using significant ($p \leq 0.1$) differentially abundant proteins. Immune response, amyloid-beta, and beta-catenin related pathways were significantly ($p \leq 0.05$) altered by CT1812 vs placebo at 1 mo, with similar pathways observed at 6 mo. Fifteen proteins were commonly altered in 1 and 6 mo plasma (CT1812 vs placebo; $p \leq 0.1$). Nine proteins were significantly ($p \leq 0.1$) changed in CT1812-treated patients across plasma and CSF at 6 mo. Pathways affected by CT1812 in SPARC were similarly enriched in SHINE-A plasma proteomic analyses, further supporting CT1812 mechanism of action.
Conclusions: SPARC plasma biomarker findings shed light on potential biological pathways affected by CT1812. Comparative analyses identify candidate biomarkers that replicate across independent clinical trial cohorts and/or biofluids.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0306 / #2129

Poster Topic: *Theme A: β-Amyloid Diseases / A03.b. Drug Development, Clinical Trials: Amyloid clearance*

APOE4/4 HOMOZYGOUS ALZHEIMER'S PATIENTS WITH COMORBID CEREBRAL AMYLOID ANGIOPATHY: BASELINE ANALYSES FROM PHASE 3 TRIAL OF ORAL ANTI-AMYLOID AGENT ALZ-801/VALILTRAMIPROSATE

POSTERS: A03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

Aidan Power[1], Earvin Liang[1], Rosalind Mclaine[1], Susan Abushakra[1], David Watson[2], Merce Boada Rovira[3], Jon Snaedal[4], Anton Porsteinsson[5], Marwan Sabbagh[6], Susan Flint[1], Winnie Pak[1], John Hey[1], Martin Tolar[7]
[1]Alzheon, Medical, Framingham, United States of America, [2]Alzheimer's Research and Treatment Center, Alzheimer's Research And Treatment Center, Wellington, United States of America, [3]Ace Alzheimer Center Barcelona, Research Center And Memory Clinic, Barcelona, Spain, [4]National University Hospital, Department Of Geriatrics, Reykjavik, Iceland, [5]University of Rochester, Department Of Psychiatry, Rochester, United States of America, [6]St. Joseph's Hospital and Medical Center, Barrow Neurological Institute, Phoenix, United States of America, [7]Alzheon, Ceo, Framingham, United States of America

Aims: APOE4 is a major risk factor for Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA) with gene-dose effect. APOE4 carriers with CAA have higher risk of amyloid-related imaging abnormalities (ARIA) with anti-amyloid antibodies, including ARIA-E/edema, microhemorrhages (MH), lobar macrohemorrhages, and cortical superficial siderosis. APOE4 carriers have higher risk of hyperlipidemia and cardiovascular disease (CVD). Prevalence of CVD risk factors was analyzed in the Phase 3 trial of ALZ-801/valiltramiprosate, an oral inhibitor of amyloid oligomer formation.
Methods: APOLLOE4 Phase 3 trial (NCT04770220) enrolled 325 APOE4/4 Early AD subjects (MMSE ≥22, 50-80 years); 313 had baseline MRIs, centrally read. Subjects with MH and siderosis were allowed; ARIA-E was exclusionary. Subjects with CAA (>4 MH, any siderosis, any macrohemorrhage) were compared to rest of population.
Results: Study population: 51% female, age 69 years, MMSE 26, 65% MCI, 82% Caucasians. CAA group included 47/313 subjects (15%), mostly male (70% vs 45%), older (71 vs. 68 years, p=0.004), more advanced (MMSE 25 vs 26, p=0.018; ADAS-cog 27 vs. 23, p=0.002) with more severe deep white matter disease (p=0.015). Both groups had similar prevalence of hypertension, diabetes, obesity, hyperlipidemia, and statin use. CAA group had higher prevalence of coronary artery disease (CAD; 17% vs. 8%, p=0.049) and anti-platelets use (38% vs 22%, p= 0.026). Anticoagulants were not allowed.
Conclusions: ALZ-801 showed no ARIA-E in prior studies, providing potential safer alternative to anti-amyloid antibodies. Th pivotal APOLLOE4 trial evaluating ALZ-801 enrolled homozygous APOE4/4 AD subjects with higher CAA burden than anti-amyloid antibody trials. APOE4/4 CAA subjects were older with more advanced AD and higher rates of CAD and antiplatelets use than non-CAA subjects, which may increase brain edema and microhemorrhage risk, requiring heightened vigilance with anti-amyloid antibody infusions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0307 / #2964

Poster Topic: *Theme A: β-Amyloid Diseases / A03.b. Drug Development, Clinical Trials: Amyloid clearance*

IDENTIFICATION OF NEW PHARMACODYNAMIC BIOMARKERS OF CT1812 THAT CORRELATE WITH FAVORABLE FUNCTIONAL CONNECTIVITY OF THE BRAIN

POSTERS: A03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

Valentina Di Caro[1], Kiran Pandey[2], Eunah Cho[1], Duc Duong[3], Willem De Haan[4], Michael Grundman[5], Nicholas Seyfried[3], Anthony Caggiano[6], Everard Vijverberg[7], Mary Hamby[1]
[1]Cognition Therapeutics, Inc., Research, Pittsburgh, United States of America, [2]Emtherapro, Inc., R&d, Atlanta, United States of America, [3]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [4]Alzheimer Center, Department Of Neurology, amsterdam, Netherlands, [5]Global R&D Partner, -, San Diego, United States of America, [6]Cognition Therapeutics, Inc., R&d, Purchase, United States of America, [7]Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands

Aims: Synaptic function and brain functional connectivity is impaired in Alzheimer's disease (AD). Recently, in the SEQUEL phase 2 clinical trial (NCT04735536) in AD patients, we have shown that our drug candidate, CT1812, can favorably impact the functional connectivity as measured by the quantitative EEG measure corrected Amplitude Envelope (AECc p=0.034). To identify synaptic markers of CT1812 associated with this favorable change, we performed Pearson correlation analyses between multiple EEG parameters and the CSF proteome from SEQUEL.
Methods: Participants (n=16) receive four-weeks of either CT1812 (300 mg, PO, qD) or placebo following a two-week washout, then switched treatment for another four-week period. Tandem-mass tag mass spectrometry proteomics was performed on CSF at baseline, after both treatment periods. Pearson correlation analyses were performed across EEG parameters including AECc and each protein (2,612) in the CSF proteome ($p<0.05$) from CT1812 treated patients only. Comparative analyses were performed across EEG parameters followed by pathway analysis using STRING ($p<0.05$).
Results: Sets of proteins were identified to be significantly correlated, using Pearson correlation analyses, with global alpha AECc power ($p\leq 0.05$). Amongst the most correlated biomarkers identified were SLC4A1 (r=0.86), ALDH1A1 (0.79), PIK3IP1 (r=-0.83) and MALRD1 (r=-0.77). Pathway analysis of proteins commonly associated across multiple alpha AECc parameters indicated an impact on proteasomal (PSMA, PSMB), extracellular exosomal (WNT4, ALDL1A1) and vesicular (PRDX2) biologies.
Conclusions: In summary, here we identify potential molecular correlates to parameters of brain activity as assessed via EEG. Whether these molecular correlates could be surrogate biomarkers of brain connectivity warrants further study. These findings are consistent with the mechanism of action of CT1812 in impacting synaptic function, and may support the clinical development of therapeutics that impact functional connectivity or synaptic activity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0309 / #2486

Poster Topic: *Theme A: β-Amyloid Diseases / A03.b. Drug Development, Clinical Trials: Amyloid clearance*

VPS35-BASED THERAPEUTIC TARGET EFFICACY IN SUBTYPES OF ALZHEIMER'S DISEASE DEMENTIA BASED ON NEUROPATHOLOGICAL PROFILES

POSTERS: A03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

Shadi Ghourchian[1], Oluwaseun Ogunbona[2], Jaclyn Lilek[3], Callen Spencer[4], Kaouther Ajroud[4], Margaret Flanagan[5]
[1]Downstate University at OBH, Department Of Neurology, Brooklyn, United States of America, [2]Bigg's institute, Pathology, Texas, United States of America, [3]Mesulam Center, Northwestern University, Chicago, United States of America, [4]Northwestern University, Mesulam Center, Chicago, United States of America, [5]University of Texas Health San Antonio, Pathology And Bigg's Institute, San Antonio, United States of America

Aims: Previously, we showed the potential protective effect of vacuolar protein sorting ortholog 35 (VPS35) on cognitive function in Alzheimer's Disease (AD), for the first time in the human brain. Recent studies have introduced a VPS35-based therapeutic approach for neurodegenerative diseases. This study aims to identify the most responsive patient group for this new VPS35-targeted therapy based on analyzing proteins via digital spatial profiling (DSP).
Methods: We employed NanoString GeoMx™ Digital Spatial Profiling to analyze protein levels in NeuN "masked" neurons within the hippocampus of individuals with mixed pathologies (Amyloid Beta (Ab) plaques, Tau tangles, TDP43 proteinopathy). We compared neuronal VPS35 levels in hippocampal areas across autopsy brain samples with various combinations of Tau tangles, Ab plaques, and TDP43 proteinopathy. Correlation tests were used to assess how VPS35 might vary regionally and across individuals with different combinations of Ab plaques, Tau tangles and TDP-43 proteinopathy. AD-associated proteins (Ab1-42, pTau231, pTDP43) were also compared across groups.
Results: Findings revealed that the dentate region had the most variation in neuronal VPS35 compared to CA1 and entorhinal cortex. Neuronal VPS35 changes appeared to be most significant, in addition to Ab1-42, and Amyloid precursor protein in the Tau+/TDP43+ cases lacking co-existing Ab plaques in the dentate region, specifically.
Conclusions: Our results highlight the utility of a personalized medicine approach when treating dementia. Individuals may be assessed using Tau and amyloid PET combined with a TDP43 biomarker in CSF to identify which patients will benefit the most from a VPS35-based approach. Individual patient benefit to VPS35 targeted therapies may be attributed to VPS35's overexpression, aiding in the clearance of Ab. Enhancing VPS35 expression levels or improving VPS35 function may offer therapeutic benefits for specific patient groups

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0310 / #1461

Poster Topic: *Theme A: β-Amyloid Diseases / A03.e. Drug Development, Clinical Trials: Neuroprotective & mitochondrial compounds*

SYSTEMIC AND CENTRAL NERVOUS SYSTEM BIOLOGICAL PATHWAY ALTERATIONS ASSOCIATED WITH GINKGO BILOBA TREATMENT IN NON-DEMENTED SUBJECTS

POSTERS: A03.E. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS

Julius Popp[1,2], Christopher Clark[1]
[1]University of Zurich, Department For Psychiatry, Psychotherapy And Psychosomatics, Zurich, Switzerland, [2]Lausanne University Hospital, Old Age Psychiatry, Department Of Psychiatry, Lausanne, Switzerland

Aims: Ginkgo biloba extract showed neuroprotective effects in animal studies but little is known about how it affects cognition in humans. Here, we sought to identify the biological pathways affected by Ginkgo treatment in non-demented older subjects.
Methods: Twenty-six non-demented subjects undergoing a treatment by Ginkgo extract for 3 months or longer and 35 subjects without treatment matched for age and BMI were selected from a well-characterised cohort of participants from an Alzheimer's disease biomarker study. Clinical and neuropsychological data, the APOEε4 genotype and albumin ratio were available in both groups. Targeted and untargeted omics approaches were used to quantify analytes covering over 8 biological modalities in paired cerebrospinal fluid (CSF) and peripheral blood samples. Group comparisons and multivariate ROC analysis using MetaboAnalyst 5.0 were used to identify features differing between groups. Pathway enrichment analysis was performed using hypergeometric distribution tests in the Reactome database.
Results: Group comparisons identified 22 molecules in CSF and 29 in peripheral blood with different concentration levels. The identified neuroinflammatory markers, proteins, minerals and lipids were related to changes in insulin signalling and hemostasis in blood and to intracellular signaling in the CSF. Multivariate analysis of untargeted metabolomics data in peripheral blood further identified 463 differentially expressed features between groups, mainly related to amino acid and energy metabolism.
Conclusions: We have identified biological alterations in blood and in CSF at neuroinflammatory, proteomic, lipidomic, and metabolite levels associated with Ginkgo treatment. Some of the identified analytes have previously been shown to be associated with dementia and cognitive decline. In further steps, we will relate these alterations to clinical evolution, considering both cognitive and non-cognitive symptoms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0311 / #2965

Poster Topic: *Theme A: β-Amyloid Diseases / A03.b. Drug Development, Clinical Trials: Amyloid clearance*

ANALYSIS OF CSF SAMPLES FROM A PHASE 2 CLINICAL TRIAL IN ALZHEIMER'S PATIENTS SHOW THAT CT1812 CAN MODULATE A-SYNUCLEIN

POSTERS: A03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: AMYLOID CLEARANCE

Valentina Di Caro[1], Kiran Pandey[2], Duc Duong[2,3], Nicholas Seyfried[3], Michael Grundman[4], Everard Vijverberg[5], Anthony Caggiano[1], Charlotte Teunissen[6], Mary Hamby[1]
[1]Cognition Therapeutics, Inc., Research, Pittsburgh, United States of America, [2]Emtherapro, Inc., R&d, Atlanta, United States of America, [3]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [4]Global R&D Partner, -, San Diego, United States of America, [5]Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [6]Amsterdam UMC, Neurochemistry Lab, Amsterdam, Netherlands

Aims: Objectives: The presynaptic protein α-synuclein (αSyn), mainly associated with synucleinopathies like dementia with Lewy bodies (DLB), is also involved in the pathophysiology of AD. To understand if our clinical leading candidate, CT1812, can modulate αSyn, we assessed the αSyn level in CSF samples from a phase 2, cross-over, clinical trial in patients with mild/moderate AD (NCT04735536) and performed Pearson correlation analysis between αSyn concentrations and the CSF proteome.
Methods: Methods: Participants (n=16) received four-weeks of either CT1812 (300 mg, orally, daily) or placebo following a two-week washout, then switched treatment for another four-week period. αSyn in CSF was measured by ELISA. TMT-mass spectrometry proteomics was performed on CSF at baseline and after both treatment periods. Pearson correlation analysis was performed between αSyn levels and CSF proteomes ($p \leq 0.05$) from CT1812 treated patients only. Pathway analysis was performed using STRING ($p \leq 0.05$).
Results: Results: After period 1, a statistically significant change from baseline was seen for αSyn (mean -82.32 ng/L p=0.02) in CSF samples of CT1812 treated patients. Sets of proteins were identified to be significantly correlated using Pearson correlation analyses with αSyn levels ($p \leq 0.05$). Highly correlated protein included HSPA8 (r=0.99), PLXDC1 (r=0.99), LINGO1(r=0.99) and SERPINA5 (r=-0.99), Pathways analysis of the correlated protein ($p \leq 0.05$; $r = |0.5|$) showed to be associated to the GO terms complement, lysosomes, and dopamine metabolic processes.
Conclusions: Conclusions: A decrease in CSF αSyn levels was observed after 4-weeks of treatment with CT1812. Proteins correlated with the change from baseline of αSyn level were associated with inflammation, dopaminergic, and lysosome pathways. These findings support our mechanism of action hypothesis for CT1812 and we plan to validate findings the upcoming readout of the Phase 2 CT1812 clinical trial in DLB (NCT05225415).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0312 / #1354

Poster Topic: *Theme A: β-Amyloid Diseases / A03.e. Drug Development, Clinical Trials: Neuroprotective & mitochondrial compounds*

FROM CLINIC TO CELL: COBALAMIN'S MULTI-FACETED APPROACH TO UNDERSTANDING DEFENSE AGAINST AMYLOID BETA OLIGOMER NEUROTOXICITY

POSTERS: A03.E. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS

Atsushi Kimura[1], Mayumi Tsuji[2], Hitoshi Shimada[1,3], Hidetomo Murakami[4], Kenjiro Ono[5]
[1]Niigata University, Brain Research Institute, Niigata, Japan, [2]Showa University, Pharmacology Research Center, Tokyo, Japan, [3]National Institutes for Quantum Science and Technology, Department Of Functional Brain Imaging, Chiba-shi, Japan, [4]Showa University, Department Of Internal Medicine, Division Of Neurology, Tokyo, Japan, [5]Kanazawa University, Department Of Neurology, Kanazawa, Japan

Aims: Amyloid beta oligomers (Aβo) play a major role in Alzheimer's disease (AD). Recently, we have observed that cobalamin (vitamin B12) may be effective in alleviating cognitive dysfunction in AD. However, the mechanism is still unclear. We investigated the relationship between cobalamin and cognitive function, regional cerebral blood flow, and structural MRI in AD patients. Furthermore, we evaluated the mechanism of cobalamin's protective effect against Aβo neurotoxicity from both basic and clinical perspectives.
Methods: MMSE, SPECT, high-resolution MRI, and serum cobalamin levels were measured in 151 patients aged 51 to 93 who visited our memory clinic from 2016 to 2020. Cortical structures were analyzed by measuring the gyrification index, which represents cortical complexity, using surface-based morphometry. The protective effect of cobalamin against neuronal cell injury induced by 5 μM Aβo was evaluated using human neuroblastoma cells (SH-SY5Y cells).
Results: We discovered an association between cobalamin levels and hippocampal cerebral blood flow and a correlation between cobalamin levels and the cortical gyrification index in memory-related areas. In cellular experiments, Aβo increased the production of reactive oxygen species (ROS) and decreased cell viability. In mitochondria, it elevated mitochondrial ROS species, reduced MnSOD levels and mitochondrial permeability transitions, and increased ATP production. Cobalamin mitigated these oxidative stresses and significantly inhibited cellular injury caused by Aβo.
Conclusions: Cobalamin suppressed Aβo-induced cell injury through its robust antioxidant effect, suggesting that cobalamin may help protect brain microstructures in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0313 / #563

Poster Topic: *Theme A: β-Amyloid Diseases / A03.f. Drug Development, Clinical Trials: Neurotransmitter-based modulators*

SINGLE ASCENDING DOSE STUDY OF THE NOVEL DONEPEZIL LONG-ACTING INJECTION VERSUS ARICEPT® TABLETS IN HEALTHY ADULT PARTICIPANTS

POSTERS: A03.F. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROTRANSMITTER-BASED MODULATORS

Heesun Kim[1], Sangno Lee[2], Mase Lee[3], Juhee Kim[4]
[1]Inventagelab, Clinical Development, Seongnamsi, Korea, Republic of, [2]Inventagelab, Ifc Research Center, Seongnamsi, Korea, Republic of, [3]Inventagelab, Ivc Development Division, Seongnamsi, Korea, Republic of, [4]Inventagelab, Ceo, Seongnamsi, Korea, Republic of

Aims: IVL3003 (donepezil-loaded microspheres) is a long-acting injectable(LAI) form for the treatment of dementia of alzheimer's type. The use of a LAI formulation offers potential benefits, including sustained drug levels in the blood, fewer adverse effects, and improved patient compliance. The purpose of this study was to evaluate the safety profiles and characterize the pharmacokinetic(pk) and pharmacodynamic profiles of IVL3003 and Aricept® 10mg tablets in healthy adult participants.
Methods: Approximately 52, healthy adult males between ≥18 and ≤55 years of age were planned to be included in this study across 4 cohorts. Tolerability of the injections were assessed throughout the study. The plasma concentrations of donepezil, 6-O-desmethyl donepezil and AChE levels will be determined using a validated analytical method.
Results: Overall, the safety profiles of single SC IVL3003 dose and multiple doses of Aricept (donepezil) 10mg tablets in healthy adult subjects was generally safe and well tolerated. A major difference in the observed PK over 672hours following SC IVL3001 was the more consistent donepezil plasma concentrations without initial burst and the absence of sharp fluctuations in peak and trough levels which are typical of daily oral dosing. The exposure to IVL3003 (AUC and Cmax) following single SC ascending doses, increased in a dose proportional manner. The PD effects of IVL3003 were consistent with the expected mechanism of action.
Conclusions: The safety and pharmacokinetic/pharmacodynamic properties of IVL3003 confirmed through this trial showed that it achieved a fast effective concentration and maintained a stable effective concentration, unlike the conventional oral drug administered daily. IVL3003 was confirmed to be developed as a therapeutic agent for Alzheimer's disease (AD).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0314 / #2808

Poster Topic: *Theme A: β-Amyloid Diseases / A03.h. Drug Development, Clinical Trials: Medicinal chemistry approaches, drug repurposing*

ALZHEIMER'S DISEASE : PLEIOTROPIC PRODRUGS WITH POTENTIAL THERAPEUTIC INTEREST

POSTERS: A03.H. DRUG DEVELOPMENT, CLINICAL TRIALS: MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING

Thomas Curel[1], Alice Wang[2], Marie Jouanne[2], Valentin Travers-Lesage[2], Cédric Lecoutey[2], Anne-Claire Groo[2], Sophie Corvaisier[2], Audrey Davis[2], Marc Since[2], Jean-Marie Billard[3], Thomas Freret[3], Aurélie Malzert-Fréon[2], Christophe Rochais[2], Michel Boulouard[3], Marie-Claude Potier[4], Patrick Dallemagne[2], Sylvie Claeysen[1]
[1]Institut de Génomique fonctionnelle (CNRS UMR5203 - INSERM U1191), Neurosciences, Montpellier, France, [2]Centre d'étude et de recherche sur le médicament de Normandie (UR 4258 - CERMN), Polypharmacology, Caen, France, [3]COMETE (Normandie Université - UNICAEN - INSERM U1075), Neurodegenerative Diseases, Caen, France, [4]Paris Brain Institute - ICM, Alzheimer And Prion's Diseases Team, Paris, France

Aims: With age, people with Down syndrome (DS) develop dementia due to Alzheimer's disease (AD). Both pathologies share a high production of ß-amyloid peptides from the APP gene located on human chromosome 21 and several studies suggest that a common pathogenic mechanism exists between AD and DS, involving alterations in neurotransmitter systems (the cholinergic, GABA-ergic, serotonergic, glutamatergic and adrenergic). Therefore, some common therapeutic targets have been identified. Faced with the multifactorial origin of these diseases, a pleiotropic intervention is now widely recommended. This project aims at designing new multi-target directed ligands (MTDL) for intranasal administration, acting as prodrugs, with potential therapeutic interest in DS and AD. The prodrugs are activated by the covalent inhibition of butyrylcholinesterase (BuChE), capable of counteracting cholinergic neurodegeneration in AD. The released drugs will then target the 5-HT_4 serotonin receptors to display a potential disease-modifying effect. Liposomal formulation and intranasal administration will enhance central nervous system distribution of prodrugs for selective activation by brain BuChE, to enhance central effects of released drugs and potentially avoid their peripheral side effects.
Methods: First, the synthetized prodrugs and their associate active metabolites have been tested and selected on their capacity to inhibit or activate their target. Then, the canditate's ability to counteract amyloid toxicity is evaluated *in vitro*, on stressed primary neuronal culture of rat hippocampal neurons, and finally *in vivo* in 5xFAD transgenic mice model.
Results: After caracterization of the pharmacological profile of the synthetized drugs, the screening of the drugs allowed to select candidates that protect neurons from amyloid toxicity *in vitro*, and that will be tested *in vivo* in 5xFAD transgenic mice model.
Conclusions: At the end, this project should provide a multi-fonction drug with therapeutic interest in Alzheimers disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0315 / #518

Poster Topic: *Theme A: β-Amyloid Diseases / A03.h. Drug Development, Clinical Trials: Medicinal chemistry approaches, drug repurposing*

PHASE 1 CLINICAL STUDY OF LEUCETTINIB-21, A DYRK1A KINASE INHIBITOR DRUG AIMING AT THE CORRECTION OF COGNITIVE DISORDERS

POSTERS: A03.H. DRUG DEVELOPMENT, CLINICAL TRIALS: MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING

Laurent Meijer, Emilie Chretien, Emmanuel Deau, Gaëlle Hogrel, Mattias Lindberg
Perha Pharmaceuticals, Neurosciences, Roscoff, France

Aims: Cognitive disorders (memory, learning) observed in patients with **Down syndrome** (**DS**) and **Alzheimer's disease** (**AD**) are associated with an excess activity of **DYRK1A** (dual specificity, tyrosine phosphorylation regulated kinase). Genetic and pharmacological inhibition of DYRK1A corrects these cognitive disorders in DS/AD animal models, encouraging the development of a clinical DYRK1A inhibitor to treat memory/learning difficulties in patients with AD or DS.
Methods: Inspired by **Leucettamine B**, a marine sponge natural product, we synthesized, optimized and extensively characterized >500 analogues, **Leucettines**, followed by a second-generation family, **Leucettinibs** (>670 analogues) and selected an orally available drug candidate, **Leucettinib-21**.
Results: Regulatory preclinical toxicity/tolerance studies, carried out with rats (NOAEL: 20 mg/kg) and mini-pigs (NOAEL: 100 mg/kg), showed that Leucettinib-21 is well tolerated in these animals at doses much higher than active doses (correcting memory disorders) on animal models of DS and AD (0.3-0.5 mg/kg). **Immediate-release tablets** of Leucettinib-21 and placebo have been prepared. A double-blind, placebo-controlled clinical phase 1 study ('Leucetta') involving 120 participants, will be launched in Q4-2023, to investigate safety and pharmacokinetics of Leucettinib-21. Blood samples collected from all participants will be used to analyze plasma proteomic and phosphoproteomic profiles as well as AD-specific biomarkers. The Leucetta trial comprises Single Ascending Dose, Food Effect and Multiple Ascending Dose studies in 96 healthy volunteers. Furthermore, 12 adults with DS and 12 AD patients will receive a single Leucettinib-21 dose for pharmacokinetics and biomarkers analysis.
Conclusions: The first results of this phase 1 clinical study will be presented. The study should be completed by Q4-2024, hopefully opening the door to phase 2a studies to evaluate the ability of Leucettinib-21 to correct cognitive disorders in children with DS and patients with early AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0316 / #796

Poster Topic: *Theme A: β-Amyloid Diseases / A03.h. Drug Development, Clinical Trials: Medicinal chemistry approaches, drug repurposing*

THE BRAIN PERMEABLE IMMUNOPROTEASOME-SPECIFIC INHIBITOR AR-55 IS A PROMISING DRUG CANDIDATE FOR ALZHEIMER'S DISEASE

POSTERS: A03.H. DRUG DEVELOPMENT, CLINICAL TRIALS: MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING

Ji Eun Park[1], Chhabi Chaudhary[2], Deepak Bhattarai[2], Kyung Bo Kim[1]
[1]Florida International University, Center For Translational Research, Port St. Lucie, United States of America, [2]University of Kentucky, College Of Pharmacy, Lexington, United States of America

Aims: We previously reported that inhibition of the immunoproteasome (iP), which has been shown to be upregulated in reactive glia surrounding amyloid-β (Aβ) plaques in the brain of patients with Alzheimer's disease (AD), improves cognitive function in AD amyloidosis mouse model via suppressing microglia-mediated inflammation in an Aβ independent manner.
Methods: We assessed the pharmaceutical properties of our lead iP inhibitors developed based on macrocyclic peptide epoxyketone backbone, investigating the stability and blood-brain barrier (BBB) permeability using human liver microsomes and Caco-2 monolayers mimicking BBB, respectively. Among the compounds investigated, AR-55 has been identified as the most promising AD drug candidate and thus further evaluated for its pharmacokinetic properties and biodistribution in healthy mice.
Results: The macrocyclic AR-55 displayed significantly improved metabolic stability (29-fold increased half-life), permeability (4-fold lower efflux ratio), and solubility, compared to carfilzomib (Kyprolis®), the FDA-approved linear peptide epoxyketone proteasome inhibitor. Furthermore, AR-55 effectively inhibited the activity of the mouse brain iP with no apparent signs of toxicity up to 100 mg/kg i.v. for 72 hr, indicating its ability to cross the BBB.
Conclusions: The results suggest that AR-55 may hold great potential as an AD drug that needs further investigation in clinical settings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0317 / #181

Poster Topic: *Theme A: β-Amyloid Diseases / A03.h. Drug Development, Clinical Trials: Medicinal chemistry approaches, drug repurposing*

COMPUTATIONAL SCREENING OF COUMARIN DERIVATIVES AS INHIBITORS OF THE NACHT DOMAIN OF NLRP3 INFLAMMASOME FOR THE TREATMENT OF ALZHEIMER'S DISEASE

POSTERS: A03.H. DRUG DEVELOPMENT, CLINICAL TRIALS: MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING

Sushil Kumar Singh, Powsali Ghosh, Ravi Singh, Chayanika Chatterjee, Ashok Kumar
Indian Institute of Technology (BHU), Department Of Pharmaceutical Engineering & Technology, Varanasi, India

Aims: Our study aimed to find coumarin derivatives that can inhibit NLRP3 inflammasomes to combat neuroinflammation in Alzheimer's Disease (AD).
Methods: A library of coumarin derivatives was constructed from four different databases. OpenBabel was used to remove duplicates based on InChI code, and Knime was used to eliminate compounds violating the 'Lipinski Rule of Five' and 'REOS rule', having TPSA above 70 Å and PAINS fragments. HTVS and molecular docking studies were performed to obtain compounds exhibiting better binding affinity than standard ligand MCC950. *In silico* ADMET studies were performed using SwissADME, eMolTox, and PreADMET webservers to retain only the molecules showing acceptable physicochemical properties. The best three virtual hits were subjected to molecular dynamics (MD) simulations in the MD simulation software Desmond in an environment replicating the human cell conditions to analyze the stability of protein-ligand complexes. The results were analyzed using the 'simulation event analysis' panel and interpreted to find the best virtual lead compound.
Results: The initial dataset comprising 9762 compounds was cleaned and 203 duplicates were removed. Among 9559 unique compounds, 688 were found to have drug-like properties. HTVS study revealed 175 molecules to have better protein binding than the co-crystal ligand. In the three-stage molecular docking studies, 36 compounds displayed better binding affinity than MCC950. Three of these compounds are predicted to be bioavailable, BBB-permeable, and non-toxic. MD simulation results showed that MolPort-050-872-358 formed the most stable protein-ligand complex.
Conclusions: Among a diverse set of compounds containing the coumarin nucleus, which has proven anti-inflammatory properties, MolPort-050-872-358 was found to be a promising NLRP3 inhibitor. Utilizing the coumarin scaffold to develop novel therapeutic treatments for AD can block neuroinflammation by inhibiting the NLRP3 inflammasome.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0318 / #1507

Poster Topic: *Theme A: β-Amyloid Diseases / A03.i. Drug Development, Clinical Trials: Personalized medicines, sex /race, AI, and combination therapy*

COMBINATION OF CIPROFLOXACIN/CELECOXIB AS A NOVEL THERAPEUTIC APPROACH FOR ALZHEIMER'S DISEASE

POSTERS: A03.I. DRUG DEVELOPMENT, CLINICAL TRIALS: PERSONALIZED MEDICINES, SEX /RACE, AI, AND COMBINATION THERAPY

Shiran Salomon-Zimri[1], Rachel Ben-Hayun[2], Nitai Kerem[1], Niva Russek-Blum[1], Diana Shtossel[1], Vered Sasson[1], Eidan Lushi[1], Rafi Hadad[2], Natalia Yarovinsky[2], Judith Aharon Peretz[2], Ferenc Tracik[1], David Tanne[2]
[1]NeuroSense Therapeutics, Research And Development, Herzliya, Israel, [2]Rambam Health Care Campus, Stroke And Cognition Institute, Haifa, Israel

Aims: AD's pathophysiology is complex and underlies multiple pathways including neuroinflammation, impaired recycling, and autophagy. Due to its complexity and diverse manifestation, combined multi-targeted therapy is needed. PrimeC is a combination of ciprofloxacin, a miRNA regulator, and celecoxib, a COX-2 inhibitor reducing inflammation, oxidative stress, and amyloid aggregation. PrimeC showed beneficial synergistic effects in ALS, where it altered key pathologies such as neuroinflammation, autophagy, and TDP-43 levels. NeuroSense's AD studies showed alterations in indicative biomarkers related to PrimeC's MoA (TDP-43 $p<0.05$; LC3 $p<0.01$). The combined treatment affected Aβ-induced inflammatory response of microglia, survival, and morphology of neurons. We aim to assess the safety and tolerability of PrimeC in AD patients. Clinical outcomes, AD hallmarks and target engagement markers from plasma and CSF will be examined. Furthermore, a PoC *in-vitro* study will be conducted in an AD cell line to elucidate PrimeC's MoA.
Methods: 20 mild to moderate non-familial AD patients will be recruited at Rambam Health Care Campus, Israel, for a Phase 2 randomized, prospective double-blind, placebo-controlled study. Participants will be administered with PrimeC BID for 12 months. Plasma and CSF will be measured for a cassette of biomarkers, and clinical outcomes (e.g., ADCS-iADL, MMSE, etc.) will be monitored. The *in-vitro* study will observe PrimeC and each of its comprising compounds' effect on neurite outgrowth of an AD transgenic SH-SY5Y cell line.
Results: from the clinical study could illuminate the safety, tolerability, and efficacy of PrimeC on AD patients, complemented by the *in-vitro* results advancing our understanding of PrimeC's MoA.
Conclusions: This work could potentially shed light on a new therapeutic approach to halt AD progression using a combined therapeutic strategy targeting multiple pathways. It may also identify new biomarkers for target engagement.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0319 / #2696

Poster Topic: *Theme A: β-Amyloid Diseases / A03.i. Drug Development, Clinical Trials: Personalized medicines, sex /race, AI, and combination therapy*

MEDICATIONS FOR ALZHEIMER'S DISEASE: ANALYSIS OF THE COGNITIVE CHANGES AFTER TWO YEARS OF THERAPY IN ALZHEIMER'S DISEASE PATIENTS FROM THE NATIONAL ALZHEIMER'S COORDINATING CENTER.

POSTERS: A03.I. DRUG DEVELOPMENT, CLINICAL TRIALS: PERSONALIZED MEDICINES, SEX /RACE, AI, AND COMBINATION THERAPY

Krisztina Marosi[1], Liana Apostolova[2,3,4], Sophie Sokolow[1,5]
[1]UCLA, School Of Nursing, Los Angeles, United States of America, [2]Indiana University School of Medicine, Radiology And Imaging Sciences, Indianapolis, United States of America, [3]Indiana University School of Medicine, Department Of Medical And Molecular Genetics, Indianapolis, United States of America, [4]Indiana University School of Medicine, Department Of Neurology, Indianapolis, United States of America, [5]UCLA, Brain Research Institute, Los Angeles, United States of America

Aims: The goal of the study was to analyze the changes in cognitive function after 2-year use of Alzheimer's Disease (AD) medication in AD patients using the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS).
Methods: AcetylCholinesterase Inhibitors [AChEIs] and memantine use, AD diagnosis, MMSE and CDR-scores were retrieved from the NACC UDS. Linear regression models were used to compare the treatment effect on cognitive changes after 2-year pharmacotherapy in AD patients.
Results: AD subjects treated with AChEIs or memantine showed a greater decline in MMSE and a greater rise in CDR-SB scores after 2 years compared to non-treated ones. There was no significant difference in MMSE at baseline between AChEIs and untreated groups. However, a significant difference in MMSE at baseline was observed between memantine-treated patients compared to the untreated ones. A significant difference in CDR-SB scores at baseline was observed between those on AD medication compared to untreated controls.
Conclusions: These findings indicate that AD patients who were prescribed memantine were more severely affected cognitively when their pharmacotherapy was initiated. This is in accordance with the FDA-approval of memantine for moderate to severe AD. Our data also show that AD patients on any AD medications were more severely affected by the disease compared to their untreated counterpart, as the progression of their cognitive decline was faster despite 2-years of pharmacotherapy. This observation extends our previous study in MCI subjects from the AD Neuroimaging Initiative showing that physicians prescribe AChEIs to those who present with more severe clinical impairment. Furthermore, these findings underscore the importance of personalized medicine approaches in the treatment of AD, as individual patient characteristics and disease severity play a significant role in the choice and timing of therapeutic interventions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0320 / #1078

Poster Topic: *Theme A: β-Amyloid Diseases / A03.i. Drug Development, Clinical Trials: Personalized medicines, sex /race, AI, and combination therapy*

SCOP: A COMPUTATIONAL TOOL TO PREDICT INTERCELLULAR CROSSTALK OF ALZHEIMER'S DISEASE USING SINGLE-NUCLEUS RNA SEQUENCING DATA

POSTERS: A03.I. DRUG DEVELOPMENT, CLINICAL TRIALS: PERSONALIZED MEDICINES, SEX /RACE, AI, AND COMBINATION THERAPY

Li Yang, Jianting Sheng, Shaohua Qi, Yuliang Cao, Amna Irfan, Stephen Wong
Houston Methodist research institute, T. T. & W. F. Chao Center For Brain, Houston, United States of America

Aims: The epidemiological studies of Alzheimer's disease (AD) have been benefited from single-nucleus RNA sequencing (snRNA-seq) to delineate cell-type-specific communications. However, deciphering the intricated intracellular crosstalk between the different executive functional cells identified in the brain remains challenging. The main objective of this study is to develop a computational tool to fill the gap.
Methods: Database Curation: The study curates a cell-cell communication database by collecting data on ligand and receptor pairs from the KEGG database, supplemented with subsequent signaling and gene interaction information from KEGG, Reactome, and Ingenuity Pathway Analysis (IPA). Development of SCOP: SCOP (**S**ingle-cell **C**r**O**sstalk **P**redictor) is developed as a computational tool that utilizes the curated database and snRNA-seq data input to predict intercellular crosstalk and intracellular pathways in AD. Machine Learning Models: SCOP employs machine learning to predict the impact of individual genes on downstream pathways.
Results: SCOP takes various inputs, including gene expression data, protein-protein interaction networks, and ligand-receptor interactions, to provide a comprehensive view of intercellular crosstalk in the AD brain and rank potential crosstalk targets for AD treatment as outputs. SCOP is applied to human AD brain snRNA-seq datasets, leading to the identification of the top 18 pairs of crucial ligand-receptor interactions, and 11 pathways involved in AD pathology different cell types, including microglia, astrocytes, and inhibitory/excitatory neuron cells. Eight top-ranking interactions within astrocyte-neuron crosstalk are selected as case studies for validation. *In vitro* and *in vivo* validation experiments confirm the selected gene expression levels and immunocytochemical signals with the systemic analysis conducted by SCOP.
Conclusions: SCOP acts as a valuable tool for comprehensively analyzing and understanding the heterogeneous cell-cell communication in the AD brain, benefiting early marker detection and novel therapeutic strategies development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0321 / #1299

Poster Topic: *Theme A: β-Amyloid Diseases / A03.j. Drug Development, Clinical Trials:New clinical trial designs; Simulation of progress-digital twins*

DESIGN OF A STATE-OF-THE-ART PHASE 2B TRIAL TO EVALUATE THE EFFICACY OF A SPECIFIC INHIBITOR OF 11B-HSD1, XANAMEM®, IN MILD AND MODERATE ALZHEIMER'S DISEASE

POSTERS: A03.J. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

Jack Taylor[1], Dana Hilt[1], Tamara Miller[1], John Harrison[2,3,4], Chistopher Chen[5], Craig Ritchie[2]
[1]Actinogen Medical, Clinical Science, SYDNEY, Australia, [2]Scottish Brain Sciences, Neuropyschology, Edinburgh, United Kingdom, [3]Institute of Psychiatry, Psychology & Neuroscience, King's College London, Department Of Psychological Medicine, London, United Kingdom, [4]Amsterdam UMC, Alzheimer's Center, Amsterdam, Netherlands, [5]Yong Loo Lin School of Medicine, National University of Singapore, Department Of Pharmacology, Singapore, Singapore

Aims: Xanamem®, a brain-penetrant inhibitor of 11β-HSD1, which converts intracellular cortisone to cortisol, has been evaluated in 3 independent placebo-controlled trials. These trials suggest Xanamem may be both a procognitive drug and disease-course modifying agent. The XanaMIA Phase 2b trial aims to evaluate the cognitive and clinical benefits of Xanamem.
Methods: XanaMIA is a phase 2b, double blind, randomized, placebo-controlled, 36-week trial to assess the safety, tolerability, and efficacy of Xanamem 10 mg daily in patients with mild or moderate dementia due to AD. This multi-centre trial will randomise (1:1) 220 participants over 50 years old meeting the diagnostic criteria for AD with a CDR global score of 0.5-1, a MMSE of 18-26, and elevated plasma p-tau181. Participants will also be required to have a 0.5 SD cognitive deficit compared to normative data as measured by a symbol coding test. The study design includes a 6-week pre-screening period (to assess AD plasma biomarker positivity), 4-week screening period, a 36-week treatment period, and a 4-week follow-up period. The primary efficacy endpoint is change from baseline to week 36 on a computerized, global cognitive composite including measures of attention, working memory, executive function, and episodic memory. The key secondary outcome, the CDR-SB, will assess integrated cognition and function. Other measures of cognition, function, and behavior will also be examined.
Results: The results of the XanaMIA Phase 2B trial are expected in 2025.
Conclusions: The XanaMIA Phase 2B trial is a robustly designed trial using a contemporary rationale to select validated and treatment-sensitive endpoints, and patient enrichment strategies to demonstrate the procognitive and disease-course modifying benefits of Xanamem.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0322 / #2723

Poster Topic: *Theme A: β-Amyloid Diseases / A03.j. Drug Development, Clinical Trials:New clinical trial designs; Simulation of progress-digital twins*

A PHASE 3 CLINICAL PROTOCOL TO STUDY THE SAFETY AND EFFICACY OF NA-831 IN COMBINATION WITH LECANEMAB IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE

POSTERS: A03.J. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

Lloyd Tran, Fern Vu, Markku Kurkinen
Biomed Industries, Inc., Neurosciences, San Jose, United States of America

Aims: The aim of the multi-centers, double blind, placebo controlled parallel Phase 3 trials is to evaluate the efficacy and safety of combination therapy of NA- 831 with Lecanemab for patients with Early Alzheimer's Disease.
Methods: Enrolment: 600 participants. Ages: 50 to 90 Years. All sexes are eligible for the study. Core Study: Participants will be divided in 3 groups, randomly assigned in a 1:1 ratio to receive a drug or a combination of two drugs or placebo. Group 1: will receive one 30 mg of NA-831 capsule orally once a day or placebo, Group 2: will receive and intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. Group 3: will receive one 30 mg of NA-831 capsule orally once a day and intravenous lecanemab (5 mg per kilogram of body weight every 2 weeks) or placebo. Open Label Extension Phase: Participants completing the core study will receive one 30 milligram (mg) NA-31 capsule orally once a day, and intravenous lecanemab (5 mg per kilogram of body weight every 2 weeks)
Results: The study will be completed in 2025. I. Key Outcome Measures: Core Study: Change from Baseline in the CDR-SB at 18 Months [Time Frame: Baseline, 18 months] Extension Phase: Number of Participants Reporting One or More Treatment-emergent Adverse Events (TEAEs) [Time Frame: From first dose of study drug up to approximately 24 months (including 3 months follow up) for the extension phase] II. Secondary Outcome Measures: Core Study: Change from Baseline in Alzheimer Disease Assessment Scale - Cognitive Subscale 14 (ADAS-cog14) at 18 Months [Time Frame: Baseline, 18 months]
Conclusions: The results of the phase 3 study will be availlabe in 2025. The details of the Phase 3 methodology and protocol will be presented and discussed.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0323 / #2725

Poster Topic: *Theme A: β-Amyloid Diseases / A03.j. Drug Development, Clinical Trials:New clinical trial designs; Simulation of progress-digital twins*

A PHASE 2 CLINICAL PROTOCOL TO CONFIRM THE SAFETY AND EFFICACY OF NA-831 IN COMBINATION WITH ADUCANUMAB IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE

POSTERS: A03.J. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

Lloyd Tran, Fern Vu, Markku Kurkinen
Biomed Industries, Inc., Neurosciences, San Jose, United States of America

Aims: To evaluate the efficacy and safety of combination therapy of NA- 831 and aducanumab with patients with Early Alzheimer's Disease.
Methods: ENROLMENT: 240 participants. Ages: 50 -90 Years. All sexes are eligible for study. Core Study: (12 months) Participants will be divided in 3 groups, assigned in a 1:1 ratio to receive a drug or a combination of drugs or placebo. Group 1: will receive one 30 mg of NA-831 capsule orally once a day or placebo, Group 2: will receive and intravenous aducanumab- schedule: Infusions 1-2: 1 mg/kg IV q4Weeks or placebo Infusions 3-4: 3 mg/kg IV q4Weeks or placebo Infusions 5-6: 6 mg/kg IV q4Weeks or placebo Infusion 7 and beyond: 10 mg/kg IV q4Weeks or placebo Group 3: will receive one 30 mg of NA-831 capsule orally once a day, and intravenous aducanumab-schedule: Infusions 1-2: 1 mg/kg IV q4Weeks or placebo Infusions 3-4: 3 mg/kg IV q4Weeks or placebo Infusions 5-6: 6 mg/kg IV q4Weeks or placebo Infusion 7 and beyond: 10 mg/kg IV q4Weeks or placebo Open Label Extension Phase: (18 months) Participants completing the core study will receive one 30 milligram (mg) NA-31 capsule orally once a day, and intravenous aducanumab (6 mg per kilogram of body weight every 4 weeks).
Results: Core Study: Change from Baseline in the CDR-SB at 12 Months [Time Frame: Baseline, 12 months] Extension Phase: Number of Participants Reporting One or More Treatment-emergent Adverse Events (TEAEs) [Time Frame: From first dose of study drug up to approximately 18 months (including 3 months follow up) for the extension phase]
Conclusions: The results of the study will be available in 2025. The details of the Phase 2 methodology and protocol will be presented and discussed.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0324 / #807

Poster Topic: *Theme A: β-Amyloid Diseases / A03.k. Drug Development, Clinical Trials: Non-pharmacological interventions*

EFFECTS OF TRANSCRANEAL PULSE STIMULATION FOR THE TREATMENT OF ALZHEIMER´S DISEASE- SPANISH EXPERIENCE WITH A CONTROL GROUP STUDY

POSTERS: A03.K. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

Cristina Guijarro-Castro[1], Miguel Ángel Fernández Blázquez[2], Rubén Sebastián-González[1], Lucía Fernández-Arana[1], Javier Martín[3], Karin Freitag[4]
[1]Clínica DKF, Neuroscience Department, Madrid, Spain, [2]Universidad Autónoma de Madrid, Department Of Biological And Health Psychology, Madrid, Spain, [3]Clínica DKF, R&d Department, Madrid, Spain, [4]Clínica DKF, Rheumatology Department, Madrid, Spain

Aims: Recent studies have shown that Transcranial pulsed stimulation (TPS; Neurolith®) may have beneficial effects on brain glucose metabolism and cognitive function in patients with Alzheimer's Disease (AD). In our study, we expect to confirm the usefulness of TPS on patients with AD at 3 months.
Methods: Fifteen patients (males and females aged 61 to 89) diagnosed with MCI due to AD or mild to moderate AD underwent TPS treatment. Also, to compare the effect of treatment with the natural course of the disease, data from 15 matched control patients who had not received TPS treatment were retrospectively included. The safety, tolerability, cognitive and clinical effects of the TPS therapy vs. control participants have been evaluated. Inclusion criteria: diagnosed of probable AD dementia or MCI due to AD, MMSE > 10, baseline MRI scan excluding other potential causes of dementia, Fazekas score ≤ 2, anticholinesterase drugs or memantine treatments were allowed. Cognitive impairment was screened using MoCA. A comprehensive neuropsychological evaluation was conducted for all patients, before and after treatment.
Results: After treatment, 47% of the patients presented higher scores at the 3-month follow-up, 40% showed no change and 13% manifested a slight worsening (MoCA test). In episodic memory, 45% showed improvement on the 3-month follow-up scores, another 45% remained invariable, and the remaining 10% worsened. Strikingly, no patient reported significant impairment of depressive symptomatology whereas 60% even improved; three patients showed indeed a relevant reduction. In comparison, during the same follow-up control patients showed a worsening in all domains evaluated.
Conclusions: Based on our findings, we can conclude TPS is a safe and effective therapeutic option for AD that benefits cognition and mood. Neurolith ® accompanies and complements currently available treatments.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0325 / #2726

Poster Topic: *Theme A: β-Amyloid Diseases / A03.j. Drug Development, Clinical Trials:New clinical trial designs; Simulation of progress-digital twins*

WHAT DOES AMYLOID-BETA (AB) HAVE TO DO WITH ALZHEIMER'S DISEASE: A HISTORY OF FAILURE

POSTERS: A03.J. DRUG DEVELOPMENT, CLINICAL TRIALS:NEW CLINICAL TRIAL DESIGNS; SIMULATION OF PROGRESS-DIGITAL TWINS

Lloyd Tran, Zung Tran
Biomed Industries, Inc., Neurosciences, San Jose, United States of America

Aims: To review and analyze clinical data of major anti-Aβ monoclonal antibody drugs including recent FDA approved Aducanumab and Lecanemab for the treatment of Alzheimer's Disease.
Methods: We systematically searched, reviewed, and analyzed the clinical data of anti-Aβ monoclonal antibody drugs. We focused on two important outcome measures: CDR-SB and ADAS-Cog. Nearly all trials reported the difference between scores of the treatment relative to the placebo at the end of the trial. On a scale where a higher score is "worse," a negative (-) difference "favors" treatment (lower score – higher score = - value). We use the bootstrapping method, a statistical procedure that resamples a single dataset to create simulated samples. This resampling process allows for the calculation of means, median, standard errors, confidence intervals (CI), hypothesis testing, and other statistics. For our study, we estimated the mean and 95%CI of these published differences by performing 10,000 resamples.
Results: All the clinical trials analyzed were randomized, placebo controlled. Sample sizes varied for the phase 3 trials, from 253 to 1072 per arm (median=519 participants); trial lengths were from 76 to 105 weeks (median=78 weeks). The estimated bootstrap mean and 95%CI for differences between placebo and drug, for CDR-SB and for ADAS-Cog were: CDR-SB; mean (95%CI) = *-0.08* (-0.31 to +0.22), range of differences = -0.70 to 1.30; ADAS-Cog; mean (95%CI) = *-0.53* (-1.03 to +0.22), range of differences = -1.60 to +4.74.
Conclusions: The cumulative mean changes for CDR-SB were -0.08; for ADAS-Cog it was -0.53, with both 95%CI including zero. The score range for CDR-SB is 0 to 18; the range for ADAS-Cog is 0 to 70/90. These mean differences across the many trials conducted cannot be either clinically or statistically significant.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0326 / #1495

Poster Topic: *Theme A: β-Amyloid Diseases / A03.k. Drug Development, Clinical Trials: Non-pharmacological interventions*

A MULTIMODAL LIFESTYLE PROTOCOL IMPROVES HEALTH AND COGNITION IN C57BL/6J MICE

POSTERS: A03.K. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

Vilma Alanko[1,2], Francesca Eroli[1], Alina Solomon[2,3,4], Tobias Hartmann[5,6], Miia Kivipelto[2,4,7,8], Per Nilsson[1], Silvia Maioli[1], Anna Matton[1,2,4]
[1]Karolinska Institutet, Division Of Neurogeriatrics, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden, [2]Karolinska Institutet, Division Of Clinical Geriatrics, Centre For Alzheimers Research, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden, [3]University of Eastern Finland, Institute Of Clinical Medicine, Neurology, Kuopio, Finland, [4]Imperial College London, Ageing Epidemiology Research Unit (age), School Of Public Health, Faculty Of Medicine, London, United Kingdom, [5]Saarland University, Institute Of Clinical Medicine/neurology, Homburg, Germany, [6]Saarland University, Deutsches Institut Für Demenz Prävention (didp), Homburg, Germany, [7]Karolinska University Hospital, Theme Inflammation And Aging, Solna, Sweden, [8]University of Eastern Finland, Institute Of Public Health And Clinical Nutrition, Kuopio, Finland

Aims: We have set up a novel protocol to study multimodal lifestyle intervention in mice to recapitulate recent successful clinical trials FINGER and LipiDiDiet. The protocol was developed to identify the biological mechanism underlying the positive findings of multimodal lifestyle interventions.
Methods: In the Lifestyle group, mice were given access to running wheels (voluntary exercise), Fortasyn Connect (healthy diet), and they were subjected to cognitive training in an IntelliCage environment. To separately investigate the effects of pharmacological vascular monitoring, a group of mice was given Atorvastatin and Enalapril in the diet (Pharma group). Control mice were housed in normal conditions. We included 12 wild-type female C57BL/J6 mice 6 months of age per group. The full intervention lasted for 8 weeks. Blood pressure was measured using a tail-cuff system at baseline and the end of the intervention. Additionally, all mice underwent a battery of behavioural testing after the eight weeks of intervention.
Results: During the intervention, the Lifestyle group demonstrated effective learning in the different cognitive training tasks and actively used the running wheels. At the end of the intervention, the Pharma and the Lifestyle groups showed a medication- and a lifestyle-induced lowering of blood pressure, respectively. Furthermore, the Lifestyle group displayed an improved short-term spatial working memory compared to the control group as assessed by the spontaneous alternation in the Y maze test.
Conclusions: The lifestyle protocol had both health and cognitive performance-enhancing effects in adult WT mice proving that the protocol can be back-translated from humans to mice. Now we will continue to determine the brain protein and lipid changes associated with these beneficial effects. The future steps involve studying animal models of cognitive decline, Alzheimer's disease and vascular/metabolic dysfunction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0327 / #1301

Poster Topic: *Theme A: β-Amyloid Diseases / A03.k. Drug Development, Clinical Trials: Non-pharmacological interventions*

COGNITO'S EVOKED GAMMA OSCILLATION TREATMENT AFFECTS CSF BIOMARKERS RELATED TO SYNAPTIC REGULATION, GLIAL FUNCTION AND IMMUNOLOGICAL RESPONSES IN MCI-AD

POSTERS: A03.K. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

Mihaly Hajos[1], Duc Duong[2], Annabelle Singer[3], Monika Shpokayte[1], Zach Malchano[1], Ralph Kern[1], James Lah[4], Allan Levey[4], Nicholas Seyfried[2], Kiran Pandey[5]
[1]Cognito Therapeutics, R&d, Cambridge, United States of America, [2]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [3]Georgia Institute of Technology & Emory University, Coulter Dept. Of Biomedical Engineering, Atlanta, United States of America, [4]Emory University School of Medicine, Neurology, Atlanta, United States of America, [5]Emtherapro, Inc., R&d, Atlanta, United States of America

Aims: Evaluating mode of action of Cognito Therapeutics' medical device using unbiased proteomic analysis of cerebrospinal fluid (CSF) samples in participants with mild cognitive impairment (MCI) due to Alzheimer's disease (AD).
Methods: CSF samples were collected in the delayed-start FLICKER clinical trial (NCT03543878) at baseline, 4- and 8-weeks follow-up time points from participants with MCI (n=5 per arm) recruited from the Emory Goizueta Alzheimer's Disease Research Center (ADRC) who received 4 or 8 weeks of daily, one-hour treatment using Cognito Therapeutics medical device. Proteomic quantification and analysis were conducted using tandem-mass tag mass spectrometry (TMT-MS) of CSF samples. CSF proteome of FLICKER participants were compared to within-study pooled AD and healthy control CSF reference standards from the Goizueta ADRC to benchmark baseline protein levels of participants (Johnson et. al., 2022) and, to assess treatment effects, via differential expression analysis (one-way ANOVA; $p<0.05$).
Results: A total of 2,785 CSF proteins were analyzed across all CSF samples. Differential expression analysis of proteins from baseline (n=5) versus treatment (n=5, 8 weeks), normalized for baseline CSF proteomes, revealed 110 proteins that met the significance threshold ($p<0.05$, no FDR correction), with 60 proteins upregulated and 50 proteins downregulated as result of treatment. 52 of the significant proteins were classified into 12 brain-derived AD modules. Treatment had a significant impact on CSF proteins linked to AD pathologies represented by brain modules related to Synapse/Neuron (M1), Oligo/Myelination (M3), Post-Synaptic Density (M5), Complement-System/Acute Phase (M26), and Neurotransmitter Regulation (M36).
Conclusions: Unbiased CSF proteomic analysis in MCI-AD patients demonstrated that evoked gamma oscillation by Cognito Therapeutics medical device resulted in treatment-driven upregulation and downregulation of proteins associated with AD pathology, including effects on synaptic regulation, glial function and immunological responses.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0328 / #663

Poster Topic: *Theme A: β-Amyloid Diseases / A03.l. Drug Development, Clinical Trials: Regulatory aspects, Other*

DE-RISKING CLINICAL TRIAL DESIGN VIA MODEL-INFORMED DRUG DEVELOPMENT WITH THE CRITICAL PATH FOR ALZHEIMER'S DISEASE CONSORTIUM

POSTERS: A03.L. DRUG DEVELOPMENT, CLINICAL TRIALS: REGULATORY ASPECTS, OTHER

Sudhir Sivakumaran[1], Yashmin Karten[1], Nicholas Cullen[1], Corissa Lau[1], Eileen Priest[1], Hazel White[1], Michael Irizarry[2]
[1]Critical Path Institute, Critical Path For Alzheimer's Disease, Tucson, United States of America, [2]Eisai, Inc, Neurology Business Group, Nutley, United States of America

Aims: The Critical Path for Alzheimer's Disease (CPAD) consortium serves as a pre-competitive, neutral convenor to generate novel, regulatory endorsed quantitative drug development tools and solutions that are made freely available to the public. These tools accelerate drug development by de-risking key decisions in clinical trial planning.
Methods: Patient-level data from contemporary Phase II and III Alzheimer's disease (AD) clinical trials and observational studies make up the CPAD integrated database. This diverse collection of datasets is harmonized and relevant statistical model specifications (based on cognitive outcomes, biomarker modalities, study populations, etc.) are identified. Disease progression models are then fitted using subsets of the CPAD database matching these specifications. With the fitted disease progression models, clinical trial simulations are then developed by applying clinical trial dynamics such as treatment effect, placebo effect, and dropout. Finally, by altering key trial design parameters such as inclusion criteria, trial length, and visit frequency, we can better understand how trial design decisions affect clinical trial outcomes.
Results: As of August 2023, CPAD's data repository contains 73 studies with 100,812 individual anonymized patient records, with a rich source of key AD biomarkers (biofluids and imaging). Different mixed effects models have been developed with cognitive scales as outcome and different biomarker modalities (e.g., PET + MRI, CSF, and plasma) as baseline predictors. A comprehensive clinical trial simulation tool which builds on these disease progression models has been developed and made available. Additionally, harmonization of tau PET results and their impact on cognition along the Alzheimer's disease continuum have been evaluated.
Conclusions: The precompetitive collaboration pioneered by CPAD is fundamental to the generation of actionable tools for accelerating and advancing AD drug development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0329 / #2182

Poster Topic: *Theme A: β-Amyloid Diseases / A03.k. Drug Development, Clinical Trials: Non-pharmacological interventions*

PRESERVATION OF BRAIN STRUCTURE AND FUNCTION IN OLDER EXPERT MEDITATORS: LINKS TO COGNITION, PSYCHOLOGICAL AND LIFESTYLE FACTORS

POSTERS: A03.K. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS

Sacha Haudry[1], Brigitte Landeau[1], Julie Gonneaud[1], Antoine Lutz[2], Gaëlle Chételat[1]
[1]Normandie Univ, UNICAEN, Inserm, U1237, Phind "physiopathology And Imaging Of Neurological Disorders", Neuropresage Team, Cyceron, Caen, France, [2]CNRL, Lyon Neuroscience Research Center, Inserm U1028, CNRS UMR 5292, Rhône, Lyon, France

Aims: Objectives: Meditation is a mental training approach for stress reduction and attention and emotion regulation. It is expected to improve mental health and well-being in ageing, and reduce age-related decline in brain structural and functional integrity; altogether contributing to reduced risk for Alzheimer's disease. We hypothesize that long-term meditation will be associated with more preserved brain structure and function with age compared to meditation-naive controls.
Methods: Methods: 25 expert meditators (ExpMed) with > 20 years of meditation practice and 135 cognitively unimpaired meditation-naive older adults (HC) from the Age-Well cohort (all ≥65 years old) were included. All participants underwent neuroimaging, cognitive, psychological and lifestyle assessments. ExpMed were compared with HC on structural MRI and brain perfusion maps. Amongst regions showing significant between-group differences, stepwise regressions were conducted to assess i) which meditation composite score or lifestyle factor best predicted these differences and ii) which regions best predicted cognitive and psychological variables.
Results: Results: ExpMed had significantly higher volume in inferior frontal, orbitofrontal and posterior cingulate cortex as well as higher perfusion in temporo-occipito-parietal areas including the hippocampus, amygdala, temporal and angular gyrus. Higher meditation composite score and engagement in complex mental activities were associated with greater volume and perfusion in brain areas themselves associated with better working memory and attention performances and, higher self-compassion and emotion regulation.
Conclusions: Conclusions: Long-term meditation practice is associated with more preserved brain volume and perfusion in a fronto-parietal network as a result of attention, emotion regulation and introspection training. These brain changes have positive impact on cognition and psychological factors. Engagement in complex mental activities such as meditation practice could contribute to cerebral preservation in older adults.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0330 / #1500

Poster Topic: *Theme A: β-Amyloid Diseases / A03.l. Drug Development, Clinical Trials: Regulatory aspects, Other*

CLINICIAN SPECIALTY AND LOCATIONAL VARIATIONS BASED ON PRESCRIPTION PATTERNS FOR US VETERANS WITH ALZHEIMER'S DISEASE

POSTERS: A03.L. DRUG DEVELOPMENT, CLINICAL TRIALS: REGULATORY ASPECTS, OTHER

Brant Mittler[1], Joel Reisman[2], Byron J Aguilar[2], Dan Berlowitz[3], Qinqing Li[4], Raymond Zhang[5], Amir Monfared[5], Quanwu Zhang[6], Weiming Xia[7]
[1]VA San Antonio Healthcare System, Geriatric Research and Clinical Center, Medicine/geriatrics, San Antonio, United States of America, [2]VA Bedford Healthcare System, Geriatric Research and Clinical Center, Center For Healthcare Organization & Implementation, Bedford, United States of America, [3]University of Massachusetts, Department Of Public Health, Lowell, MA, United States of America, [4]University of Edinburg, Department Of Mathematics, Edinburg, United Kingdom, [5]Eisai, Inc., Alzheimer's Disease And Brain Healthe, Nutley, United States of America, [6]Eisai, Inc., Alzheimer's Disease And Brain Healthe, Nutley, NJ, United States of America, [7]University of Massachusetts, Department Of Biological Sciences, Lowell, MA, United States of America

Aims: This study aims to determine if there are variations in access to specialty care over metropolitan locations based on prescription patterns among US Veterans with Alzheimer's disease.
Methods: A cohort of Veterans with probable AD who had received any prescription in the Veterans Affairs (VA) Healthcare System was evaluated based on the United States Census metropolitan areas: non-metropolitan, small-, medium-, large fringe-, and large central-metro areas. Clinician specialties were determined using information in the VA personnel records.
Results: There were 83,909 Veterans with AD who had ≥1 prescriptions for any drug from VA clinicians in 2019, and this number was not significantly changed from 2012 (83,350). During Fiscal Year 2019, 19%, 11%, 25%, 22% and 23% of AD patients resided in non-metropolitan, small-, medium-, large fringe-, and large central-metro regions, respectively. Among clinician types, 64.4% were primary care clinicians, 25.1% were psychiatrists, 5.5% were neurologists, and 5.0% were geriatricians. Thus, among the clinicians who serve Veterans with AD, only 35% were qualified to prescribe anti-amyloid therapy in the VA. The majority (74%) of prescriptions written by neurology, psychiatry, and geriatric specialists were generated in medium to large metropolitan areas as opposed to small-metro or non-metropolitan areas.
Conclusions: This study reveals variations in treatment access to clinician specialists over metropolitan areas among US Veterans with AD. Given that anti-amyloid treatment in the VA can only be prescribed by AD specialists, these variations may result in limited access to anti-amyloid treatments, especially in non-metro and small-metro areas.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0331 / #2260

Poster Topic: *Theme A: β-Amyloid Diseases / A03.l. Drug Development, Clinical Trials: Regulatory aspects, Other*

IN ALZHEIMER'S DISEASE STUDY RECRUITMENT, SCHEDULING LAG IMPACTS PRE-SCREEN ATTENDANCE, CANCELLATION, AND NO-SHOW RATES

POSTERS: A03.L. DRUG DEVELOPMENT, CLINICAL TRIALS: REGULATORY ASPECTS, OTHER

Yu-Jay Huoh, Brenda Martinez, Elly Lee, Ralph Lee
Irvine Clinical Research, Irvine Clinical Research, Irvine, United States of America

Aims: In this study, we examined the impact of the number of days between when a prescreening appointment is created and the actual scheduled date (“scheduling lag”) on key recruitment metrics - attendance, cancellation, and no-show rates - in potential Alzheimer's Disease study participants.
Methods: Between January and August 2023, 2,322 potential Alzheimer's Disease study participants were scheduled for prescreening appointments. These potential participants were recruited through advertisements on Facebook, Instagram, and Google. After a brief phone screen for basic eligibility criteria, in-person prescreening appointments were scheduled. Reminder messages were sent in the days leading up to the appointment.
Results: The prescreening appointments were scheduled anywhere from same day up to 21 days in the future. Mean scheduling lag was 10.5 days (median 9 days, SD 5.9 days). Scheduling lag had a conclusively significant impact on nearly every performance metric - attend rate ($\beta = -0.034$, $P < 0.00001$), cancellation rate ($\beta = 0.035$, $P < 0.0001$), no show rate ($\beta = 0.038$, $P < 0.00001$). This was driven by sharp performance improvements for appointments scheduled within five to seven days.
Conclusions: Research sites are increasingly relying on advertising to recruit trial participants for traditionally difficult-to-recruit-for conditions, such as Alzheimer's Disease. Because of this shift, sites need to monitor how cost-effective these campaigns are. A key driver for successful recruitment is attendance rate (and a reduction in cancellation/no-shows), and sites can improve this by decreasing scheduling lag to less than seven days.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0332 / #2181

Poster Topic: *Theme A: β-Amyloid Diseases / A03.l. Drug Development, Clinical Trials: Regulatory aspects, Other*

THE EVOLUTION OF RANDOMIZED CONTROLLED TRIALS IN ALZHEIMER'S DISEASE

POSTERS: A03.L. DRUG DEVELOPMENT, CLINICAL TRIALS: REGULATORY ASPECTS, OTHER

Joseph Therriault[1], Angela Kwan[1], Etienne Aumont[1], Joao Pedro Ferrari-Souza[2], Marcel Woo[1], Saman Arfaie[1], Serge Gauthier[1,3], Pedro Rosa-Neto[1]
[1]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [2]University of Pittsburgh, Psychiatry, Pittsburgh, United States of America, [3]McGill University, Neurology And Neurosurgery, Montreal, Canada

Aims: To describe the key features of RCT design for interventions in AD and their changes over time.
Methods: We performed a literature review to identify phase II and phase III RCTs of Alzheimer's disease in Pubmed, Scopus and Medline. Key features of RCT design, target population and funding were extracted from published reports. Key design features were analyzed with respect to time using regression and chi-square analyses.
Results: The study included 182 RCTs testing interventions in AD. The most common endpoint was the Clinical Dementia Rating Sum-of-Boxes. The average sample size of RCTs increased substantially over time (165% increase from 1992 to 2022), as did average trial duration (119% increase from 1992 to 2022). An increase in studies testing disease-modifying treatments was observed over time in contrast to symptomatic treatments. A substantial increase in the proportion of studies funded by the pharmaceutical industry was observed, with over 75% of RCTs in AD since 2007 being funded by the pharmaceutical industry.
Conclusions: This study noted substantial changes in the key features of AD clinical trials from 1992-2022. RCTs in AD are now larger and longer and are correspondingly powered to detect smaller clinical differences. The AD research community needs a better understanding of what constitutes clinically meaning changes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0333 / #1983

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

INVESTIGATING AMYLOID PRECURSOR PROTEIN METABOLITES IN CSF IN RELATION TO NEUROIMAGING MARKERS

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Zina Abed Al Sattar[1], Emir Basic[1,2], Francesco Locatelli[1,2], Johan Svensson[3], Anders Wallin[1,2], Petronella Kettunen[1,2]
[1]University of Gothenburg, Neuroscience And Physiology, Gothenburg, Sweden, [2]Sahlgrenska University Hospital, Psychiatry, Cognition And Old-age Psychiatry, Mölndal, Sweden, [3]Sahlgrenska University Hospital, Internal Medicine And Clinical Nutrition, Gothenburg, Sweden

Aims: The Gothenburg Mild Cognitive Impairment (MCI) study is a mono-center study of patients seeking help for cognitive complaints at the memory clinic at Sahlgrenska University Hospital. Manifest dementia in patients, including Alzheimer's disease (AD), subcortical small-vessel disease (SSVD) and mixed AD/SSVD (MIX), is diagnosed based on medical history, MRI, checklists and instruments for cognitive symptoms, including scores for the Mini Mental State Examination and the Clinical Dementia Rating. Moreover, cerebrospinal fluid (CSF) AD biomarkers amyloid-β (Aβ) 1-42, total tau (t-tau) and hyperphosporylated tau (p-tau181), as well as Aβx-38, Aβx-40, Aβx-42, and soluble amyloid precursor protein (sAPP) α and β have been analyzed for the patients, although these are not used for diagnosis. In this project, we investigated the correlation between these CSF biomarkers and brain structure volumes in patients with preclinical and manifest disease.
Methods: Subjects included controls, subjective cognitive impairment (SCI), MCI, AD, MIX, SSVD. AD pathology was assessed for all patients according to the International Working Group for New Research Criteria for the Diagnosis of AD (IGW-2). The applied cut-offs indicating AD pathology in CSF were t-tau > 350 ng/L, p-tau181 > 59 ng/L, and Aβ1-42 < 530 ng/L. Correlations between brain volumes and biomarker levels were done using Spearman correlation and predictions were performed using linear regression with covariates.
Results: Our preliminary analysis showed that several of the CSF biomarkers analyzed correlated with volumetric MRI data in our cohort. For example, the ratios of Aβx-42/x-38 and Aβx-42/x-40 correlated with entorhinal cortex volumes, as well as hippocampal volumes.
Conclusions: Our findings confirms that CSF biomarkers can reflect the neurodegenerative processes in the brain as measured with MRI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0334 / #2077

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

SEVERITY OF SLEEP DISORDERS IS ASSOCIATED WITH NEUROINFLAMMATION AND MEDIATES THE RELATIONSHIP BETWEEN GLYMPHATIC SYSTEM FUNCTIONING AND WHITE MATTER INTEGRITY

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Ariane Delgado Sanchez[1], Natalia Cullell[2], Giovanni Caruana[3], Andrea Elias[3], Nicola Ray[1], Sonia Correa-Muller[4], Jurek Krupinski[2]
[1]Manchester Metropolitan University, Department Of Psychology, Manchester, United Kingdom, [2]Fundació Docència i Recerca Mútua Terrassa, Stroke Pharmacogenomics And Genetics, Terrassa, Barcelona, Spain, [3]Fundació Docència i Recerca Mútua Terrassa, Department Of Radiology, Terrassa, Barcelona, Spain, [4]Manchester Metropolitan University, Department Of Life Sciences, Manchester, United Kingdom

Aims: Obstructive sleep apnoea (OSA) is associated with increased risk of developing Alzheimer's disease (AD). White matter (WM) changes due to neuroinflammation and/or neurodegeneration are suggested to be an early event in AD and have been detected in OSA. It is possible that integrity of the glymphatic system (a brain-wide waste clearance system that is activated during sleep) underpins these relationships. We therefore explore relationships between glymphatic health, severity of OSA and neurodegeneration and neuroinflammation in whole-brain WM.
Methods: 22 participants with mild cognitive impairment completed polysomnography, anatomical MRI and diffusion tensor imaging (DTI). OSA severity was measured via the number of apnoea/hypoapnoea episodes per hour. Glymphatic health was measured via the DTI-ALPS index (analysis along the perivascular space index). Neuroinflammation and neurodegeneration in WM were measured via free water (FW) volume and free water-corrected fractional anisotropy (cFA), respectively. Tract Based Spatial Statistics were computed to examine relationships between OSA severity and glymphatic health, and WM integrity.
Results: We did not observe a relationship between OSA severity and the ALPS index. However, OSA severity was correlated with FW volume, but not cFA across widespread WM regions. Conversely, the ALPS index was correlated with cFA, but not FW cross widespread white matter regions. In follow-up analyses, the relationship between ALPS and cFA was mediated by OSA severity.
Conclusions: OSA may increase neuroinflammation in WM, while structural degeneration in WM may depend on impaired glymphatic health. Whether OSA eventually leads to impaired glymphatic function and neurodegeneration in later disease stages is supported by the finding that OSA severity mediated the relationship between ALPS and cFA. These conclusions support the use of treatments for sleep disorders for prevention of neuroinflammation and neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0335 / #1429

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

THE DEGENERATION OF LOCUS COERULEUS OCCURRING DURING ALZHEIMER'S DISEASE PROGRESSION: A NEUROIMAGING FOLLOW-UP INVESTIGATION

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Alessandro Galgani[1], Francesco Lomabrdo[2], Francesca Frija[2], Nicola Martini[2], Gloria Tognoni[3], Gabriele Siciliano[3], Nicola Pavese[4,5], Filippo Giorgi[1]
[1]University of Pisa, Department Of Translational Research And Of New Surgical And Medical Technologies, Pisa, Italy, [2]Fondazione Monasterio, Department Of Radiology, Pisa, Italy, [3]University of Pisa, Department Of Clinical And Experimental Sciences, Pisa, Italy, [4]Newcastle University, Translational And Clinical Research Institute, Newcastle, United Kingdom, [5]Aarhus University, Clinical Medicine - Department Of Nuclear Medicine And Pet, Aarhus N, Denmark

Aims: To assess the longitudinal evolution of Locus Coeruleus Magnetic Resonance Imaging (LC-MRI) parameters and their association with clinical progression in patients with Alzheimer's Disease (AD).
Methods: Twelve AD demented (ADD) patients and 45 Mild Cognitive Impaired (MCI) individuals underwent a baseline and a 2.5-year follow-up LC-MRI scan. MCI individuals were classified as converter (cMCI = 19) or non-converter (ncMCI = 26) ones at the end of the clinical follow-up, based on whether or not they converted to dementia. Using a standardized template-based approach, LC-MRI parameters were extracted, namely Locus Coeruleus Contrast Ratio (LC_{CR}) and Locus Coeruleus-belonging voxels (LC_{VOX}).
Results: Both LC-MRI parameters were reduced during follow-up across the whole population ($p<0.001$), and in all the diagnostic groups, apart from LC_{VOX} in the AD group. Linear mixed models (LMMs) analysis confirmed the reduction of LC-MRI parameters over time ($p<0.001$) and showed an association with the severity of the diagnosis. LMMs showed that both LC_{CR} and LC_{VOX} were more markedly reduced in ADD patients ($p = 0.022$ for LC_{CR} and $p = 0.006$ for LC_{VOX}) and cMCI individuals ($p = 0.002$ for LC_{CR} and $p= 0.001$ for LC_{VOX}) than in ncMCI ones. This trend was also found considering LC subregions, with the rostral LC and the left LC showing higher levels of statistical significance.
Conclusions: Our results show, for the first time in vivo in humans, the progressive degeneration the LC suffers from, during the progression of AD. They are also in line with previous neuropathological *post-mortem* data, and this supports the reliability of LC-MRI as a tool to explore the integrity of the central noradrenergic system in patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0336 / #2872

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

DATA-DRIVEN NEUROANATOMICAL SUBTYPE CLASSIFICATION IN NON-DEMENTED ELDERLY COHORT

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Na Young Shin[1], Woo Jung Kim[2], Jihye Choi[1]
[1]Yonsei University College of Medicine, Department Of Radiology, Seoul, Korea, Republic of, [2]Yongin Severance Hospital, Yonsei University College of Medicine, Psychiatry, Yongin, Korea, Republic of

Aims: Given the heterogeneous cognitive outcome of subjective cognitive decline (SCD) and mild cognitive impairment (MCI), this study aimed to identify neuroanatomical subtypes among non-demented elderly individuals using unsupervised, data-driven cluster analysis and to investigate the longitudinal trajectories of cognitive function.
Methods: A total of 148 community-dwelling non-demented elderly individuals (aged 62-79, control = 64, SCD = 60, MCI = 22) underwent 3-dimensional T1-weighted imaging, clinical assessments for SCD and depression, and neuropsychological assessments. Among them, 137 participants were followed up for an average of 2.33 ± 0.06 years. We conducted hierarchical cluster analysis on brain volumes of 84 regional areas and examined the cognitive and neuroanatomical characteristics of the identified subtypes. We employed linear mixed models to evaluate whether the proposed subtypes were more effective than the clinical diagnosis in predicting longitudinal changes in cognitive function.
Results: We identified three anatomical subtypes. Cluster 1 exhibited larger brain volumes and superior cognitive performance compared to the other clusters. Transitioning from Cluster 1 to Cluster 3, brain volumes and cognitive function gradually decreased. While Cluster 2 demonstrated intermediate cognitive performance, individuals in this subtype had the most severe SCD and depressive symptoms among the three clusters. Regarding cognitive changes, 40%, 60.4%, and 70% of Cluster 1, 2, and 3 experienced cognitive decline, respectively, while 67%, 64%, and 36% of control, SCD, and MCI individuals showed cognitive decline. The proposed subtypes (AIC = 36.525) showed a marginal improvement in predicting cognitive changes over a 2-year period compared to the clinical diagnosis (AIC = 41.053).
Conclusions: Our study suggests that the data-driven neuroanatomical subtype classification might be useful to reflect clinical and cognitive characteristics and predict future cognitive outcome in non-demented elderly population.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0337 / #1866

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

EVALUATING THE RELATIONSHIP BETWEEN OXYGEN EXTRACTION FRACTION (OEF), TAU AND AMYLOID PATHOLOGY, AND COGNITIVE STATUS IN ALZHEIMER'S DISEASE

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Seyyed Ali Hosseini[1], Stijn Servaes[1], Joseph Therriault[1], Cécile Tissot[1], Nesrine Rahmouni[1], Arthur Macedo[1], Firoza Lussier[2], Jenna Stevenson[1], Yi-Ting Wang[1], Jaime Fernandez Arias[1], Kely Quispialaya[1], Etienne St-Onge[1], Alyssa Stevenson[1], Serge Gauthier[1], Junghun Cho[3], David Rudko[1], Tharick A Pascoal[4], Pedro Rosa-Neto[1]
[1]Mcgill University, Neurology & Neurosurgery, Montréal, Canada, [2]University of Pittsburgh, Psychiatry, Pittsburgh, United States of America, [3]University at Buffalo, The State University of New York, Biomedical Engineering, New York, United States of America, [4]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America

Aims: Oxygen Extraction Fraction (OEF) is a measure of the proportion of oxygen that is removed from the blood as it flows through the brain's vascular system. This study aims to explore the role of OEF in Alzheimer's Disease (AD) using Magnetic Resonance Imaging (MRI). We specifically focus on examining the relationships between OEF and cognitive status across different age groups.
Methods: A diverse cohort of 347 participants was analyzed, including young controls (Y: n=37), Cognitively-Unimpaired older adults (CU_{65+}: n=182), individuals with Mild Cognitive Impairment (MCI: n=80), and AD patients (n=48). All subjects underwent tau-PET, amyloid-PET, and 3D gradient-recalled echo sequence MRI scans. A pipeline for generating OEF maps was constructed using TRIAD cohort preliminary data. The OEF maps were subsequently registered to the Montreal Neurological Institute (MNI) space for Region-Of-Interest (ROI) and voxel-based analyses.
Results: We observed a marked decrease in OEF values across multiple brain regions when progressing from young controls to CU, MCI, and AD groups, distinctly highlighting the age effect (Figure1). This age-related decline was especially significant and consistent, suggesting that age serves as a strong modulator for OEF values in the brain. Age-related cortical differences were further substantiated, revealing that older age groups, particularly those with MCI and AD, showed more pronounced changes in OEF, suggesting an age-dependent vulnerability to cerebral metabolic disruptions (Figure2).

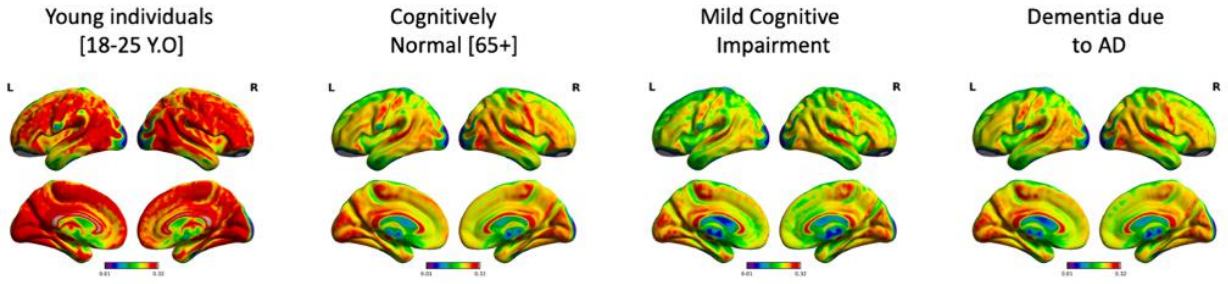


Figure1: Average OEF images

Model: OEF ~ tau + Amyloid + COV.

- COV : age, sex, Apoe4
- **(Y:** n=37), (CU_{65+}: n=182), (MCI: n=80), and (AD: n=48).
- T-statistical parametric maps were corrected for multiple comparisons using a random field theory cluster threshold of P < .001, overlaid on the Montreal Neurological Institute reference template.

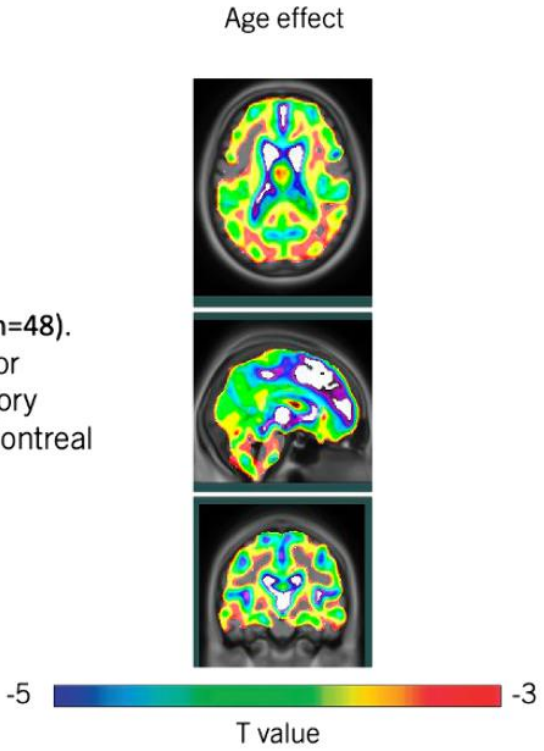


Figure2. AGE related cortical Differences

Conclusions: Our study emphasizes the potential of MRI-measured OEF as an age-sensitive marker for understanding Alzheimer's Disease. While no direct associations were identified between OEF and traditional pathological markers, our results point to the significant impact of age on OEF levels. This suggests that age may be a critical factor influencing cerebral metabolism and blood flow changes in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0338 / #1623

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

EFFECTS OF DEFACING PROGRAMS ON THE REGIONAL BRAIN VOLUME SEGMENTATION

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Dongwon Yang[1], Chunghwee Lee[1], Jung Hee Cho[1], Dong-Woo Ryu[1], Yongsoo Shim[2], Yun Jeong Hong[3], Seonggyu Kim[4], Jong-Min Lee[5]
[1]The Catholic University of Korea, Neurology, Seoul, Korea, Republic of, [2]Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea,, Neurology, Seoul, Korea, Republic of, [3]Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Neurology, Uijeongbu-si, Korea, Republic of, [4]Hanyang University, Electronic Engineering,, Seoul, Korea, Republic of, [5]Hanyang University, Biomedical Engineering, Seoul, Korea, Republic of

Aims: In brain MRI research, data sharing with collaborators can raise privacy concerns. Defacing allows for the dissemination of this data without compromising participants' identities. Brain MRI defacing, the process of obscuring facial features in these images for privacy protection, has been shown to potentially affect the accuracy of brain volume calculations in certain studies. In this study, we compared three available brain MRI defacing programs to evaluate their accuracy in volumetric analysis.
Methods: 3D T1 MRI scans from 10 subjects (age: 71.1±6.1) diagnosed with subjective cognitive decline were processed using defacing programs: FreeSurfer, BioImage Suite Web, and De-facer. Both the original non-defaced and defaced images from these programs were analyzed with the FreeSurfer and the Quick Brain Volumetry (QBraVo) program, based on SPM8 and MATLAB. The accuracy of brain segmentation was assessed by comparing the Total Intracranial Volume (TIV), Whole Brain Volume (WBV), Cortical Volume(CV), and Hippocampal Volume (HV) using the Intra-class Correlation Coefficient (ICC).
Results: The TIV for the non-defaced images, FreeSurfer, BioImage Suite Web, and De-facer were highly similar. The ICC for TIV across the four image datasets was 0.998($p<0.001$) for FreeSurfer and 0.999 ($p<0.0001$) for QBraVo. The WBV values for these datasets also demonstrated consistency, with an ICC of 0.997 ($p<0.0001$) and 0.999(p,0.001). HV displayed similar value trends, with ICCs of 0.993 ($p<0.0001$) for FreeSurfer and 0.992 ($p<0.0001$) for QBraVo, respectively.
Conclusions: All three defacing programs demonstrated successful defacing outcomes and delivered reliable volumetric results in FreeSurfer and QBraVo analysis. Among them, De-facer exhibited superior defacing image quality. While both FreeSurfer and De-facer operate on the Linux system, necessitating a prolonged training period, the BioImage Suite Web defacing program is designed for the Windows system and needs short training time.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0339 / #2682

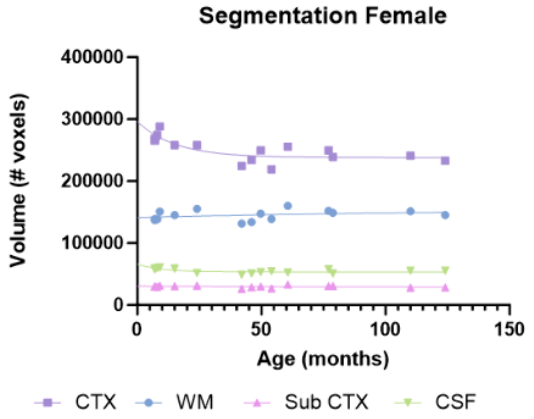
Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

MRI ASSESSMENT OF HEALTHY AGING TRAJECTORIES OF THE MARMOSET BRAIN

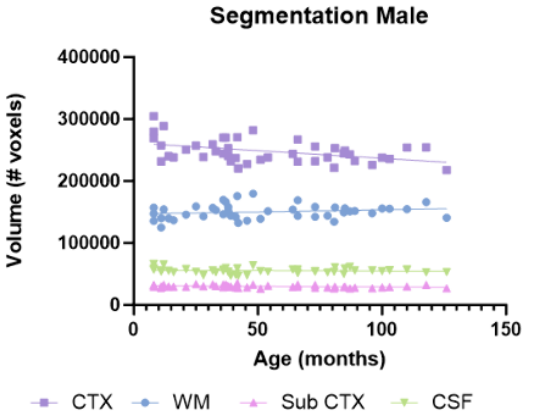
POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Diego Szczupak[1], Rebecca Bhik-Ghanie[1], Bei Zhang[1], Daniel Papoti[1,2], Vinicius Campos[3], Lauren Dubberly[1], Thomas Hitchens[1], Frank Yeh[4], David Schaeffer[1], Stacey Sukoff Rizzo[1,5], Afonso Silva[1]
[1]University of Pittsburgh, Neurobiology, Pittsburgh, United States of America, [2]São Bernardo do Campo, Universidade Federal Do Abc, Rua Arcturus, 03 – Jardim Antares, São Paulo, Brazil, [3]University of São Paulo, Department Of Electrical And Computer Engineering, Sao Carlos, Brazil, [4]University of Pittsburgh, Department Of Neurological Surgery, Pittsburgh, United States of America, [5]University of Pittsburgh, Department Of Geriatric Medicine, Aging Institute, Pittsburgh, United States of America

Aims: Objective: The common marmoset (C*allithrix jacchus*) is an important animal model in neuroscience and neurological diseases (e.g., Alzheimer's disease - AD), as they present primate-specific evolutionary features such as an expanded frontal cortex. Here, we aim to characterize healthy aging trajectories for a population of marmosets.
Methods: Methods: We imaged a cohort of 59 marmosets (45 males, 14 females) across the lifespan (8 to 150 months) using a dedicated 9.4T 30cm bore MRI scanner (Bruker BioSpin Corp, Billerica). The animals were anesthetized under isoflurane anesthesia. High-resolution (250 µm isotropic) T1-, T2-, and diffusion-weighted structural MRI were acquired. The brain images were aligned and registered to the Marmoset Brain Mapping V3 template, the brain was segmented into cortical (CTX) and subcortical (SUB CTX) grey matter, white matter (WM), and cerebral spinal fluid (CSF), and voxel-based-morphometry was used to quantify regional brain volume in the left and right hemispheres.
Results: Results: We discovered a decrease in grey matter volume in both males and females with age (Figure 1), reflected by the volume reduction in several cortical and subcortical brain regions in both sexes. Overall, we discovered that age affects female marmoset brains (38 CTX and 5 SUB CTX regions) more than males (15 CTX and 2 SUB CTX regions). We found no significant age-dependent changes in WM and CSF.
Conclusions: Conclusions: Our work is the first to thoroughly describe the normal aging of the marmoset brain, a valuable model for age-related neuropathologies (e.g., AD). This research will set the normal parameters for marmoset aging and will be vital for generating transgenic marmoset models for AD, which is the goal of the MARMO-AD consortium.



	WM	CTX	Sub CTX	CSF
R squared	0.09697	0.6459		0.5103



	WM	CTX	Sub CTX	CSF
R squared	0.03432	0.1834	0.1146	0.01195

Figure 1. Voxel-based-morphometry of marmoset brains across the lifespan. Volume of White matter (WM), Cortical grey matter (CTX), Subcortical grey matter (SUB CTX), and Cerebrum spinal fluid (CSF) of 59 marmosets (45 males and 14 females) across the lifespan.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0340 / #1584

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

LEVERAGING COMPREHENSIBLE CONVOLUTIONAL NEURAL NETWORKS TO DETERMINE AMYLOID POSITIVITY STATUS VIA MRI SCANS.

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Fedor Levin[1], Devesh Singh[1], Stefan Teipel[1,2], Martin Dyrba[1]
[1]Deutsches Zentrum für Neurodegenerative Erkrankungen e.V. (DZNE), Clinical Dementia Research, Rostock, Germany, [2]Rostock University Medical Center, Department Of Psychosomatic Medicine, Rostock, Germany

Aims: Despite recent advances in the development of antibody treatments targeting amyloid in Alzheimer's disease (AD), some questions still surround their application in a clinical setting, for example the need for the assessment of amyloid accumulation, typically done via amyloid PET or CSF biomarkers. In this study, we aim to apply convolutional neural networks (CNNs) to commonly available magnetic resonance imaging (MRI) scans to select patients at high risk for amyloid positivity for conducting additional clinical assessments.
Methods: Previously, we have developed a deep learning network that allowed detecting AD-related atrophy patterns in MRI scans and visualizing features of brain images that are relevant to the decision of the network. In the current study, we will use MRI scans from participants with subjective memory decline or mild cognitive impairment and available amyloid status data (PET, CSF) of the ADNI study to retrain the CNN models to predict amyloid positivity based on MRI. We will assess the accuracy of classification and examine the spatial distributions of relevance scores to identify brain regions that are key for detecting amyloid positivity status.
Results: The planned analyses will evaluate the feasibility of using CNNs with MRI data for detecting amyloid-positivity, as well as resulting accuracy. We will also assess relevance maps to report brain areas associated with amyloid positivity classifications.
Conclusions: Here, we present ongoing work aiming to use CNNs in combination with relevance maps to determine amyloid positivity using widely available MRI scans. This method may allow physicians to identify patients who will benefit from in-depth diagnostic assessments, such as amyloid PET or CSF analysis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0341 / #2268

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

MICROSTRUCTURAL CHANGES WITHIN BRAINSTEM NUCLEI CORRELATE WITH REM SLEEP WITHOUT ATONIA IN ISOLATED REM SLEEP BEHAVIOR DISORDER: A PILOT STUDY

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Ambra Stefani[1], Stephan Grimaldi[2,3], Firdaus Fabrice Hannanu[3], Kavita Singh[3,4], Guadalupe Garcia-Gomar[3,5], Subhranil Koley[3], Aleksandar Videnovic[1], Marta Bianciardi[3]
[1]MGH, Harvard Medical School, Neurology, Boston, United States of America, [2]University Hospital La Timone, Neurology And Movement Disorders, Marseille, France, [3]Athinoula A. Martinos Center, MGH, Harvard Medical School, Radiology, Charlestown, United States of America, [4]National Institute on Aging, NIH, Multiscale Imaging And Integrative Biophysics Unit, Lbn, Baltimore, United States of America, [5]Universidad Nacional Autónoma de México, Escuela Nacional De Estudios Superiores Unidad Juriquilla, Juriquilla, Mexico

Aims: Isolated REM sleep behavior disorder (iRBD) is characterized by REM-sleep without atonia (RWA). Animal studies show that REM atonia is regulated by brainstem nuclei, in particular the sublaterodorsal/subcoeruleus nucleus and the medullary-reticular-formation. Yet, those mechanisms are understudied in living humans. Aim of this study was to investigate the microstructure of brainstem nuclei in iRBD patients, and to correlate it to RWA indices.
Methods: We acquired 7-Tesla 0.75mm isotropic-resolution T1-weighted MP2RAGE and T2*-weighted GRE in five patients with video-polysomnography-proven iRBD (4m/1f, 66.6±8.2 years). We applied the recently developed in-vivo probabilistic Brainstem Navigator atlas to identify the subcoeruleus nucleus and the inferior medullary-reticular-formation. Then, we calculated the mean signal intensity within these nuclei. RWA was quantified in the chin (phasic, “any” and tonic) and in the flexor digitorum superficialis (FDS) muscles bilaterally in 3-s mini-epochs, according to the Sleep Innsbruck Barcelona (SINBAR) criteria.
Results: Chin tonic activity correlated with T1-weighted values within the left inferior medullary-reticular-formation (r=-0.906, p=0.034) and the left subcoeruleus-nucleus (r=-0.925, p= 0.024). “Any” chin correlated with T1-weighted values within the left subcoeruleus-nucleus (r=-0.879, p=0.049). The SINBAR-index correlated with T1-weighted values within the subcoeruleus-nucleus bilaterally (r=0.943, p=0.016; r=-0.917, p=0.028; right and left, respectively), the in ferior medullary-reticular-formationbilaterally (r=0.891, p=0.043, and r=0.899, p=0.038, left and right), and with T2*-weighted values within the right inferior medullary-reticular-formation(r=0.882, p=0.048). The FDS index correlated with T1-weighted values within the inferior medullary-reticular-formation bilaterally (T1-weighted left r=0.998, p=0.002, right r=0.995, p=0.005; T2* weighted right r=0.986, p=0.014).
Conclusions: Correlation between microstructural changes in the subcoeruleus nucleus and the medullary reticular formation and RWA indices in iRBD support the role of these nuclei in regulation of motor activity during REM sleep, supporting the concept of RWA as biomarker of neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0342 / #2634

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

CONDITIONAL DIFFUSION MODEL-BASED MRI SUPERRESOLUTION ENHANCES ALZHEIMER'S DISEASE CLASSIFICATION

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Youho Myong[1,2], Dan Yoon[3], Young Gyun Kim[3], Yongsik Sim[4], Byung-Mo Oh[2], Sungwan Kim[5]
[1]Seoul National University, Department Of Biomedical Engineering, Seoul, Korea, Republic of, [2]Seoul National University Hospital, Department Of Rehabilitation Medicine, Jongno-gu, Korea, Republic of, [3]Seoul National University, Interdisciplinary Program In Bioengineering, Jongno-Gu, Korea, Republic of, [4]Severance Hospital, Department Of Radiology, Seoul, Korea, Republic of, [5]Seoul National University, Department Of Biomedical Engineering, Jongno-Gu, Korea, Republic of

Aims: To evaluate a novel conditional diffusion model-based MRI superresolution (SR) offers superior image quality than conventional SR, and if they can enhance AI-based Alzheimer's disease (AD) classification performance.
Methods: Two networks were trained. Firstly, a U-Net-based network produced conventional SR images (c3T*). The network comprised two branches: dilated kernels for overall feature extraction and Hough Transformation for detailed feature extraction. The second network employed cDM, integrating U-shaped multi-stream networks with a multi-encoder to produce cDM-based SR images (d3T*) as in Figure 1. Both networks were trained on a subgroup (n=170) of Alzheimer's disease neuroimaging initiative data with both 1.5T and 3T T1WI from the same individuals taken at the same visit. The quality of source, c3T*, and d3T* images were evaluated using peak signal-to-noise ratio (PSNR), Structural Similarity Index (SSIM), Natural Image Quality Evaluator (NIQE), and Blind/Referenceless Image Spatial Quality Evaluator (BRISQUE). To determine if d3T* enhanced AD classification, a U-Net-based AD classifier was employed to classify healthy and AD brains. Classifier performance was evaluated using accuracy, precision, specificity, sensitivity, Matthews Correlation Coefficient (MCC), F1-score, and AUROC.

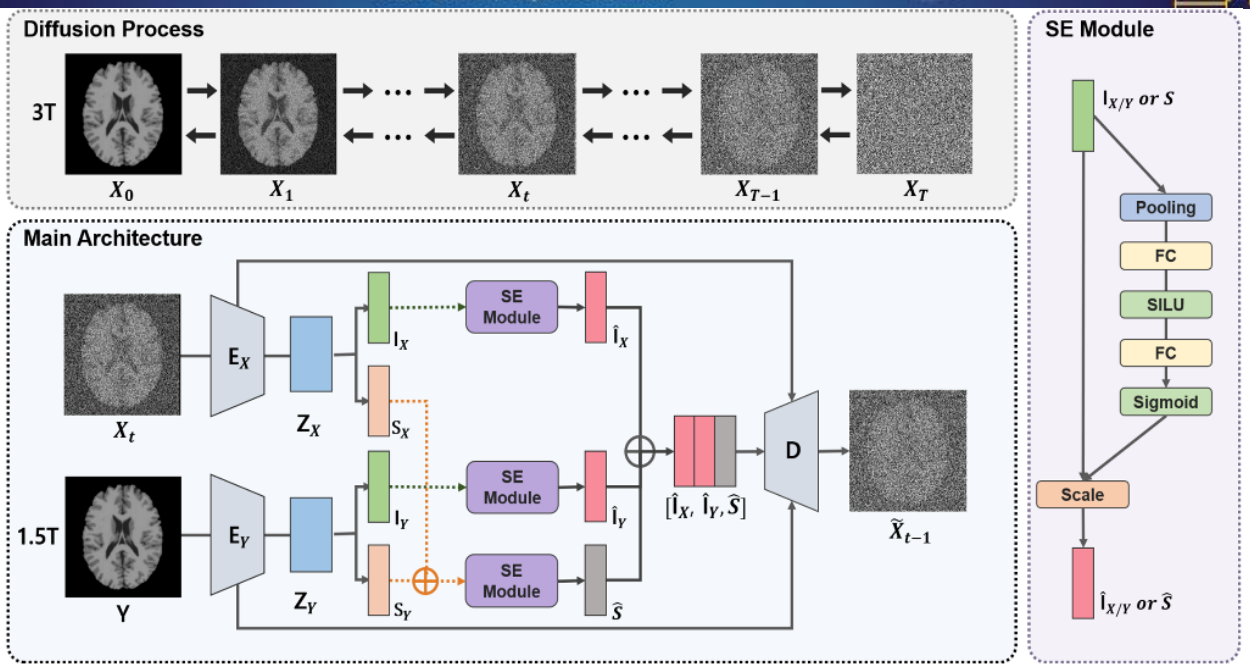


Figure 1. d3T* architecture

Results: Example source, c3T*, and d3T* images are shown in Figure 2. d3T* showed superior image quality than original source or c3T*, comparable to the 3T ground truth (Table 1, Figure 3). When given as input to AD classifier, d3T* MRI resulted in better classification performance than 1.5T images or c3T* counterparts (Table
2).

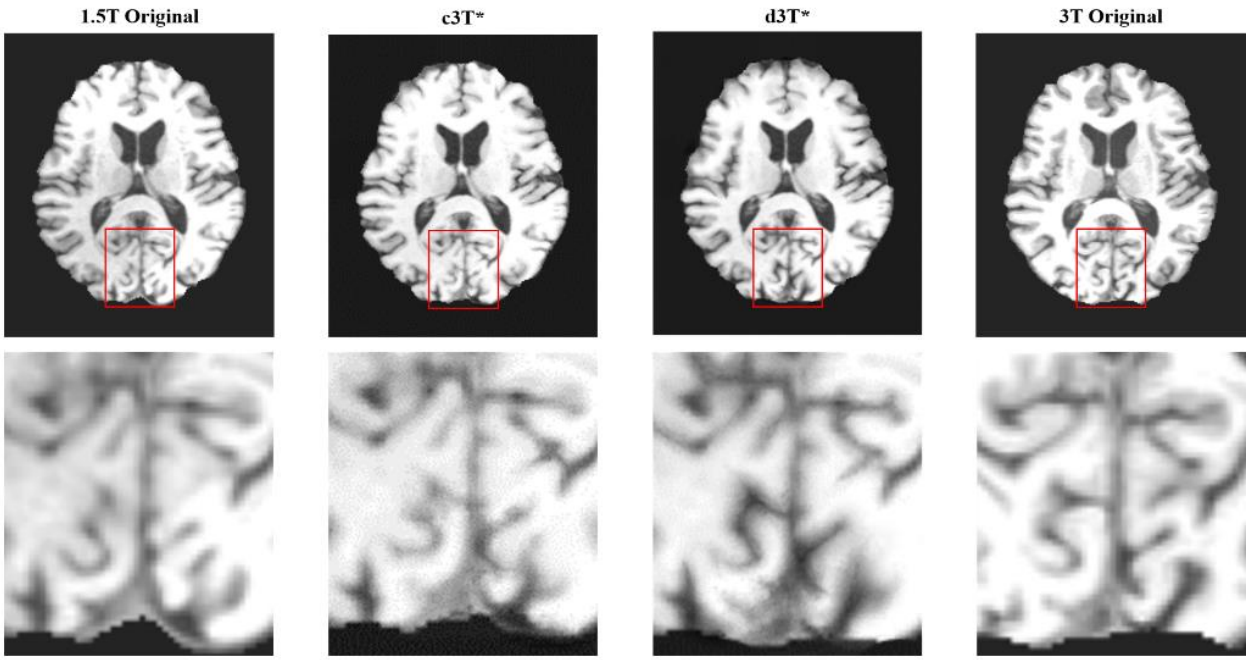
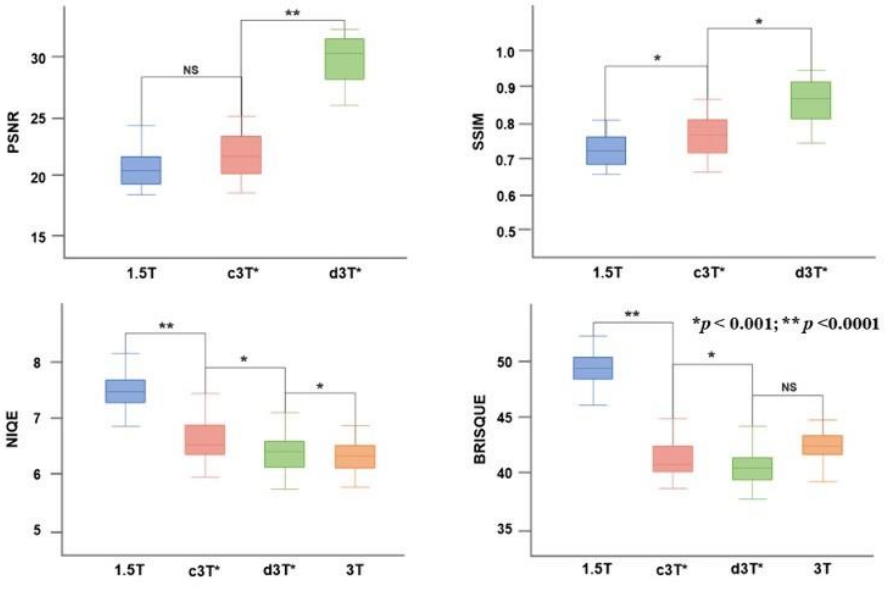


Figure 2. Example source and SR images

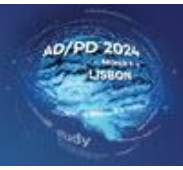


* For PSNR & SSIM, higher values mean better image quality; for NIQE & BRISQUE, lower values mean better quality.

Figure 3. Image quality metrics among source and SR images

Table 1. Alzheimer's Disease Classification Performance

Input	Accuracy	AUROC	Precision	MCC	F1 Score	Sensitivity	Specificity
1.5T	0.87	0.79	0.83	0.68	0.75	0.71	0.94
c3T*	0.83	0.84	0.67	0.63	0.75	0.86	0.81
d3T*	0.91	0.90	0.86	0.79	0.86	0.86	0.94



Conclusions: cDM-based MR SR may be a valuable tool to augment AI-aided AD diagnosis.

P0343 / #2257

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

GENETIC RISKS OF ALZHEIMER'S BY APOE AND MAPT ON CORTICAL MORPHOLOGY IN YOUNG HEALTHY ADULTS

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Li Su
University of Cambridge, Psychiatry, Cambridge, United Kingdom

Aims: Genetic risk factors such as APOE ε4 and MAPT (rs242557) A allele are associated with amyloid and tau pathways and grey matter changes at both early and established stages of Alzheimer's disease, but their effects on cortical morphology in young healthy adults remain unclear.
Methods: 144 participants aged 18 to 24 underwent 3T MRI and genotyping for APOE and MAPT to investigate unique impacts of genetic risk factors in a cohort without significant comorbid conditions such as metabolic and cardiovascular diseases. We segmented the cerebral cortex into 68 regions and calculated the cortical area, thickness, curvature, and folding index. Then, we trained machine learning models to classify APOE and MAPT genotypes using these morphological features. In addition, we applied a growing hierarchical self-organizing maps algorithm, which clustered the 68 regions into 4 subgroups representing different morphological patterns. Then, we performed general linear model analyses to estimate the interaction between APOE and MAPT on cortical patterns.
Results: We found that the classifiers using all cortical features could accurately classify individuals carrying genetic risks of dementia outperforming each individual feature alone. APOE ε4 carriers had more convoluted and thinner cortex across the cerebral cortex. A similar pattern was found in MAPT A allele carriers only in the regions that are vulnerable for early tau pathology. With the clustering analysis, we found a synergetic effect between APOE ε4 and MAPT A allele i.e., carriers of both risk factors showed the most deviation of cortical pattern from the typical pattern of that cluster.
Conclusions: Genetic risk factors of dementia were associated with variations of cortical morphology, which can be observed in young heathy adults more than 30 years before pathology and 50 years before symptoms may begin.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0344 / #755

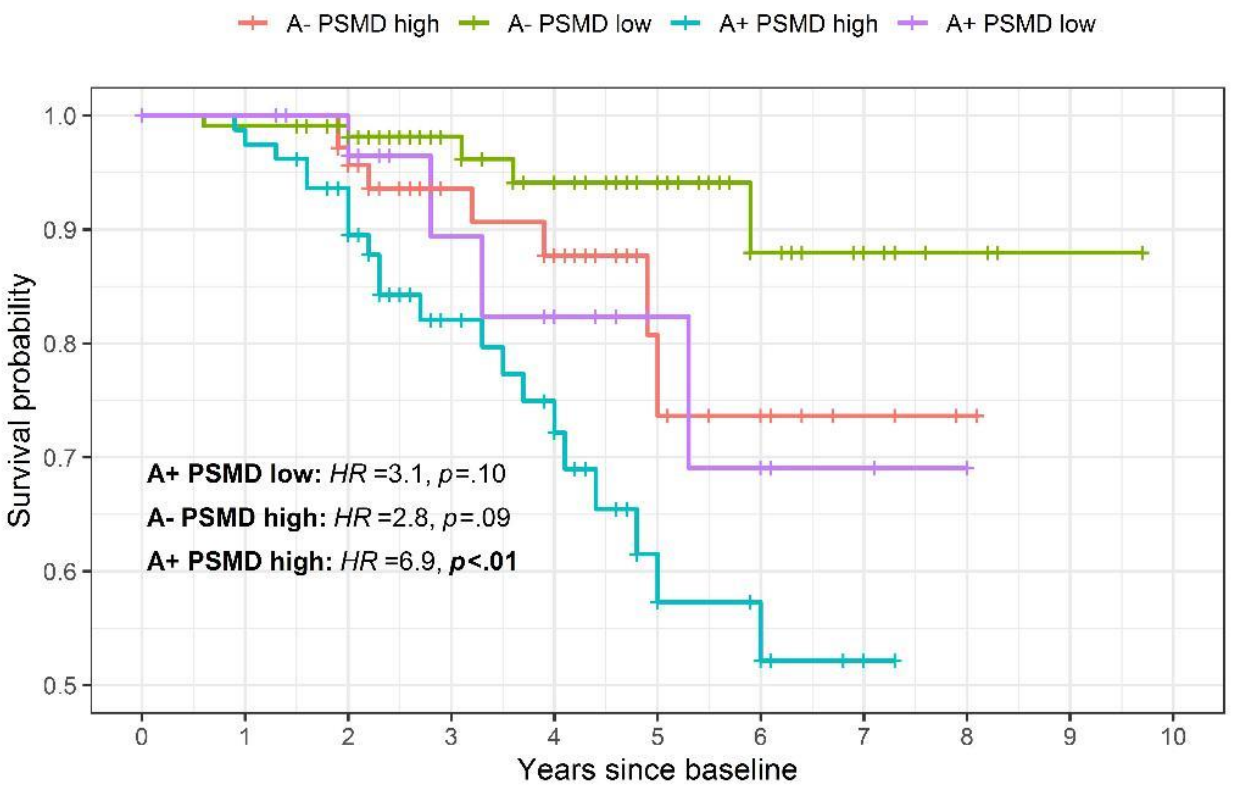
Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

IMPROVING DEMENTIA PROGRESSION PREDICTION: THE ADDED VALUE OF PSMD BEYOND AMYLOID STATUS

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Sandra Tecelão[1], Bjørn-Eivind Kirsebom[1,2], Lene Pålhaugen[1,3], Atle Bjørnerud[4,5], Per Selnes[1,3], Tormod Fladby[1,3]
[1]Akershus University Hospital, Department Of Neurology, Lørenskog, Norway, [2]University Hospital of North Norway, Department Of Neurology, Tromsø, Norway, [3]Institute of Clinical Medicine, Campus Ahus, University Of Oslo, Lørenskog, Norway, [4]Department of Diagnostic Physics, Oslo University Hospital, Oslo, Norway, [5]Department of Physics, University Of Oslo, Oslo, Norway

Aims: Studies have shown the potential of Peak width of Skeletonized Mean Diffusivity (PSMD) as a neuroimaging marker for cerebral small vessel diseases (cSVD). Considering cSVD's significant role in vascular-related cognitive decline, this study aims to verify whether PSMD can predict the risk of MCI/dementia progression beyond amyloid (A) status.
Methods: 176 subjects from the Dementia Disease Initiation cohort (88 cognitively unimpaired (CU) and 88 with mild cognitive impairment (MCI) at baseline) underwent 1 to 5 evaluations, resulting in 462 observations. Baseline PSMD was computed from DTI images acquired on 5 different scanners. Scanner effect correction was done using ComBat harmonization in R, with age and sex as covariates. Harmonised baseline PSMD was divided into 'PSMD low' and 'PSMD high' for values below and above the median respectively. Baseline A status was determined from Amyloid PET or from Abeta42/40 ratio. Results were categorized as A- PSMD low, A- PSMD high, A+ PSMD low and A+ PSMD high. Survival function was performed using the "survival" package from R, with progression from CU to MCI/dementia as the event of interest. Hazard ratios were assessed with the Cox proportional-hazards model with age and A status/PSMD at baseline and sex as covariates.
Results: show that individuals with A+ PSMD high have a 6.9-fold higher risk of MCI/dementia progression compared to A- PSMD low ($p<0.01$). A+ PSMD low increases the risk by 3.1-fold ($p = 0.10$), while A- PSMD high results in a 2.8-fold higher risk ($p = 0.09$) (Figure 1).



Conclusions: These findings suggest that a combination of PSMD and A status has the potential to improve the prediction of MCI/dementia progression, and that a combination of these risk factors more than doubles the risk of progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0345 / #2016

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

WHOLE BRAIN BETA-AMYLOID DETECTION BY HIGH-RESOLUTION QUANTITATIVE SUSCEPTIBILITY MAPPING

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Nian Wang
Indiana University, Radiology And Imaging Sciences, Indianapolis, United States of America

Aims: To detect and quantify the beta-amyloid plaques through the whole mouse brain using high-resolution Quantitative susceptibility mapping (QSM).
Methods: Animal experiments were carried out in compliance with the local IACUC Committee. The B6, 5xFAD, 5xFAD^{P522R}, and 5xFAD^{M28L} mice were chosen for brain imaging. The specimens were scanned at 9.4T scanner using a modified 3D multi-gradient echo pulse sequence . The phase data from the MGRE acquisition was used to reconstruct QSM images using STI Suite. The magnetic susceptibility was then obtained from the local tissue phase by solving an inverse problem using the improved LSQR (iLSQR) method.
Results: Figure 1. The representative T2*-weighted images of both WT (B6) and AD (5xFAD) mice. Compared to B6, there are hyperintensities areas in 5xFAD
mice.

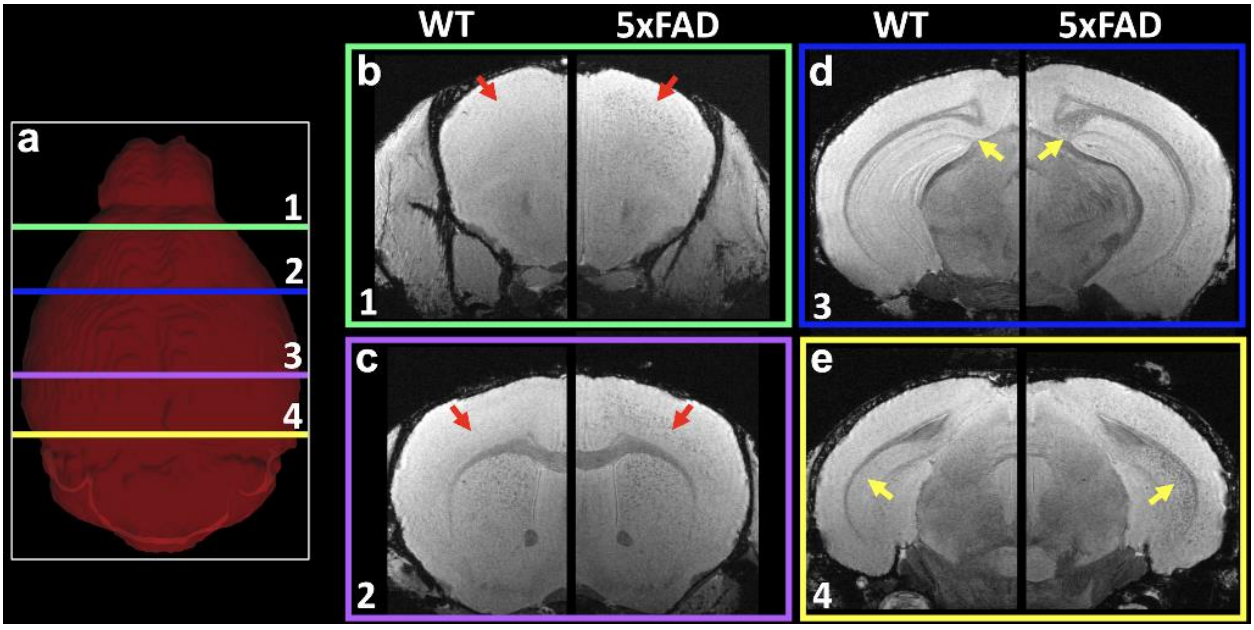


Figure 2. The plaque loading is comparable between QSM and conventional histology.

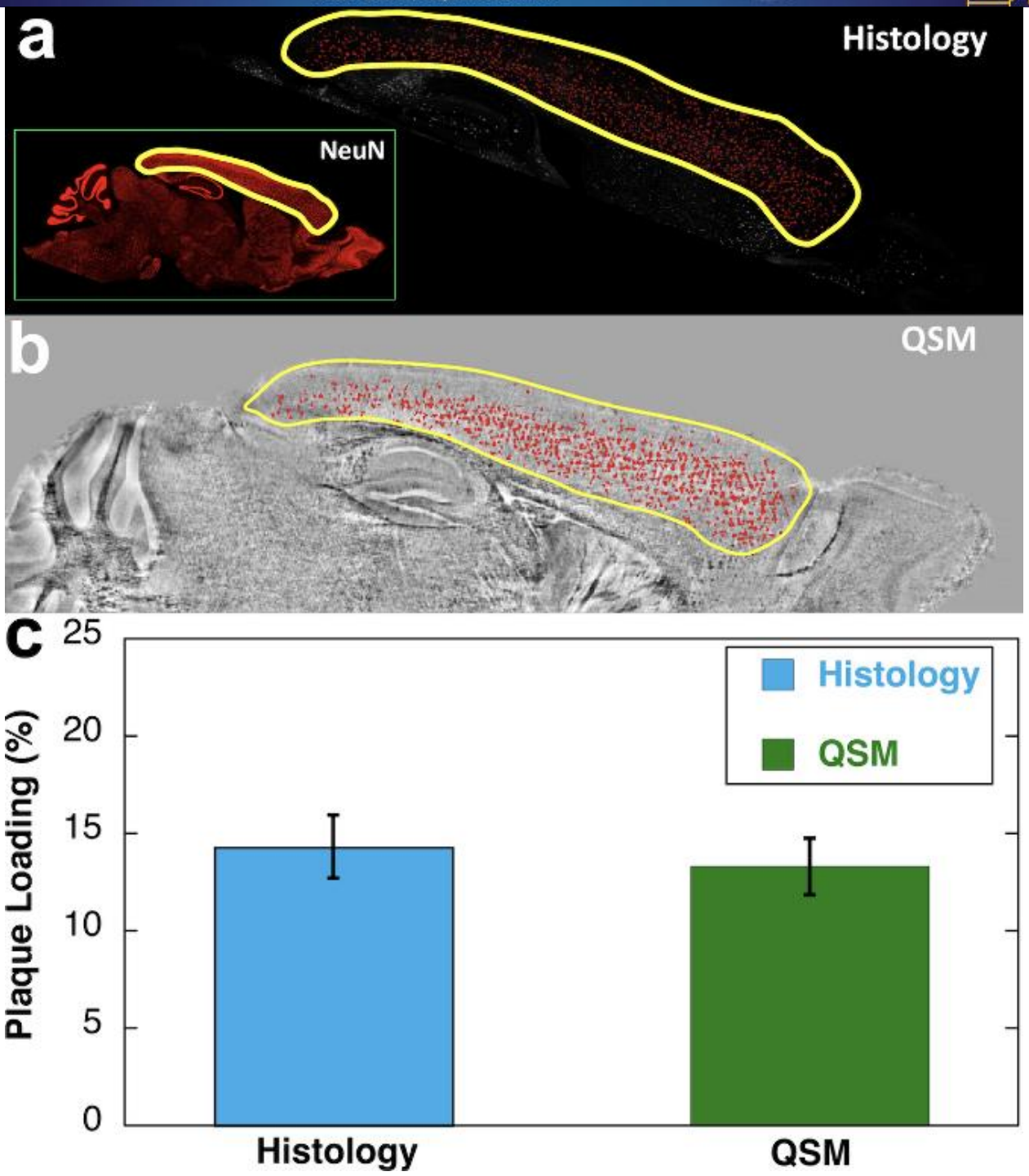


Figure 3. The QSM and T2* map of the 5xFAD mice.

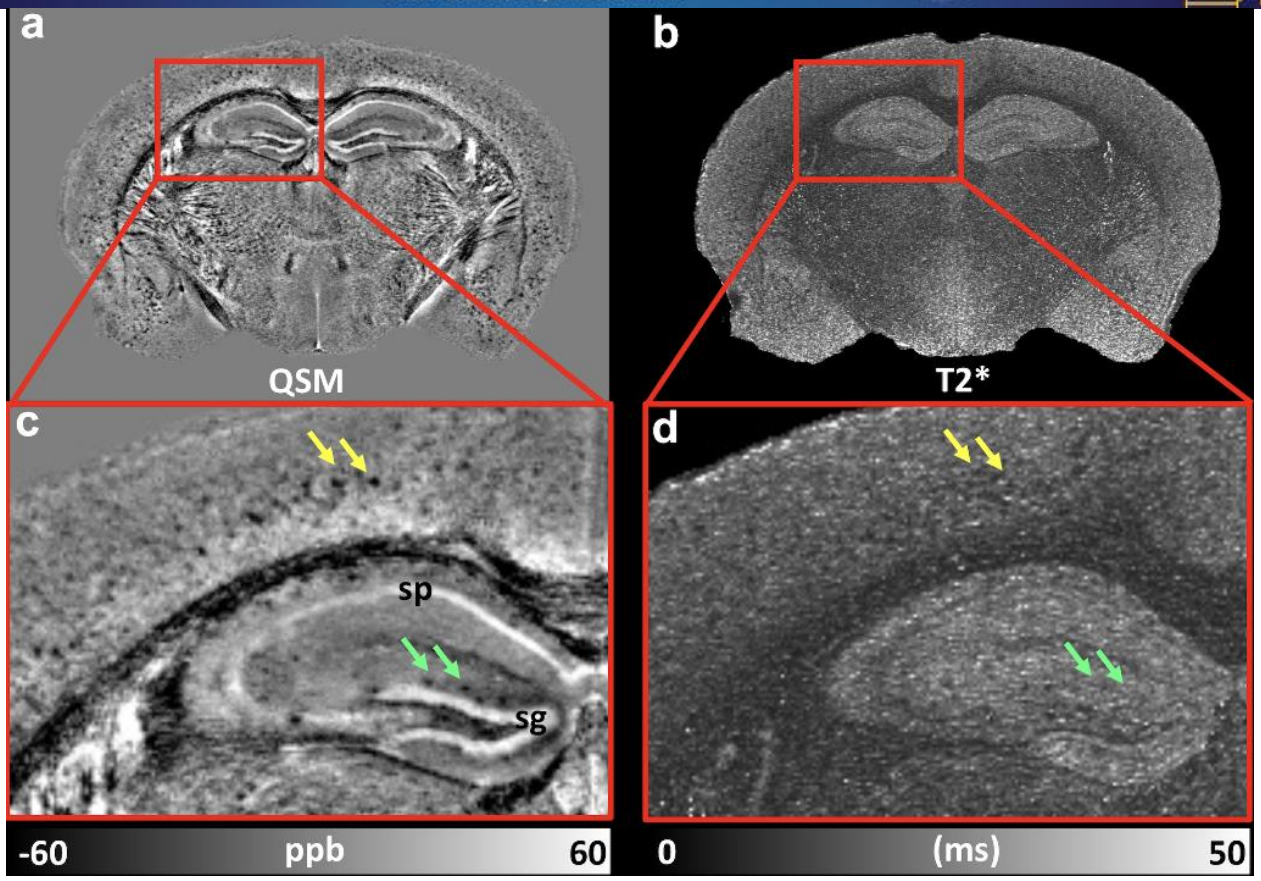
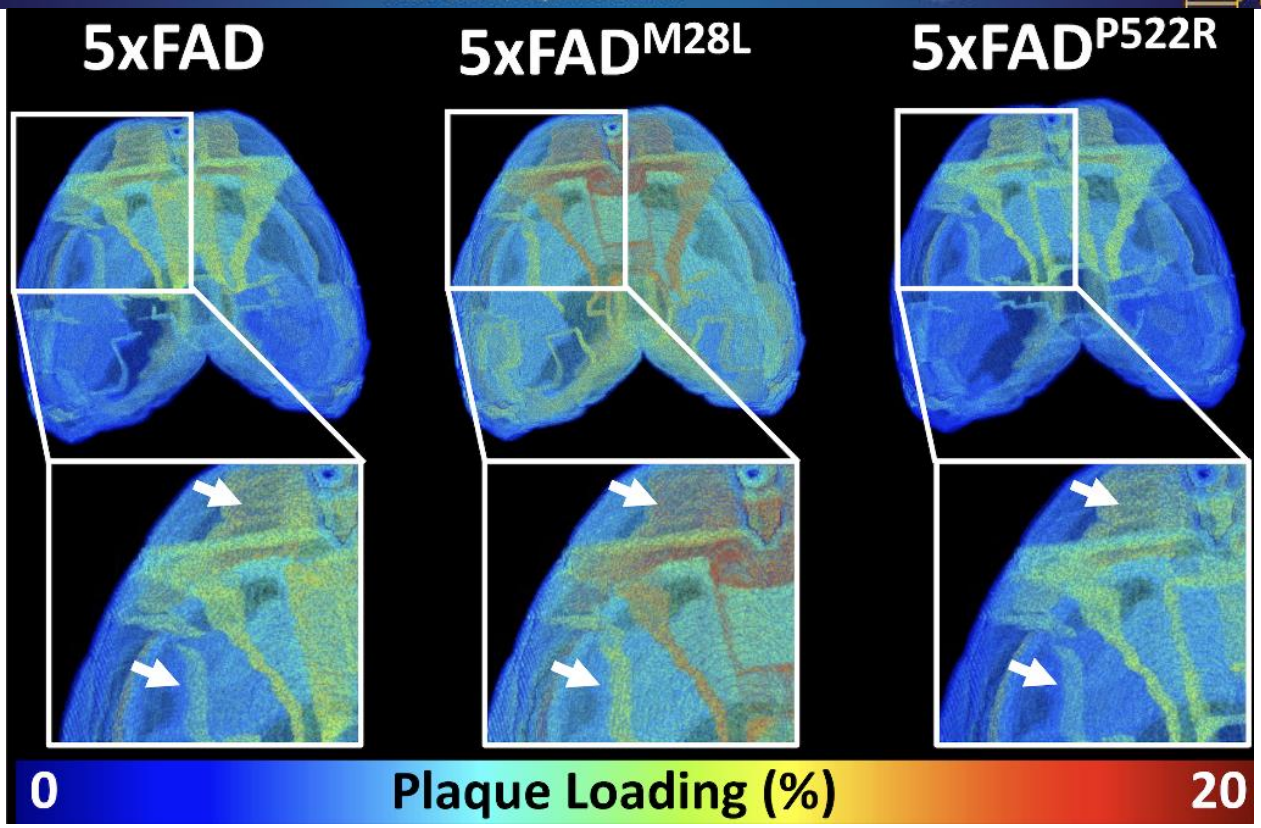


Figure 4. The plaque loading in 5xFAD, 5xFAD^{M28L}, and 5xFAD^{P522R}.



Conclusions: Although the cause of AD is not fully understood, clinical and neuropathological studies have hypothesized that the formation of beta-amyloid (Aβ) plaques and tau neurofibrillary tangles are crucial to the pathogenesis of AD. It has been reported that Amyloid plaque is one of the earliest hallmarks of AD and can occur up to 20 years before clinical diagnosis. In this study, we demonstrated that high-resolution QSM can be used to detect the individual beta-amyloid plaque through the whole mouse brain. We also showed that plaque loading is different in AD risk variant (M28L) mice and AD protective variant (P522R), which suggested that QSM may be a sensitive imaging-based biomarker to detect and monitor AD progression and understand the complicated mechanism of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0346 / #2961

Poster Topic: *Theme A: β-Amyloid Diseases / A04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

COGNITION AND BRAIN STRUCTURE IN COGNITIVELY ACTIVE PEOPLE

POSTERS: A04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Clara Iñesta, Javier Oltra-Cucarella, Esther Sitges-Maciá, Beatriz Bonete-López
Universidad Miguel Hernández de Elche, Departamento De Psicología De La Salud, Elche, Spain

Aims: Aging is associated with cognitive alterations that lead to dementia. The cognitive reserve hypothesis suggests that people with higher cognitive performance have a lower risk of developing cognitive decline or dementia. Therefore, it is important to study people with high cognitive reserve to identify protective factors against dementia. Previous works found that older people who attend university programs for Seniors are involved in more cognitively stimulating activities than people from the general population and might have better preserved cognitive function through an increased cognitive reserve. This work aims to analyze the association of cognition and brain structure in cognitively active older people through a neuropsychological battery and structural magnetic resonance imaging (MRI) data.
Methods: Data on brain structure and cognitive functioning of 40 people (30 women, 75%) over 55 years of age enrolled in university courses at the Miguel Hernández University of Elche are presented.
Results: The mean age was 68.9 (SD=6.14) and the mean educational level was 13.47 (SD=3.89). All participants were evaluated using a neuropsychological battery and underwent an MRI study to identify brain volume. In this sample, age was associated with the volume of the bilateral putamen, the bilateral accumbens, and the left hippocampus. Education was associated with the left pallidum and hippocampus. Left hemisphere brain volume and total brain volume were associated with processing speed, semantic memory, and naming, but not with episodic memory. Right brain volume was associated with semantic memory. Brain volume was not associated with the risk of presenting one or more low scores ($p = .150 - .273$)
Conclusions: A preserved processing speed could be key to preserving better cognitive functioning in older people, regardless of the brain volume of memory-related structures.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0347 / #274

Poster Topic: *Theme A: β-Amyloid Diseases / A04.b. Imaging, Biomarkers, Diagnostics: Functional MRI*

ALTERED BRAIN NETWORK DYNAMICS IN THE RESTING-STATE AND BEHAVIOURAL CORRELATIONS IN THE TGF344-AD RAT MODEL OF ALZHEIMER'S DISEASE

POSTERS: A04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

Sam De Waegenaere[1,2], Alya Al-Awlaqi[1,2], Lori Berckmans[1,2], Ignace Van Spilbeeck[1,2], Marleen Verhoye[1,2], Mohit Adhikari[1,2]
[1]University of Antwerp, μneuro Research Centre Of Excellence, Antwerpen, Belgium, [2]University of Antwerp, Bio-imaging Lab, Antwerpen, Belgium

Aims: A network-level perspective has gained prominence in Alzheimer's Disease (AD), besides the molecular approach, emphasizing dynamic brain region interactions. By evaluating these interactions, resting-state functional magnetic resonance imaging (rsfMRI) offers insights into AD's functional deficits. We studied AD's functional impact at different stages in the TgF344-AD rat model using rsfMRI functional connectivity (FC), transient co-activation patterns (CAPs), and behavioural readouts.
Methods: 15 TgF344-AD and 15 wildtype rats underwent anesthetised (isoflurane/medetomidine) rsfMRI scans at 4 (pre-plaque) and 10 (plaque stage) months using a 9.4T MRI-system. Post 10-month scans, we assessed learning and memory using a radial arm maze. After pre-processing the scans, regional and network-level FC was calculated. We obtained CAPs by concatenating pre-processed images from all scans and clustering individual volumes by spatial similarity. Group and age effects on FC, spatial and temporal properties of the CAPs were assessed using repeated measures ANOVA. Behavioural learning curves were analysed and correlated with FC. We evaluated the accuracy of CAP features to classify the animals according to genotypes and ages.
Results: We identified six CAPs (Fig.1A) and observed functional hyperactivation and hypoactivation in the TgF344-AD rats of the default mode-like network (DMLN), especially in the hippocampus and frontal DMLN regions, at the pre-plaque and plaque stages respectively in CAP 1 and 6 (Fig1D,E). Spatial properties of CAPs predicted the pre-plaque transgenic group most accurately and showed confusion between genotypes at the post-plaque stage (Fig2). Behaviourally, transgenic rats showed memory impairments correlating with FC changes in the lateral-cortical network (LCN) (Fig3).

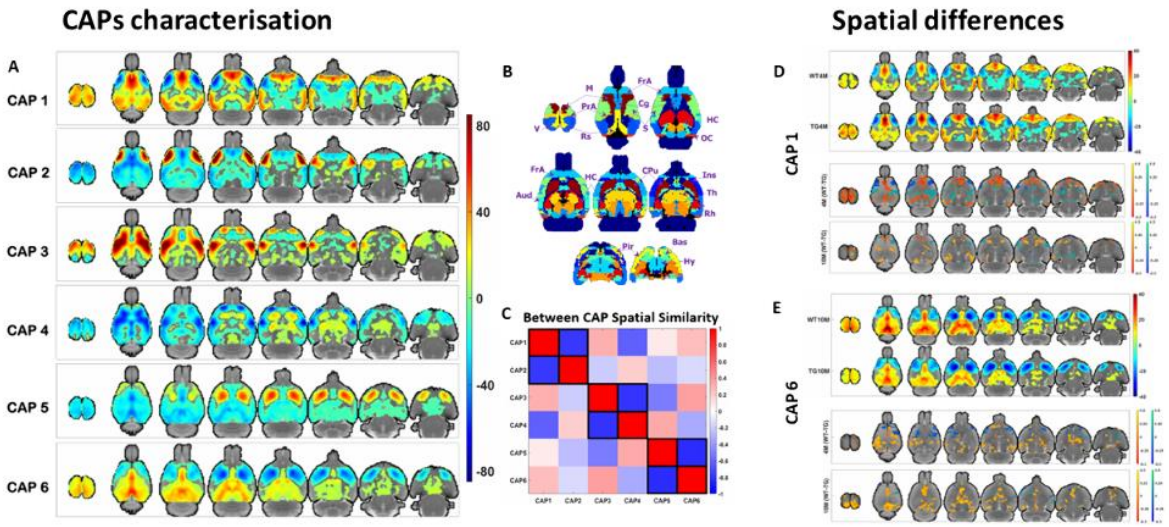


Figure 1. CAP spatial characteristics and differences. (A) Voxels with significant (de)activation levels ($p < 0.01$; Bonferroni corrected). **(B)** Anatomical reference atlas. **(C)** Correlation matrix showing distinct CAP anti-CAP pairs. **(D, E)** (Top panels) Age-wise genotype 1-sample t-tests and (bottom two panels) post-hoc comparisons after 2-way ANOVA between genotypes at pre-plaque and plaque stages (FDR corrected; $p < 0.05$)

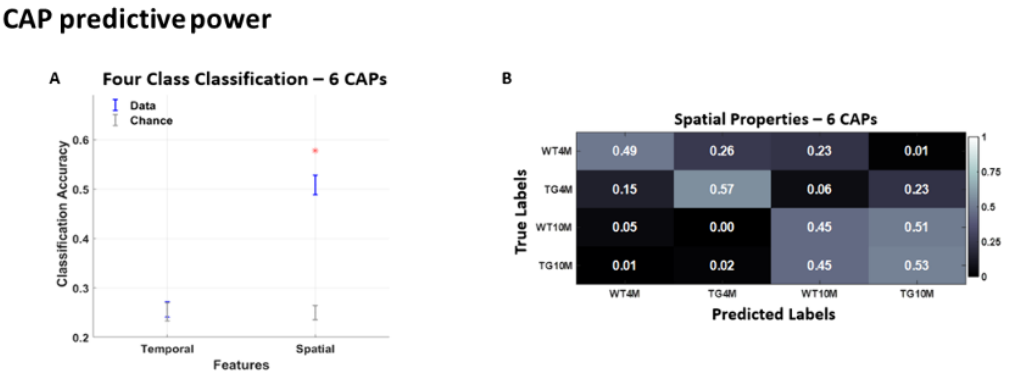


Figure 2. CAP classification analysis. (A) Classification accuracy for different CAP features (mean +/- SEM). Temporal features consist of CAP duration and occurrence rate, spatial features correspond to BOLD intensities of voxels whose activations within the corresponding group-level CAP were found to be significantly different from zero. Red asterisk: significantly higher than chance-level (FDR corrected, $p < 0.05$). **(B)** Confusion matrix using spatial properties.

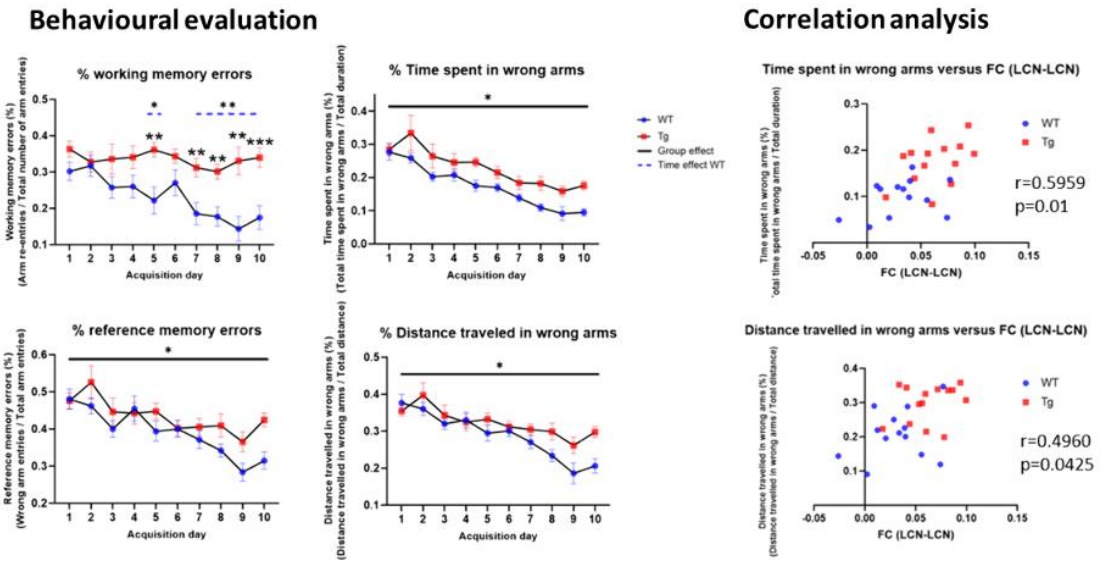


Figure 3. Behavioural evaluation through radial arm maze (RAM) test. (A-D) Learning curves of the RAM. Mean ± SEM is shown. *p ≤0.05, **p ≤0.01, ***p ≤0.001 (repeated measures 2-way ANOVA). **(E, F)** Scatterplots for behavioural parameters on day 10 that correlated significantly with the within LCN FC in 10-month-old rats.

Conclusions: Our findings demonstrate hyper- and hypo-activations of DMLN regions in transient brain-states at pre- and post-plaque stages respectively in transgenic animals. Behavioural readouts correlate with functional connectivity, emphasising a network perspective in AD understanding.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0348 / #392

Poster Topic: *Theme A: β-Amyloid Diseases / A04.b. Imaging, Biomarkers, Diagnostics: Functional MRI*

VALUE OF BLOOD-BASED BIOMARKERS FOR NEURODEGENERATION PREDICTING MRI AND COGNITIVE CHANGES IN EARLY ALZHEIMER'S DISEASE

POSTERS: A04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

Fernando Gonzalez-Ortiz[1], Thomas Karikari[2], Kaj Blennow[1], Tormod Fladby[3], Bjørn-Eivind Kirsebom[4], Julia Gundersen[3], Per Selnes[3], Lene Pålhauge[4], Berglind Gísladóttir[3], Sandra Tecelão[4]
[1]Gothenburg University, Psychiatry And Neurochemistry, Göteborg, Sweden, [2]Gothenburg University, Psychiatry And Neurochemistry, Gothenburg, Sweden, [3]Akerhus University Hospital, Neurology, Oslo, Norway, [4]Akerhus University Hospital, Neurology, Lørenskog, Norway, Norway

Aims: While promising blood biomarkers for brain Alzheimer's disease (AD)-type Aβ pathophysiology now exist, there is an unmet need for a biomarker that tracks neurodegenerative changes in AD. Neurofilament light chain (NfL) is a general marker of neurodegeneration/axonal injury across multiple disorders. Total-tau (t-tau) has very large overlaps between AD, non-AD dementias and control groups to be diagnostically useful. We recently presented a novel blood-based neurodegeneration biomarker brain-derived tau (BD-tau) that showed higher levels in biomarker-confirmed AD versus non-AD dementia and unaffected controls.
Methods: In the present study we examined plasma NfL, T-tau and BD-tau associations with longitudinal cognition and AD-signature atrophy rates in the Dementia Disease Initiation (DDI) cohort (n=364) which includes patients in early stages of the AD continuum. Longitudinal linear mixed models were fitted to assess associations between biomarkers at baseline and the pertinent dependent variable (cognition or MRI) over time
Results: Plasma BD-tau, but not plasma t-tau or NfL, was significantly associated with future AD meta-Region of Interest (ROI) atrophy (b=-0.06, p<0.01). Moreover, plasma BD-tau was associated with baseline performance on both the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) memory recall and the Trail Making Test-B (TMT-B); b=-0.16, p<.001 and b=0.12, p<.01 respectively), as well as the longitudinal worsening in performance on both tests over up to 8 years later (b=-0.05, p<.05; b=0.04, p<.001 respectively). Plasma NfL was not associated with baseline cognitive performance on either CERAD memory recall or TMT-B.
Conclusions: Plasma BD-tau was the only marker associated with future AD meta-ROI atrophy and both baseline and cross-sectional performances on the CERAD and TMT-B. Together, these results show that plasma BD-tau associates with brain neurodegenerative signatures that interact with Aβ pathophysiology to synergistically drive cognitive decline.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0349 / #2889

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

VALIDATION OF THE AUTOMATED CENTILOID SCALE UTILIZATION IN MULTIPLE B-AMYLOID PET TRACER QUANTIFICATION

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Yeong Sim Choe, Hye Weon Kim, Min-Woo Lee, Hajin Kim, Jiyeon Lee, Zunhyan Rieu, Minho Lee, Donghyeon Kim, Regina Kim
NEUROPHET Inc., Research Institute, Seoul, Korea, Republic of

Aims: The Centiloid scale was introduced to standardize the quantification of β-amyloid PET tracers in Alzheimer's disease. However, the original method requires technical expertise and manual parameter calibration. An automated Centiloid scale that process results within 5 minutes is currently accessible, and we aimed to validate the feasibility of the automated Centiloid scale in comparison to the original method employed in the Centiloid Project.
Methods: We used 286 participants who underwent amyloid PET (^{11}C-PiB, ^{18}F-Florbetaben, ^{18}F-Flutemetamol, ^{18}F-Florbetapir, and ^{18}F-NAV4694) and 3D T1-weighted MRI scans obtained from GAAIN dataset (https://www.gaain.org/centiloid-project). We processed the SUVR calculation using SCALE PET (Neurophet Inc.) in global cortical regions (frontal, lateral parietal, lateral temporal, cingulate cortices, and striatal regions) with the cerebellum as the reference. Results were then converted to the Centiloid scale by PiB SUVR translation and compared to the original method using MATLAB R2018a (SPM12).
Results: Our results showed a strong correlation with the original method (slope = 1.00, intercept = 0.02 R^2 = 0.99). Individual tracers showed varying slopes when comparing their SUVR values to PiB SUVR. Notably, ^{18}F-NAV4694 showed a slope closest to 1.0 (0.997), while ^{18}F-Florbetapir showed a more distant value (0.51). After converting SUVR to the Centiloid scale, most tracers displayed high R^2 values (0.89 to 0.99), slopes (1.00 to 1.07), and intercepts (0.14 to 2.52) when compared to the original Centiloid scales. Except for ^{18}F-Florbetapir, which had a large intercept (2.52), other tracers affirmed their suitability as Centiloid scales by showing intercept below 2.0 (^{18}F-Florbetaben: 0.46, ^{11}C-PiB: 0.82, ^{18}F-Flutemetamol: 1.07, ^{18}F-NAV4694: 1.90).
Conclusions: The automated Centiloid scale has been validated for its applicability in comparison to the original method with various amyloid tracers, providing time-saving benefits and accessibility for various users.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0350 / #941

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

SYNTHESIS AND PET IMAGING BIODISTRIBUTION STUDIES OF A NEW RADIOLABELED IODODIFLUNISAL, A TRANSTHYRETIN TETRAMER STABILIZER, CANDIDATE DRUG FOR ALZHEIMER'S DISEASE

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Gemma Arsequell[1], Sameer Joshi[2], Thomas Wilson[3], Zibo Li[4], Vanessa Gómez Vallejo[5], Veronique Gouverneur[3], Jordi Llop[5]
[1]Institute of Advanced Chemistry of Catalonia (IQAC-CSIC), Biological Chemistry, Barcelona, Spain, [2]The University of North Carolina at Chapel Hill, Department Of Radiology,, North Carolina, United States of America, [3]Chemistry Research Laboratory, Department Of Radiology, Oxford, United Kingdom, [4]Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Department Of Radiology, North Carolina, United States of America, [5]CIC biomaGUNE, Basque Research and Technology Alliance (BRTA), Radiochemistry And Nuclear Imaging Lab, Donostia-San Sebastián, Gipuzkoa, Spain

Aims: Transthyretin (TTR) has a well-established role in neuroprotection in Alzheimer's Disease (AD). Iododiflunisal (IDIF), a TTR tetramer stabilizer, is a chemical chaperone enhancing TTR/Amyloid-beta peptide (Aβ) interactions. Previous studies with this potential disease modifying drug showed that IDIF enhances TTR blood brain barrier penetration and reduces brain amyloidosis *in vivo*. Here, we investigate different strategies for efficient radiolabeling of IDIF in different positions of the molecule for *in vivo* nuclear imaging studies.
Methods: Precursors of IDIF and derivatives of the NSAID diflunisal have been obtained by organic synthesis procedures. Different radioiodination and radiofluorination procedures have been assayed to achieve the synthesis of [^{123}I]IDIF and [^{18}F]IDIF. Dynamic 90-min positron emission tomography (PET) images have been acquired immediately after intravenous administration in mice.
Results: Two new radiolabeled IDIF derivatives, [^{123}I]IDIF and [^{18}F]IDIF, containing either the gamma emitter ^{123}I or the positron emitter ^{18}F, have been independently synthesized. Radioiodination of a pinacol ester (Bpin) of a diflunisal derivative was performed with Na^{123}I using a copper(II)-mediated radioiododeboronation reaction. Initial attempts for the copper-mediated radiofluorination of a labile pinacol ester (Bpin) of an IDIF derivative with [^{18}F]KF/K_{222} in the presence of *tetrakis*(pyridine)copper(II) triflate [$Cu(OTf)_2(py)_4$] were unsuccessful. However, [^{18}F]IDIF could be synthesized from IDIF by isotopic exchange using [^{18}F]KF/K_{222}. PET Biodistribution studies with [^{18}F]IDIF show slow blood clearance, prolonged retention in the liver, progressive elimination via urine and significant brain accumulation. The results are in good agreement with those previously described using [^{131}I]IDIF and dissection/gamma counting.
Conclusions: IDIF can be efficiently radiolabeled with ^{123}I and ^{18}F using copper(II)-catalyzed radioiododeboronation and isotopic exchange reactions, respectively. PET studies confirmed previous biodistribution results obtained with [^{131}I]IDIF, opening opportunities for future studies in larger species or humans.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0351 / #2453

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

STRIATUM INVOLVEMENT IS ASSOCIATED WITH MORE PRONOUNCED MEMORY IMPAIRMENT IN AMYLOID PET POSITIVE PATIENTS

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Jiri Cerman[1], Adela Skorvagova[1], Martin Vyhnálek[2], Jakub Hort[2]
[1]Charles University, 2nd Faculty Of Medicine, Prah, Czech Republic, [2]Second Faculty of Medicine, Charles University, Department Of Neurology, Prague, Czech Republic

Aims: Today, many tools are being investigated with the aim of refining the prognosis of patients with Alzheimer's disease (AD), but none has yet been introduced into clinical practice. One of these is amyloid PET, where recent work has shown that the involvement of subcortical structures, particularly the striatum, is associated with more rapid cognitive decline. Our aim was to build on this work using memory tests specific to AD.
Methods: From a cohort of 60 patients with positive amyloid PET and mild cognitive impairment or mild dementia who also underwent neurological and neuropsychological assessment, volumetric MRI and other tests, a total of 8 patients with negative striatal involvement were identified. These patients were matched for age, education and global cognition (MMSE) to 8 patients with positive striatal involvement from the same cohort and their results in Enhanced cued recall test (ECR; a short picture version of Free and Cued Selective Reminding Test) were compared. PET images were evaluated visually using the GM-EDGE method.
Results: Amyloid PET positive patients with striatal involvement had significantly worse performance on the ECR free recall test compared to patients with unaffected striatum ($p=0.027$; $F=6.089$), although performance on the global cognition test (MMSE) did not differ ($p=0.514$; $F=0.447$). There was no difference in ECR total recall possibly due to its ceiling effect ($p=0.238$; $F=1.554$).
Conclusions: Amyloid PET positive patients with MCI or mild dementia who also have striatal involvement have more pronounced impairment in free recall FCSRT compared to patients with negative striatal impairment. This is consistent with previous data. Further and also longitudinal data are however needed to evaluate the use of amyloid PET in prognostic assessment of AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0352 / #998

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

ETHNIC DIFFERENCES IN AMYLOID PET POSITIVITY AND COGNITIVE TRAJECTORIES RELATED TO ALZHEIMER'S RISK FACTORS

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Min Young Chun[1,2,3], Hyemin Jang[1], Jihwan Yun[1], Jun Pyo Kim[1], Hee Jin Kim[1], Duk L Na[1], Sook-Young Woo[4], Sang Won Seo[1]
[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Department Of Neurology, Seoul, Korea, Republic of, [2]Yonsei University College of Medicine, Department Of Neurology, Seoul, Korea, Republic of, [3]Yongin Severance Hospital, Yonsei University College of Medicine, Department Of Neurology, ongin-si, Gyeonggi-do, Korea, Republic of, [4]Samsung Biomedical Research Institute, Biostatistics Team, Seoul, Korea, Republic of

Aims: Ethnic differences in amyloid-β (Aβ) marker characteristics and in cognitive trajectories related to Alzheimer's risk factors should be considered when recommending Aβ targeted therapies in various ethnic populations. We aimed to investigate the prevalence of Aβ (+) and cognitive trajectories related to Alzheimer's risk factors in two separate cohorts of Koreans and non-Hispanic whites (NHWs).
Methods: In the cross-sectional study, we included 3,785 Koreans from multiple centers in Korea and 914 NHWs from the Alzheimer's Disease Neuroimaging Initiative. In the longitudinal study, we followed 1,130 Koreans and 1,130 NHWs who were matched for cognitive stage and age between Koreans and NHWs using the Mini-mental State Examination (MMSE) scores. All participants underwent Aβ PET scans, and were categorized into three cognitive stages: cognitively unimpaired (CU), amnestic mild cognitive impairment (aMCI), and dementia of the Alzheimer type (DAT).
Results: In the cross-sectional study, in the CU stage, the odds of Aβ (+) in Koreans compared to NHWs were lower (odds ratio [OR], 0.521), while those did not differ in the aMCI and DAT stages. The effects of *APOE* ε4 on Aβ (+) seemed to be greater in NHWs (adjusted OR [aOR], 14.0) than in Koreans (aOR, 5.9) in the DAT stage, but not in the CU stage. In the longitudinal study, Aβ (+) Koreans showed a faster decline in MMSE compared to Aβ (+) NHWs ($p < 0.001$). Sex, *APOE*, and education levels had less pronounced impacts on cognitive trajectories in Aβ (+) Koreans than in Aβ (+) NHWs over time (p-for-interaction < 0.001).
Conclusions: Ethnic differences in the prevalence of Aβ (+) and in cognitive trajectories related to Alzheimer's risk factors highlight the consideration of ethnicity for developing the Aβ-targeted treatment strategy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0353 / #2431

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

PREDICTING GLOBAL AND REGIONAL TAU TANGLES USING AMYLOID PET, PLASMA PTAU 181, AND COGNITIVE ASSESSMENTS

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Viswanath Devanarayan, Arnaud Charil, Pallavi Sachdev, Harald Hampel, Lynn Kramer, Shobha Dhadda, Michael Irizarry
Eisai, Inc., Clinical Evidence Generation, Nutley, United States of America

Aims: Objectives: This study aims to develop and validate prediction models for detecting whole cortical and regional Tau tangles, facilitating clinical and research studies lacking Tau-PET scans, and minimizing screen failures.
Methods: Methods: We analyzed MK6240 Tau-PET SUVR data from a clinical trial training cohort of 354 amyloid-positive early AD patients. Global and Braak stage-specific Tau positivity thresholds were established using 52 cognitively unimpaired individuals from the Lantheus/Cervaux cohort through robust one-sided 95% upper confidence limits. Bayesian models were built to predict global Tau positivity and Tau tangles across Braak stages 1-6. Predictors included amyloid-PET Centiloid (CL), cognitive assessments (sub-scores and composites of CDR-SB, ADAS-Cog-13, and MMSE), and plasma pTau181, alongside demographics and ApoE4 status. Prediction performance was evaluated via internal cross-validation (IV) within the training cohort and external validation (EV) using an independent ADNI cohort of 243 subjects with the Flortaucipir tracer.
Results: R**esults:** Global Tau positivity prediction with amyloid-PET CL achieved AUROCs of 81% (IV) and 80% (EV). This matched performance obtained by combining cognitive assessments and plasma pTau181 (AUROCs: IV 77%, EV 81%) and surpassed individual predictors. For Braak stage prediction, a separate model using amyloid-PET CL effectively distinguished earlier from later stages (Braak 0-2 vs. 3-6; AUROCs: IV 90%, EV 87%) and performed well in advanced Braak-6 stage (AUROCs: IV 79%, EV 83%). The combination of pTau181 and cognitive assessments also accurately predicted Tau across Braak 0-2 versus 3-6 (AUROCs: IV 88%, EV 80%) and Braak-6 (AUROCs: IV 74%, EV 72%).
Conclusions: Conclusion: Global Tau presence and Braak-staging can be predicted accurately using amyloid-PET CL, plasma pTau181, and cognitive assessments. Validated across different Tau-PET tracers, these models enhance the efficiency of Tau-PET screening, benefiting clinical and research endeavors.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0354 / #449

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

AN AUTOMATED PIPELINE FOR CENTILOID QUANTIFICATION OF AMYLOID-B USING MULTIPLE 11C-PIB-PET AND 18F- PET TRACERS

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Elizabeth Gordon, Ayoub Gueddou, Mathilde Borrot, Luca Villa, Thomas Jubault, Nicolas Guizard
Qynapse, Clinical Science, Paris, France

Aims: To develop and validate a single and fully automated Centiloid quantification pipeline for multiple amyloid PET compounds in support of standardizing multi-site investigations.
Methods: QyScore®'s fully-automated pipeline was validated on ^{11}C-PiB-PET images from the Centiloid project (https://www.gaain.org/centiloid-project): 34 young controls [age=31.5±6.3 years] and 47 AD patients [age=67.5±10.5 years; CDR= 0.5–1]. ^{18}F tracers included Florbetapir (FBP, N=46), Florbetaben (FBB, N=35), Flutemetamol (FTM, N=74) and NAV4694 (NAV, N=55) validation datasets from the project. PET/MR image pairs were co-registered to MNI template space. The standardized uptake value ratio (SUVr) was computed as the ratio of the mean signal in the grey matter composite (target) and the whole cerebellum (reference) (Figure 1). Linear regression analyses investigated replication of the original validation Centiloid cohort; concordance of QyScore®'s ^{11}C-PIB and ^{18}F tracer SUVr values; and the concordance between QyScore®'s SUVr results with published validation cohorts. Equations for converting QyScore®'s ^{18}F-SUVr to Centiloid values were derived using the Centiloid project recommended validation process.
Results: QyScore®'s fully-automated quantitative pipeline produced SUVr's closely matching the Centiloid method (SUVr_AD-100=2.08+/-0.2; SUVr_YC-0=1.01+/-0.05; R^2=0.99; slope=1.00; intercept=-0.44). R^2 for QyScore®'s ^{18}F SUVr with paired ^{11}C-PiB SUVr were high across all tracers: 0.91, 0.95, 0.95 and 0.99 (Figure 2). ^{11}C-PiB SUVr correlation coefficients with published values were all above 0.98 (Figure 3) and QyScore®'s Centiloid conversions, (using the following equations) showed clear differentiation between AD and healthy controls across all tracers (Figure 4). **Centiloid conversion equations:** Centiloid=233.39 x SUVr_FBP – 243.48 Centiloid=160.57 x SUVr_FBB – 183.35 Centiloid=136.94 x SUVr_FTM – 156.18 Centiloid=94.67 x SUVr_NAV – 98.72

Figure 1: Example of a PET/MR image pairs co-registered and normalized in the MNI template space with the regions of interest (ROI) segmentations produced using QyScore® displayed.

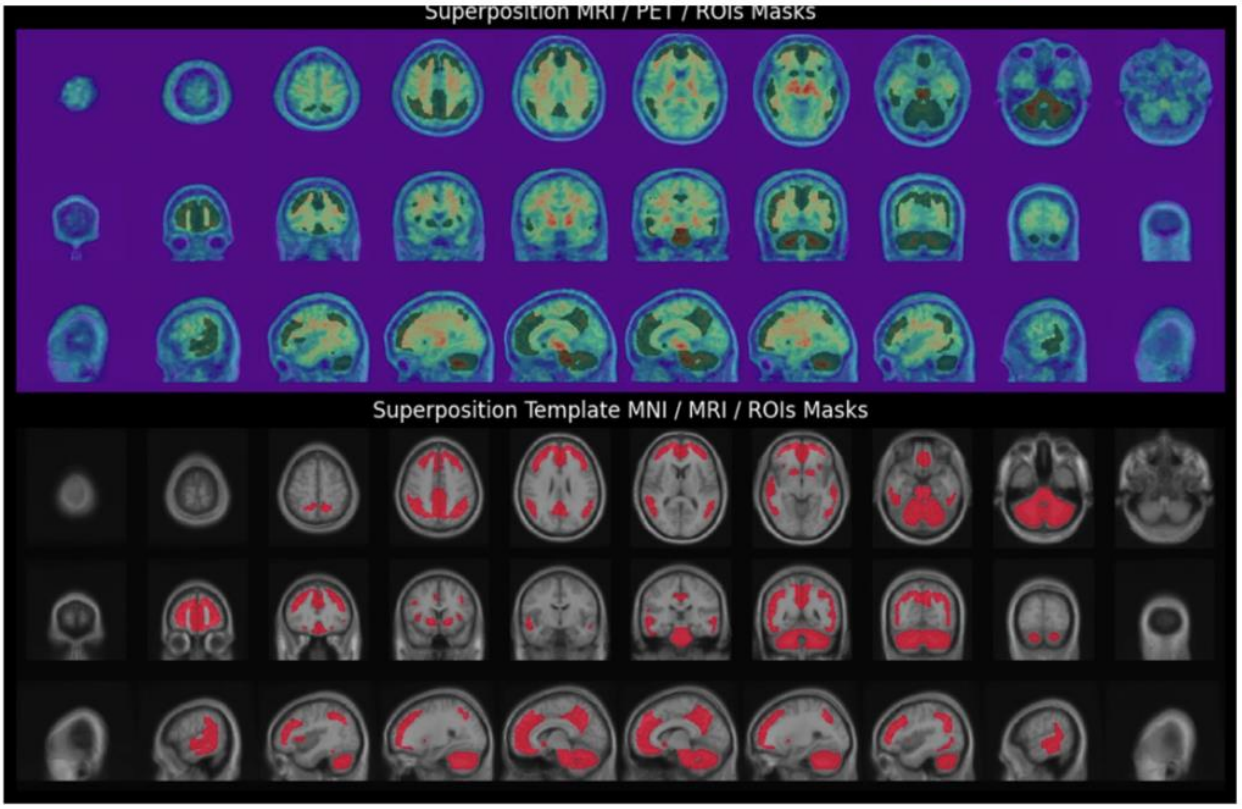


Figure 2. Correlation between each ^{18}F tracer and paired ^{11}C-PIB SUVr produced using QyScore®'s fully automated quantitative PET pipeline

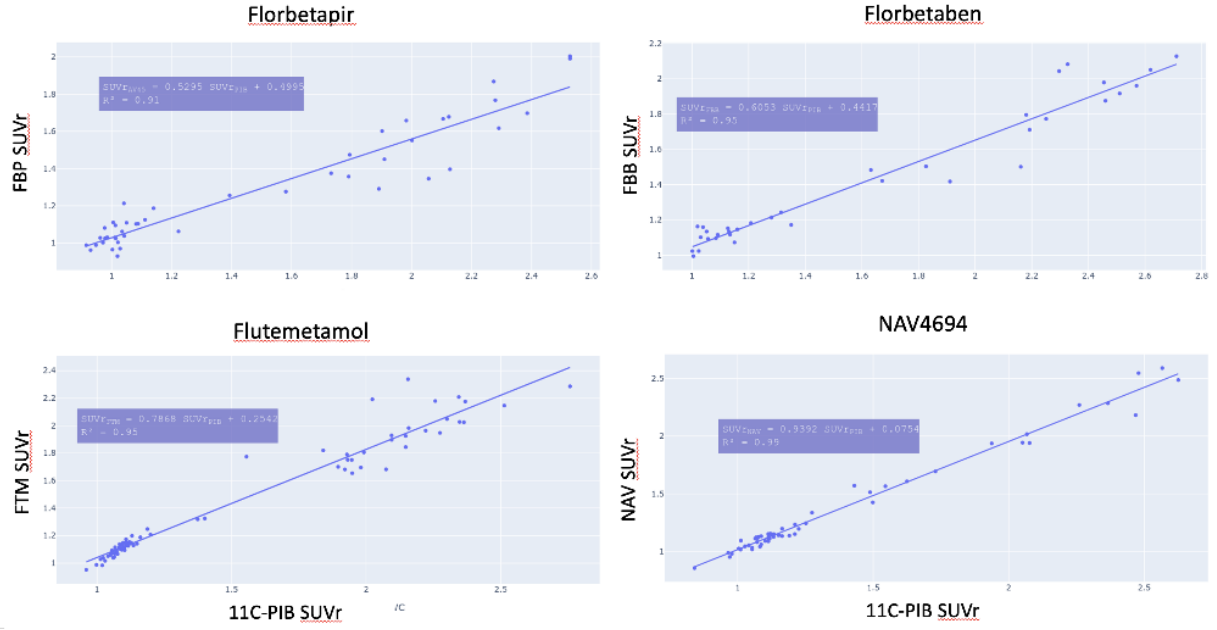


Figure 3. Correlation between QyScore®'s ^{18}F tracer SUVr with the Centiloid GAAIN validation gold-standard SUVr

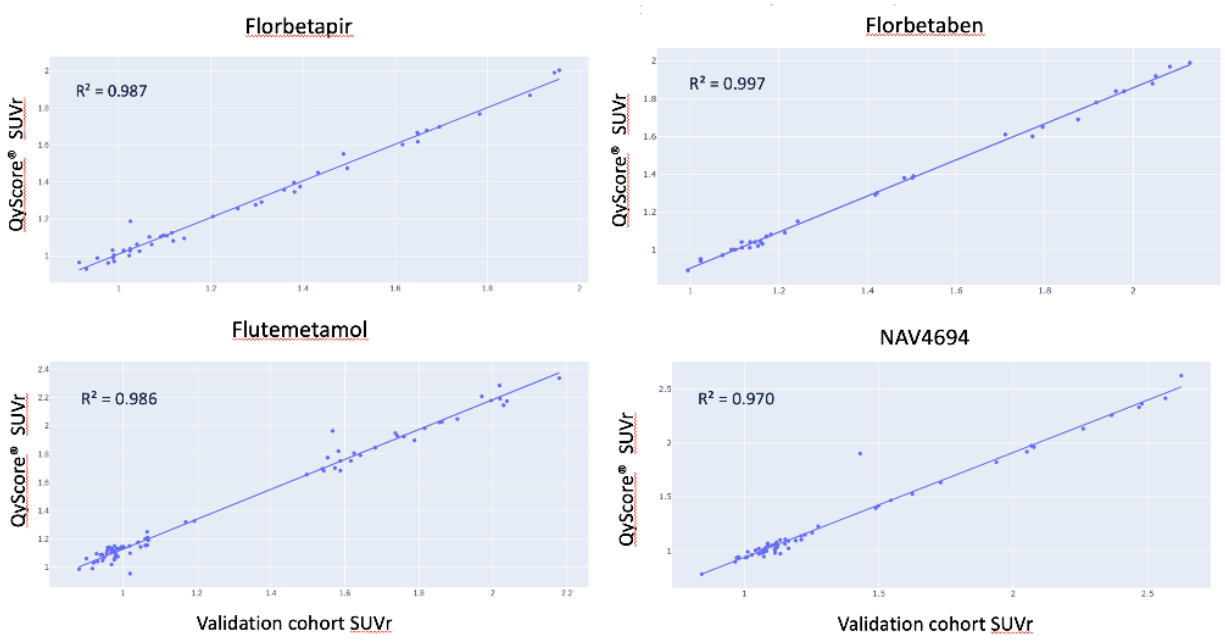
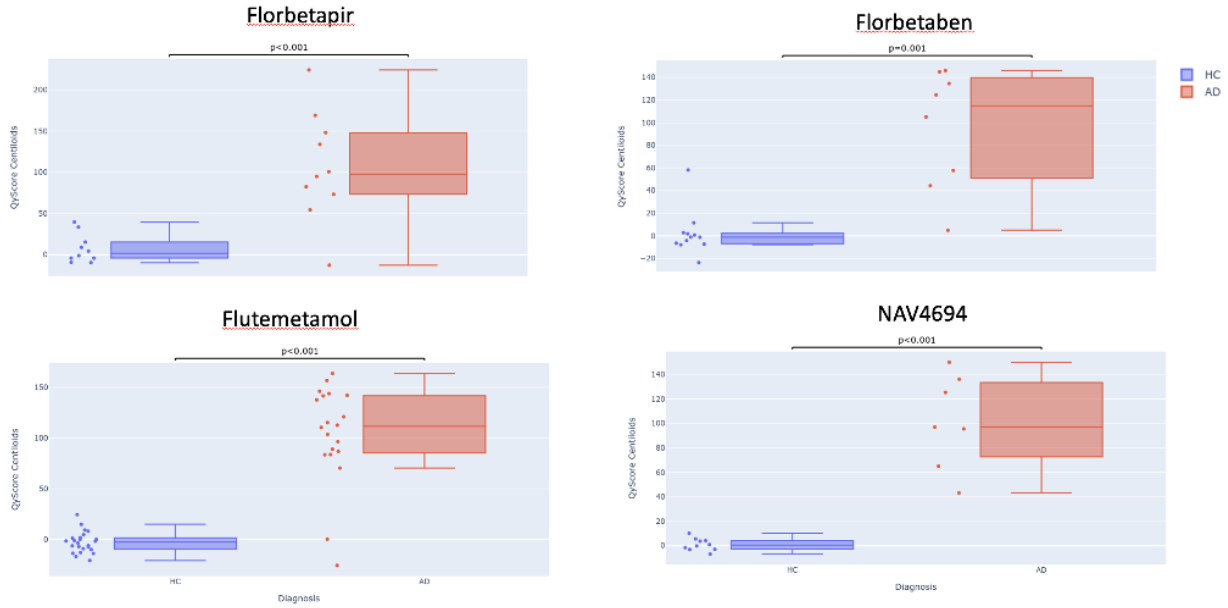


Figure 4. QyScore®'s converted Centiloid results for Heathy Controls (HC) and Alzheimer's Disease (AD) patient amyloid-PET quantification across all four ^{18}F tracer validation datasets



Conclusions: We demonstrate the strong performance of QyScore®'s fully-automated amyloid-PET pipeline for analysing multiple amyloid-PET compounds (^{11}C-PiB and ^{18}F) and validated conversion to the standardized Centiloid scale suitable for multi-site clinical trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0355 / #992

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

INCREASED CEREBRAL PERFUSION PROXY WITH INCREASED BETA-AMYLOID BURDEN IN THE PRECLINICAL PHASE OF ALZHEIMER'S DISEASE: EVALUATION USING DUAL-PHASE 18F-FLORBETABEN PET

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Jee Hyang Jeong[1], Geon Ha Kim[2], Hai-Jeon Yoon[3], Hae Ri Na[4]
[1]Ewha Womans University Seoul Hospital, Neurology, Seoul, Korea, Republic of, [2]Ewha Womans University College of Medicine, Neurology, Seoul, Korea, Republic of, [3]Ewha Womans University College of Medicine, Nuclear Medicine, Seoul, Korea, Republic of, [4]Bobath Memorila Hospital, Neurology, Seongnam, Korea, Republic of

Aims: This study aimed to investigate the earliest change in cerebral blood flow (CBF) in preclinical Alzheimer's disease using early-phase ^{18} F-florbetaben (FBB) PET scans. Additionally, the relationship between CBF and β-amyloid (Aβ) burden, measured by delayed-phase FBB PET scans, was examined in cognitively normal (CN) subjects.
Methods: A total of thirty-six subjects, including 19 with Aβ-negative normal cognition (AβNC) and 17 with Aβ-positive NC (Aβ+NC) were enrolled. A dynamic PET scan was obtained in the early phase (0-10 min, eFBB) and delayed phase (90-110 min, dFBB), which were then averaged into a single frame, respectively. In addition to the averaged eFBB, an R1 parametric map was calculated from the eFBB scan based on a simplified reference tissue model (SRTM). Between-group regional and voxel-based analyses of the images were performed. Correlations between eFBB PET-derived CBF proxies and dFBB PET-derived Aβ burden were analyzed.
Results: The eFBB revealed hyper-perfusion in the superior frontal, mid frontal, and postcentral cortices ($p < 0.005$). R1 revealed hyper-perfusion in the precentral, superior motor, paracentral lobule, postcentral, cuneus, superior occipital, and superior temporal pole cortices ($p < 0.005$). There was a significant positive correlation between R1 and dFBB in the frontal (rho = 0.373, p = 0.025), posterior cingulate and precuneus (rho = 0.409, p = 0.013), and lateral parietal (rho = 0.388, p = 0.020) cortices.
Conclusions: To our knowledge, this is the first study to utilize a dual-phase FBB PET protocol for investigating preclinical AD. The results reveal an increase of CBF and positive correlation between CBF and amyloid pathology. These findings may indicate a potential compensatory hemodynamic mechanism that offers protection against pathology during the very early stages of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0356 / #1642

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

EXPERIENCES FROM CLINICAL RESEARCH AND ROUTINE USE WITH NEURACEQ AMYLOID PET DURING 10 YEARS POST-AUTHORISATION – PRIMED FOR THE FUTURE

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Aleksandar Jovalekic, Santiago Bullich, Nuria Roe-Vellve, Floriana Elsholz, Mariana Lagos-Quintana, Rossella Gismondi, Audrey Perrotin, Andre Mueller, Andrew Stephens, Norman Koglin
Life Molecular Imaging, Clinical R&d, Berlin, Germany

Aims: The amyloid positron emission tomography (PET) tracer Neuraceq® (florbetaben F18) obtained approval in Europe and the US in 2014 following a histopathology study. This abstract presents integrated real-world evidence gathered recently, including outcomes from two post-authorization safety studies (PASS) conducted within the EU.
Methods: The data encompass three key aspects: first, evaluating the efficacy of the approved visual assessment method in the routine clinical practice (PASS1 study, EUPAS12145); second, elucidating prescribing patterns of Neuraceq® in routine clinical practice (PASS2, EUPAS13366); and third presenting quantification results of an extended dataset to underscore reliability and the additional value of quantification.
Results: The PASS1 results confirmed that both experts and naïve readers comprehend SmPC risk-minimization measures, accurately assess Neuraceq® PET scans, and maintain these abilities over time (correct assessments: 96% at baseline and 92% at 6 months follow-up). The PASS2 results revealed that the majority of referring physicians adhered to SmPC specifications in all aspects of their practice, i.e. of the evaluated 126 patient reports only 4 patients (3.2%) were categorized “off-label”. Quantitative methods, employing both CE-marked software and widely available processing tools, consistently demonstrated robust and homogeneous performance, offering valuable support for visual assessments.
Conclusions: Since its approval, Neuraceq® has undergone additional validation across diverse settings in the US and Europe, with effective and enduring reader training, robust quantification for image interpretation, and alignment with clinical selection practices. The presented data are in line with results presented from larger real-world studies, such as AMYPAD, IDEAS, ABIDE or NEUUS. Neuraceq® PET imaging significantly contributed to the advancement of AD drug development and is now primed for use in the forthcoming era of approved disease-modifying AD drugs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0357 / #2312

Poster Topic: *Theme A: β-Amyloid Diseases / A04.b. Imaging, Biomarkers, Diagnostics: Functional MRI*

CAIDE DEMENTIA SCORE RELATES TO INCREASED RISK OF COGNITIVE DECLINE IN HEALTY ELDERLY POPULATION: A NEUROIMAGING STUDY

POSTERS: A04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: FUNCTIONAL MRI

Andras Horvath, Katalin Farkas, Dalida Berente
National Institute of Mental Health, Neurology and Neurosurgery, Neurocognitive Research Center, Budapest, Hungary

Aims: The CAIDE (Cardiovascular Risk Factors, Aging, and Incidence of Dementia) Dementia Risk Score is an established tool to identify late-life dementia risk (20 years later), based on midlife vascular risk and epidemiological factors. The aim of our study was to investigate the utility of CAIDE score in relation to objective biomarkers of cognitive impairment in an elderly population.
Methods: Seventy participants were enrolled from the AlzEpi Cohort Observational Library (ACOL database) of the National Institute of Mental Health, Neurology and Neurosurgery, Budapest, Hungary. Every participant of this study is classified as a healthy elderly control individual (age>65, no cognitive impairment with neuropsychological tests, negative neurological status and brain MRI). All participant underwent a comprehensive cognitive test tool including neuropsychology, structural MRI, resting state fMRI. Subjects were divided into high risk (CAIDE>6) and low risk individuals (CAIDE<7). Intergroup comparisons with covarietes were performed on psychological test results, neural volumes, cortical thickness, global functional connectivity and intranetwork connectivity of default mode network (DMN).
Results: Patients with low CAIDE score had significantly better cognitive performance (e.g., TMT-A test time for low risk group is 34+/−11.9 vs 39.84+/−11.32 in high risk group, $p<0.001$). Reduced brain volumes in entorhinal cortex and precuneus were demonstrated in the high risk population (p:0.011). Subjects with high CAIDE score showed reduced global connectivity indexes, and significant disconnection between the medial prefrontal cortex and posterior cingulate gyrus of the DMN ($p<0.001$).
Conclusions: Our observations reinforce the application of CAIDE score in the prediction of cognitive decline. It also shows that CAIDE score system could be useful even in the risk assessment of healthy elderly since high CAIDE values associate with changes of objective biomarkers related to cognitive deterioration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0358 / #2397

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

GRAPH CONVOLUTIONAL NETWORKS WITH TRANSFER LEARNING FOR ALZHEIMER'S DISEASE CLASSIFICATION USING MULTIMODAL DATA

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Gyu Bin Lee[1,2], Young Jin Jeong[1], Do-Young Kang[1], Hyun Jin Yoon[1], Min Yoon[2]
[1]Dong-A University College of Medicine, Nuclear Medicine, Busan, Korea, Republic of, [2]Pukyong National University, Department Of Applied Mathematics, Busan, Korea, Republic of

Aims: This study evaluates the classification performance of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) using Amyloid PET images and mini-mental state examination (MMSE) scores. Incorporating transfer learning, we compared the 3D Densely Connected Convolutional Networks (DenseNet) using only Amyloid PET images to the Graph Convolutional Networks (GCN) employing both modalities.
Methods: 282 patients from Dong-A University Hospital, comprising 158 with AD and 124 with MCI, underwent Amyloid PET scans and MMSE. The Amyloid PET images were preprocessed using techniques including realignment, cerebellar region-based count normalization, skull stripping, pixel normalization, and trilinear interpolation. The 3D DenseNet first classified MCI and AD using only these images. Then, employing transfer learning, Amyloid PET images and MMSE scores were integrated into graph data for the GCN. Each node represents a patient, and the feature vector of the node utilized the feature extraction results from the 3D DenseNet. Edges connected patients based on image and MMSE score similarities. Various edge assignment methods were tested. The two models' performances were then compared using nested stratified 5-fold cross-validation.
Results: In the classification of MCI and AD using nested stratified 5-fold cross-validation, the 3D DenseNet achieved an accuracy of 0.71, precision of 0.72, recall of 0.80, F1-score of 0.76, and AUC of 0.76. Conversely, the GCN, using multimodal data, recorded better scores: accuracy of 0.79, precision of 0.80, recall of 0.83, F1-score of 0.82, and AUC of 0.83.
Conclusions: Utilizing feature extraction techniques with transfer learning, the GCN approach using multimodal data exhibited better performance in classifying MCI and AD than the 3D DenseNet using only Amyloid PET images. Future studies might explore additional clinical indicators for further enhancement.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0359 / #1993

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

ALZHEIMER'S DISEASE PLASMA BIOMARKER COMPARISON STUDY

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Anna Mammel
Neurocode USA Inc., Neurology, Bellingham, United States of America

Aims: Novel high-sensitivity biomarkers based diagnostic platforms of Alzheimer's disease (AD) have facilitated a movement toward the biological definition of AD. While measurement of amyloid β 42 /40, total Tau, p-Tau, and neurofilament light chain (NfL) in Cerebrospinal fluid (CSF) can distinguish AD from other neurodegenerative disorders. The feasibility of phosphorylated tau biomarkers (pTau181 & pTau217) and neurofilament light chain (NfL) in blood makes them valuable biomarkers for AD diagnosis. Our blood-based biomarker panel can accurately predict the course of cognitive decline in the mild and moderate AD.
Methods: The performance of plasma pTau 181 vs. plasma pTau 217 was studied on EDTA plasma samples of normal controls, amyloid positive (PET+) and negative (PET-) cohorts. The concentrations of plasma p-tau181 were measured by SIMOA on the Quanterix HD-X platform. The levels of plasma pTau217 were measured using a novel commercial plasma based Simoa assay which has been developed by ALZpath. NfL samples were original ran on the HD-X platform (Gothenburg) and were evaluated using the Lumipulse blood assay (Bellingham, WA).
Results: We compared the clinical performance of the two pTau SIMOA assays ran on the same HD-X plate form. pTau217 had a higher AUC (0.92) compared to pTau181 (AUC = 0.81), suggesting a pTau217 has a high predicative values compared to pTau181. NfL levels were compared for healthy controls (N = 98), non-pathological (N = 23), and pathological (N = 20) EDTA-plasma samples. A between platform comparison was performed for the Quanterix HD-X and Fujirebio Lumipulse, with a pearson correlation coefficient of 0.96.
Conclusions: Plasma pTau 217 is more accurate than pTau 181 to rule out other neurodegenerative diseases and diagnosis AD. NfL Lumipulse blood assay had a similar performance to the NfL HD-X.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0360 / #1673

Poster Topic: *Theme A: β-Amyloid Diseases / A04.c. Imaging, Biomarkers, Diagnostics: PET - amyloid*

CENTILOID-BASED PREDICTION FROM STANDARD CLINICAL ASSESSMENTS FOR AMYLOID PET TRIAGE

POSTERS: A04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - AMYLOID

Chris Page, Jan Wolber
GE HealthCare, Pharmaceutical Diagnostics, Chalfont St Giles, United Kingdom

Aims: Deposition of B-amyloid in the brain is a hallmark of Alzheimer's Disease. Demand for robust detection of amyloid presence, such as positron emission tomography imaging, is expected to rise with the advent of anti-amyloid therapies. We propose a model to predict amyloid plaque levels using routine information from early diagnostic workup. The model could help optimise both diagnostic and clinical trial workflows by identifying mild cognitive impairment patients to prioritise for confirmatory amyloid assessments.
Methods: Regression models were trained and evaluated on baseline data from the ADNI-GO/ADNI2, AIBL, BioFINDER-1, and GE Healthcare-sponsored Vizamyl™ ([^{18}F]flutemetamol) Phase 3 and Japanese extension studies, where amyloid PET imaging provides the standard of truth. The models use MRI volumetrics, neuropsychological test scores, patient demographics and APOE genotype to estimate the centiloid (CL) score. An exhaustive data-driven approach to model and feature selection, and hyperparameter tuning, was used to train the models. Use of a synthetic population to further optimise models for a target population was assessed.The models were evaluated as classifiers of negative/uncertain/positive amyloid status by applying thresholds of CL=15 and CL=50 to the predicted score.
Results: A general model for amyloid status prediction trained using five independent studies was built. Use of centiloids allowed the model to leverage dynamic range information instead of the standard dichotomous rating. The model showed classification accuracy for each category of 74-76%. The synthetic population model increased accuracies by ~2%.
Conclusions: The resulting models allow quantitative estimation of amyloid plaque levels in the brain, based on standard demographic, neuropsychological, genetic, and structural imaging measures. Further work using blood-based biomarkers and more granular neuropsychological tests is expected to improve performance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0361 / #2101

Poster Topic: *Theme A: β-Amyloid Diseases / A04.d. Imaging, Biomarkers, Diagnostics: PET - glucose*

DYNAMIC RECONFIGURATION OF METABOLIC BRAIN CONNECTIVITY DURING PROGRESSION FROM MCI TO ALZHEIMER'S DISEASE DEMENTIA

POSTERS: A04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - GLUCOSE

Silvia Paola Caminiti[1], Alice Galli[2], Arianna Sala[3], Marianna Inglese[4], Luca Presotto[5], Cristina Tassorelli[6], Daniela Perani[7]
[1]University of Pavia, Department Of Brain And Behavioral Sciences, Pavia, Italy, [2]University of Brescia, Neurology Unit, Department Of Clinical And Experimental Sciences, Brescia, Italy, [3]Giga Coma Group, University Of Liege, Liege, Belgium, [4]Department of Biomedicine and Prevention, University Of Rome Tor Vergata, Rome, Italy, [5]Università degli Studi Milano-Bicocca, Dipartimento Di Fisica "giuseppe Occhialini", Milano, Italy, [6]University of Pavia, Department of Brain and Behavioral Sciences, Irccs Mondino Foundation, Pavia, Italy, [7]Vita-Salute San Raffaele University, Division Of Neuroscience, Milano, Italy

Aims: To investigate brain connectivity reconfigurations along the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) dementia, using a unique longitudinal design based on metabolic information provided by FDG-PET at three time points.
Methods: We longitudinally analyzed the FDG-PET images of patients with AD according to ATN-classification in the stages of MCI (AD-MCI, N=31), mild dementia (mild-AD, N=31) and full-blown dementia (AD-D, N=20). A group of age/sex-matched healthy controls (HC) was longitudinally evaluated for comparison. We evaluated between-group metabolic connectivity changes at each time point by applying a z-test to the correlation coefficients. Extent of connectivity changes for each region was quantified trhough summary indices indicating hypo and hyperconnectivity. The obtained indices also served as input for a k-means (KM) cluster analysis: KM1)each time point was considered individually to assess the specific hallmark of the disease stage; KM2)three time points analyzed as a single event, to exploit the patterns of connectivity reconfiguration in the AD course.
Results: In AD-MCI, fewer alterations observed compared to mild-AD and AD-D stages. KM1)At AD-MCI stage, "alteration cluster" encompassed subcortical and limbic regions, occipito-parietal cortices, and cerebellum. In mild-AD and AD-D stages, this cluster predominantly involved occipito-parietal cortices and the cerebellum. KM2)Four clusters emerged: Cluster1)Including frontal cortex, insula, and basal ganglia nodes, remained unaffected throughout disease; Cluster2)Prevalent hyperconnectivity in cortical occipito-temporo-parietal nodes; Cluster3)Prevalent hypoconnectivity in subcortical and limbic regions; Cluster4)Featured both hypo and hyperconnectivity in the precuneus throughout disease course.
Conclusions: The current study describes metabolic connectivity changes along the disease course from prodromal to full-blown dementia. Connectivity alterations started from subcortical and AD-prototypical cortical regions. Then, connectivity changes mostly involved cortical associative regions and cerebellum. The precuneus represents a mediator between hyperconnected and hypoconnected hubs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0362 / #1790

Poster Topic: *Theme A: β-Amyloid Diseases / A04.d. Imaging, Biomarkers, Diagnostics: PET - glucose*

[18F]-FDG-PET/CT ANALYSIS OF GLUCOSE METABOLISM IN A MOUSE MODEL OF ALZHEIMER'S DISEASE WITH C456R MUTATION IN NOTCH3

POSTERS: A04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - GLUCOSE

Leila Letica, Sang Ho Choi, Diego Szczupak, Jung Eun Park, David Schaeffer, Afonso Silva
University of Pittsburgh, Neurobiology, Pittsburgh, United States of America

Aims: This work aims to evaluate cortical glucose metabolism in a novel, double-transgenic mouse model of familial Alzheimer's disease (FAD) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The mouse model, referred to as 5xFAD/Notch3C456R, was created by crossing the well-characterized 5xFAD mouse with a knock-in mouse harboring the CADASIL-causing C456R mutation in Notch3, to evaluate the contributions of vascular pathology to AD onset and progression.
Methods: 18F-FDG was delivered to awake mice via a tail vein injection, with an average dose of 18.5 MBq. The mice were fasted for a minimum of 2 hours prior to 18F-FDG administration. PET and CT acquisitions were completed after a 30-minute 18F-FDG circulation period using a Bruker Si78 instrument. Static datasets were analyzed for standard uptake values relative to the brainstem (SUVr) and corrected for glucose levels (SUVglc). Statistical tests performed include unpaired t-test and 1-way ANOVA using GraphPad Prism 9.
Results: Blood glucose levels taken prior to ligand injection showed an age-dependent decrease in WT mice. 12-month-old 5xFAD/Notch3C456R mice presented decreased baseline blood glucose levels and lower whole-brain SUVglc values than age-matched WT controls. ROI analysis revealed the following regions in 5xFAD/Notch3C456R mice exhibited decreased SUVglc levels: Striatum, Cortex, Hippocampus, Thalamus, Cerebellum, Basal Forebrain Septum, Amygdala, Central Gray Matter, Olfactory Bulb, Midbrain, Superior & Inferior Colliculi.
Conclusions: Decreased 18F-FDG uptake across cortical brain regions of 5xFAD/Notch3C456R mice provides evidence of cortical glucose metabolism disruption in a novel double-transgenic mouse model of Alzheimer's Disease with CADASIL Notch3C456R mutations, suggesting that vascular pathology contributes to the etiology and disease progression in AD. We are currently preforming western blot analysis to describe changes in expression of glucose transporter proteins such as GLUT-1,3,4 due to Notch3C456R mutation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0363 / #490

Poster Topic: *Theme A: β-Amyloid Diseases / A04.d. Imaging, Biomarkers, Diagnostics: PET - glucose*

PLASMA P-TAU217 OUTPERFORMS [18F]FDG-PET IN IDENTIFYING BIOLOGICAL ALZHEIMER'S DISEASE IN ATYPICAL AND EARLY-ONSET DEMENTIA

POSTERS: A04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - GLUCOSE

Kely Quispialaya[1], Joseph Therriault[2], Antonio Aliaga[3], Andréa L. Benedet[4], Nicholas Ashton[4], Thomas Karikari[5], Arthur Macedo[2], Nesrine Rahmouni[2], Jenna Stevenson[2], Cécile Tissot[2], Jaime Fernandez Arias[2], Yi-Ting Wang[2], Tharick A Pascoal[5], Serge Gauthier[2], Bertrand Jean-Claude[1], Eduardo R Zimmer[6], Paolo Vitali[2], Jean-Paul Soucy[7], Henrik Zetterberg[8], Kaj Blennow[8], Pedro Rosa-Neto[2]
[1]McGill University, Experimental Medicine, Montréal, Canada, [2]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [3]Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil., Biochemistry (ppgbioq) And Pharmacology And Therapeutics (ppgft), Montreal, Canada, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [5]University of Pittsburgh, Psychiatry, PITTSBURGH, United States of America, [6]Department of Pharmacology, Graduate Program in Biological Sciences: Biochemistry (PPGBioq) and Phamarcology and Therapeutics (PPGFT), Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil, [7]Montreal Neurological Insitute, Neurology, Montreal, Canada, [8]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: To compare the performance of plasma p-tau217 and visual assessments of [^{18}F]FDG-PET to diagnose atypical presentations of Alzheimer's disease
Methods: We conducted a retrospective analysis of individuals with atypical and/or early-onset dementia who were assessed at a specialized memory clinic. All participants underwent CSF evaluations to measure Aβ42, phosphorylated tau (P-tau181), and total tau levels, brain [^{18}F]FDG-PET scans, and plasma p-tau217. The [^{18}F]FDG-PET data were visually examined by two nuclear medicine experts to determine whether they were indicative of AD and CSF biomarker results were categorized as either AD biomarker positive or negative. Contingency analysis was performed to assess the relationships between the PET scan interpretations and CSF biomarker groupings. CSF biomarker groupings were treated as the reference standard.
Results: 75 subjects with early-onset or atypical dementia had CSF AD biomarker evaluations, [^{18}F]FDG-PET ratings, and plasma p-tau217 assessments. Both [^{18}F]FDG-PET and plasma p-tau217 had high levels of agreement with reference standard CSF AD biomarkers ([^{18}F]FDG-PET: 69%; plasma p-tau217:81%). Although both biomarkers had similar specificity for AD ([^{18}F]FDG-PET: 67%, plasma p-tau217 70%), plasma p-tau217 had higher sensitivity for abnormal CSF AD biomarkers (97%). Overall accuracy was also higher for plasma p-tau217 (AUC=83%, 95%CI = 0.74- 0.83). The same pattern of results was observed when using amyloid-PET as the reference standard.
Conclusions: Our study provides evidence that plasma p-tau217 has excellent diagnostic performance for AD in individuals with early-onset or atypical dementia evaluated in specialized settings. The topographical information from [^{18}F]FDG-PET may give complementary information.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0364 / #2249

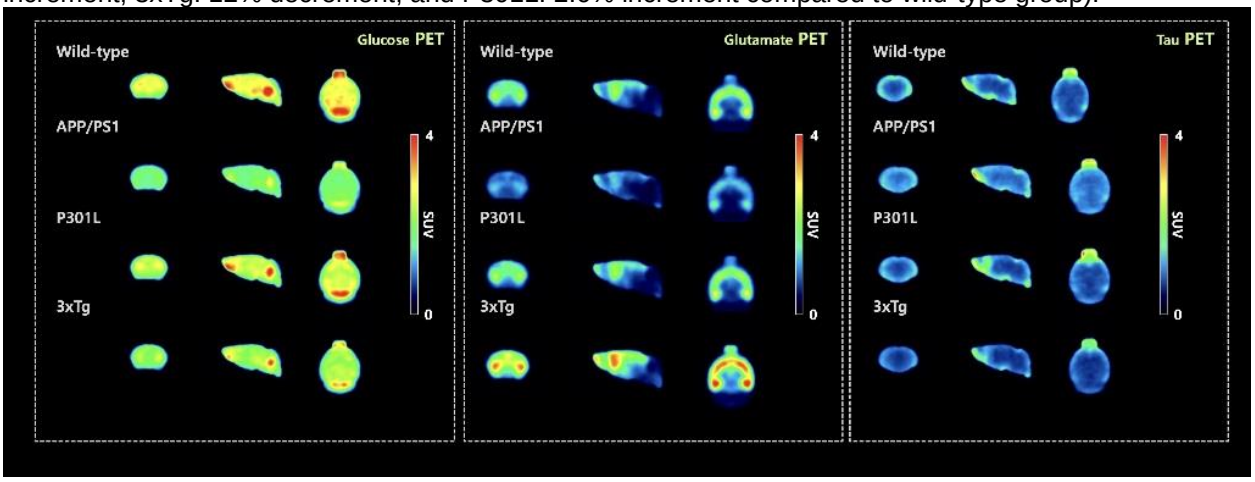
Poster Topic: *Theme A: β-Amyloid Diseases / A04.e. Imaging, Biomarkers, Diagnostics: PET - other*

EVALUATION OF THE NEURONAL CHANGES OF VARIOUS ALZHEIMER'S ANIMAL MODELS BY PET

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

Sang Jin Han[1], Se Jong Oh[1], Sungsu Lim[2], Kyung June Kang[1], Kyung Rok Nam[1], Yun Kyung Kim[2], Jae Yong Choi[3]
[1]Korea Institute of Radiological & Medical Sciences, Division Of Applied Ri, Seoul, Korea, Republic of, [2]Korea Institute of Science and Technology, Brain Science Institute, Seoul, Korea, Republic of, [3]Korea Institute of Radiological & Medical Sciences, Division Of Applied Ai, Seoul, Korea, Republic of

Aims: Alzheimer's disease (AD) is a representative senile neurodegenerative disease and its prevalence is gradually increasing. Many researchers have used animal models to elucidate the pathophysiology of AD, but there are still few animal models in vivo that reflect the progress of AD in clinical practice in a non-invasive way. Therefore, the aim of the present study is to examine neuronal changes in vivo using various AD animal models.
Methods: In this study, the various transgenic AD mice models, including APP/PS1(female, n = 2), 3xTg (female, n = 3), P301L (female, n =4), and age-matched wild-type mice (female, n = 3) were used for positron emission tomography (PET) studies. At 17 months of age, neuroPET studies were formed using [18F]FDG, [18F]FPEB, and [18F]Av-1451 for evaluation of glucose metabolism, glutamate system, and tau pathology, respectively.
Results: In glucose PET, brain uptakes in APP/PS1 mice decreased from 15.6 to 35% compared to wild-type groups, 3xTg and P301L mice showed 9.3 to 26.8%, and 2.9 to 15.8% reduced uptakes, respectively. In glutamate PET, brain uptakes in APP/PS1 mice decreased by 31-42% compared to the wild-type group, and the uptakes in 3xTg mice were increased by 52-54%. However, the uptakes in P301L mice showed similar to wild-type (0.9-2.8% decrement compared to wild-type). In tau PET, there was no significant difference between the transgenic mice and the wild-type group (APP/PS1: 6.7% increment, 3xTg: 12% decrement, and P301L: 2.6% increment compared to wild-type group).



Conclusions: From this study, we demonstrated AD animal models showed overall hypometabolism in glucose PET, but glutamate PET showed different uptake patterns depending on the group, and tau PET showed no significant difference from wild-type.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0365 / #2243

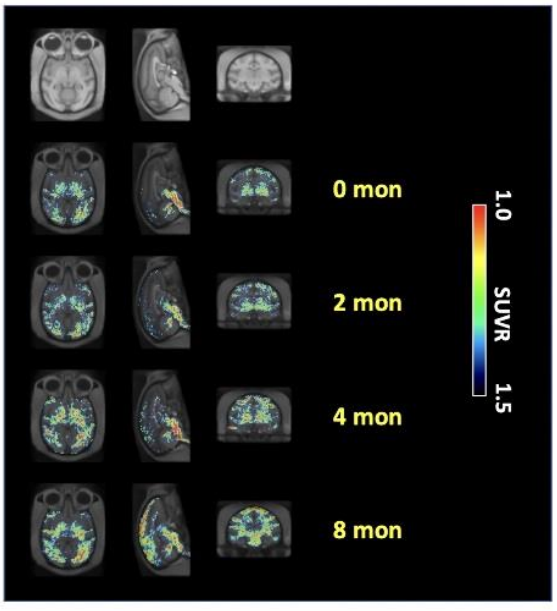
Poster Topic: *Theme A: β-Amyloid Diseases / A04.e. Imaging, Biomarkers, Diagnostics: PET - other*

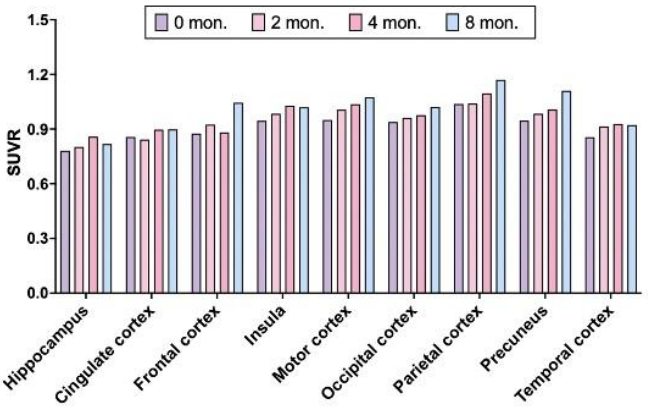
LONGITUDINAL AMYLOID PET IN PRIMATES ALZHEIMER'S MODELS USING AB OLIGOMERS

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

Kyung Rok Nam[1], Junghyung Park[2], Jinyoung Won[2], Kyung Seob Lim[2], Chang-Yeop Jeon[2], Yu Gyeong Kim[2], Seung Ho Baek[2], Youngjeon Lee[2], Jae Yong Choi[3]
[1]Korea Institute of Radiological & Medical Sciences, Division Of Applied Ri, Seoul, Korea, Republic of, [2]Korea Research Institute of Bioscience and Biotechnology, National Primate Research Center, Cheongju, Korea, Republic of, [3]Korea Institute of Radiological & Medical Sciences, Division Of Applied Ai, Seoul, Korea, Republic of

Aims: Alzheimer's disease is the most common neurodegenerative disease, and its prevalence is increasing as society becomes aging, but there are no fundamental therapeutic drugs until now. Therefore, preclinical studies, especially non-human primate experiments, are important to understand the pathophysiology of AD. In the present study, we would like to introduce a longitudinal amyloid PET in the non-human primate AD model
Methods: In the present study, we used two adult rhesus female monkeys (13 years old), and baseline amyloid PET scans were performed before Aβ oligomer injection. After Aβ oligomer administration (100μg/dose x 12 times) in artificial cerebrospinal fluid, subsequent amyloid PETs were obtained a total of 4 times every 2 months from 2 months of age. Here, [18F]florbetaben was used as a specific radiotracer to detect amyloid-β plaques. For quantitative comparison, a standardized uptake value ratio (SUVR) was used with the cerebellum as the reference region.
Results:





When evaluating the distribution of brain uptakes by dividing the early (0-20 min, p.i), mid (20-60min, p.i.), and late time windows (60-120 min) in dynamic PET, the late time zone generated the clear distinction between white and gray matter. Therefore, we used this time window as SUVR estimation. Overall, brain uptakes in cortical and sub-cortical areas gradually increased over time. In particular, PET uptake has steadily increased in motor, occipital, parietal cortices, and precuneus. At 8 months of age, brain uptakes

in these areas showed an increase of 8.7-19.2% compared with baseline PET (the rate of increase, motor cortex: 13.1%, occipital cortex: 8.7%, parietal cortex: 12.8%, precuneus: 17.8%)

Conclusions: From this study, we demonstrated that in vivo amyloid pathology in a non-human primate AD model produced by injecting amyloid oligomers increased over time.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0366 / #2422

Poster Topic: *Theme A: β-Amyloid Diseases / A04.d. Imaging, Biomarkers, Diagnostics: PET - glucose*

BRAIN HYPOMETABOLISM AND ERRORS ON THE CLOCK DRAWING TEST PREDICT CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DEMENTIA

POSTERS: A04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - GLUCOSE

Giacomo Tondo[1], Fabiola De Marchi[2], Federico Menegon[3], Martina Filippone[1], Silvia Caminiti[4], Roberta Matheoud[5], Gian Mauro Sacchetti[6], Daniela Perani[7], Cristoforo Comi[1]
[1]Neurology Unit, Sant'Andrea Hospital, Vercelli, University Of Piemonte Orientale, Vercelli, Italy, [2]University of Piemonte Orientale, Department Of Neurology, Novara, Italy, [3]University of Piemonte Orientale, Department Of Translational Medicine, Novara, Italy, [4]University of Pavia, Department Of Brain And Behavioral Sciences, Pavia, Italy, [5]University Hospital "Maggiore della Carità", Medical Physics Department, Novara, Italy, [6]Nuclear Medicine Department, University Hospital Maggiore Della Carità, Novara, Italy, [7]University Vita Salute San Raffaele, In Vivo Imaging Unit, Milan, Italy

Aims: Mild Cognitive Impairment (MCI) is associated with increased risk of developing dementia, especially Alzheimer's dementia (AD). Several markers have been explored as conversion predictors from MCI to AD. The clock drawing test (CDT) is a screening test revealing executive, working memory and visuospatial deficits. Brain FDG-PET is a neuroimaging technique underlining specific hypometabolism patterns reflecting neuronal dysfunction. We aimed to correlate CDT errors and FDG-PET hypometabolism patterns in MCI, evaluating the combination of different CDT errors and brain hypometabolism pattern in predicting conversion to AD.
Methods: We included 65 MCI (Petersen,2004) with a baseline CDT and FDG-PET scan. CDT errors were qualitatively classified (Parsey,2011) in stimulus-bound (STIMULUS), conceptual (CONCEPTUAL), spatial (VISUOSPATIAL), and perseveration (PERSEVERATION) errors. FDG-PET images were analyzed with a validated SPM method (Perani,2014) to obtain single-subject brain hypometabolism maps using a large dataset of controls for comparison (Caminiti,2021). MCI subjects were longitudinally evaluated and classified according to the diagnosis at follow-up in stable MCI, AD, frontotemporal dementia, or Lewy bodies dementia.
Results: MCI subjects performing correctly to the CDT showed a normal metabolism (NORMAL). The PERSEVERATION and the VISUO-SPATIAL error groups showed hypometabolism in temporoparietal regions, posterior cingulate, and precuneus (corresponding to typical AD pattern). The STIMULUS error group showed left hypometabolism in frontotemporal cortices. The CONCEPTUAL error group was characterised by widespread hypometabolism (frontotemporal, parietal, occipital cortices). At follow-up, none of the NORMAL MCI converted to dementia. Conversely, in PERSEVERATION group, 85% of MCI converted to dementia. An AD hypometabolism pattern in PERSEVERATION error group predicted AD conversion with high accuracy (AUC=85%).
Conclusions: Combining CDT qualitative errors and semi-quantitative analysis of brain FDG-PET accurately predicts conversion to AD or other dementia conditions, aiding, at the baseline, a clinical stratification of MCI subjects.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0367 / #2245

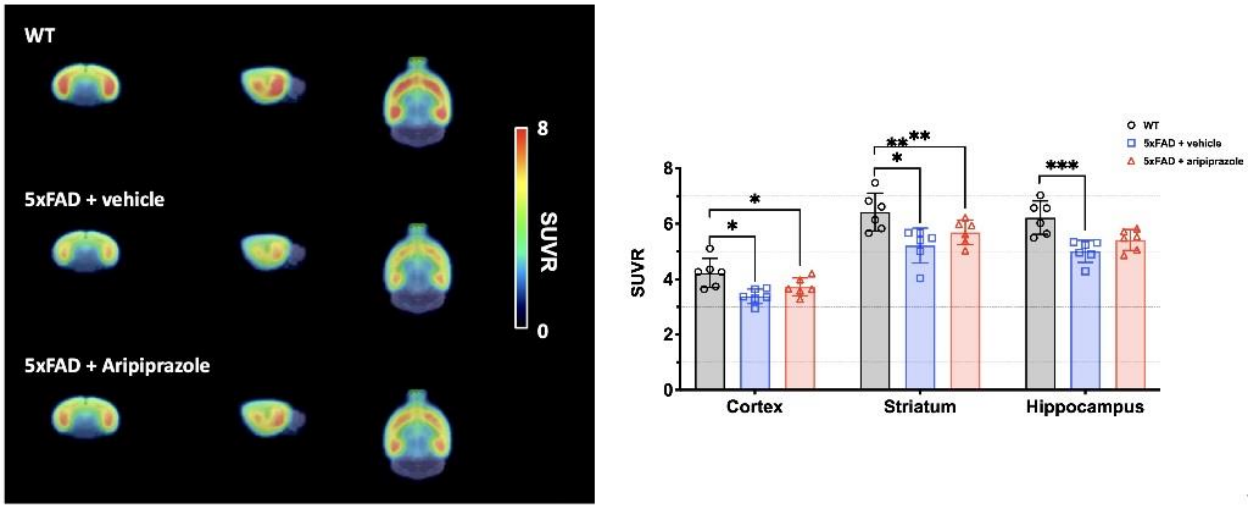
Poster Topic: *Theme A: β-Amyloid Diseases / A04.e. Imaging, Biomarkers, Diagnostics: PET - other*

EVALUATION OF THE EFFECTS OF ARIPIPRAZOLE ADMINISTRATION ON THE BRAIN GLUTAMATE SYSTEM

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

Hae-June Lee[1], Hyun-Yong Kim[1], Se Jong Oh[2], Yeonghoon Son[1], Kyung June Kang[2], Kyung Rok Nam[2], Jae Yong Choi[3]
[1]Korea Institute of Radiological & Medical Sciences, Division Of Radiation Bioscience, Seoul, Korea, Republic of, [2]Korea Institute of Radiological & Medical Sciences, Division Of Applied Ri, Seoul, Korea, Republic of, [3]Korea Institute of Radiological & Medical Sciences, Division Of Applied Ai, Seoul, Korea, Republic of

Aims: The main clinical symptom of Alzheimer's disease (AD) is cognitive impairment, and it is well-known that this cognitive dysfunction is closely related to the prevalence of psychotic symptoms. In addition, the glutamate system in the central nervous system plays an important role in learning and memory. To date, however, studies on the effects of anti-psychotic drugs on the glutamate system have been limited. The aim of the current study is to investigate the effect of aripiprazole on the glutamate system in an AD animal model using functional molecular imaging.
Methods: In this study, the transgenic 5xFAD mice were used as an AD animal model. At the age of 5 months, the female mice were classified into a wild-type, a vehicle control group, and an aripiprazole-treated group (n = 6 for each group). In addition, from 5 months to 7 months of age, the aripiprazole-treated group administered aripiprazole intraperitoneally at a dose of 1 mg/kg every day, and the vehicle group administered only solvents. At 8 months of age, glutamate PET images were acquired using a specific radiotracer for a metabotropic glutamate receptor 5 (mGlur5).
Results: A vehicle-treated 5xFAD mice showed a 19-20% reduction of brain uptakes compared to the wild-type group. However, the aripiprazole-treated 5xFAD group displayed 11-13% lowered brain uptake values compared to the wild-type. The available mGluR5 binding was 7-8% higher in the aripiprazole-treated 5xFAD group than that in the vehicle-treated group. In the immunohistochemistry experiments, aripiprazole administration resulted in decreased mGluR5 damage in the hippocampus compared to that in the vehicle group.



Conclusions: From this study, we demonstrated that the administration of aripiprazole plays a role in preventing glutamate damage.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0368 / #2065

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

A DEEP LEARNING FRAMEWORK FOR CLINICAL TRIAL ENRICHMENT IN ALZHEIMER'S DISEASE

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Luis Peraza Rodriguez, Robin Wolz, Colm Mcginnity, Richard Joules
IXICO, Research & Development, London, United Kingdom

Aims: Selection of participants at risk of cognitive decline in clinical trials, trial enrichment, increases the probability of trial success. Here we present a deep-learning (DL) framework for trial enrichment that uses a combination of imaging and clinical/demographic variables as input, and has built-in redundancy allowing the system to work effectively with missing inputs.
Methods: We employed T1w and amyloid-PET images from ADNI (CN=270, MCI=595, AD=59), OASIS-3 (CN=367, MCI=20, AD=67) and AMYPAD (CN=808, MCI=4) repositories. Images were pre-processed by validated pipelines for volumetric and SUVR estimation. Training-set participants were labelled as stable or decline through hierarchical clustering, where a stable participant experienced no significant decline within a 36-month period. Our framework comprises two phases: first, Siamese convolutional neural networks (CNN) were trained with decline/stable targets and neuroimages as inputs. Then, a battery of random forest classifiers were trained with CNN outputs, neuroimaging derivatives, and demographics/clinical data inputs and decline/stable targets.
Results: When using complete inputs, our framework reached mean accuracy of 93% and a positive predictive value (PPV) of 87% in test sets, and a mean accuracy of 90%, with 86% PPV in cross-dataset validations (e.g., train on ADNI, test on OASIS-3, AMYPAD and so on). The best predictor of decline was baseline CDR-SB score, followed by CNN-PET, CNN-MRI, hippocampal volume, and SUVR. In the absence of PET data, our framework reached a mean accuracy of 88% and 87% PPV in cross-dataset validations. In the absence of baseline CDR-SB, our framework reached 87% mean accuracy and 80% mean PPV in cross-dataset validations, with CNN-PET becoming best predictor.
Conclusions: Our trial enrichment framework showed high accuracy when predicting future cognitive decline. The DL models highly contributed to the prediction of decline which guarantees further research.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0369 / #1399

Poster Topic: *Theme A: β-Amyloid Diseases / A04.e. Imaging, Biomarkers, Diagnostics: PET - other*

HIPPOCAMPAL SYNAPTIC DENSITY ESTIMATED WITH 11C-UCB-J PET AND ITS ASSOCIATION WITH COGNITIVE PERFORMANCE IN HEALTHY ELDERLY APOE4 CARRIERS

POSTERS: A04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - OTHER

Anniina Snellman[1], Jouni Tuisku[1], Laura Ekblad[1], Mikko Koivumäki[1], Saara Wahlroos[2], Mira Karrasch[3], Juha Rinne[1]
[1]University of Turku, Turku Pet Centre, Turku University Hospital, Turku, Finland, [2]University of Turku, Turku Pet Centre, Turku, Finland, [3]Åbo Akademi University, Department Of Psychology, Turku, Finland

Aims: Synaptic loss is one of the pathological features of Alzheimer's disease (AD). Here, we investigated **i)** differences in hippocampal synaptic density *in vivo* using ^{11}C-UCB-J positron emission tomography (PET) in cognitively unimpaired individuals with varying number of *APOE4* alleles and risk for sporadic AD, **ii)** association between hippocampal synaptic density, brain Aβ load and cognitive performance in the whole study sample.
Methods: 46 individuals (*APOEε4ε4* n=14; *APOEε4ε3* n=16; *APOEε4ε4* n=16) from the ASIC-E4 study participated in ^{11}C-UCB-J PET, brain MRI and cognitive testing using CERAD and APCC batteries during years 2020-2022. Amyloid PET was performed 21 months (median, interquartile range 19-22) earlier with ^{11}C-PiB. Hippocampal ^{11}C-UCB-J standardized uptake value ratios (SUVr) were calculated using centrum semiovale as a reference region, and hippocampal volumes obtained by FreeSurfer. Differences between the *APOE* genotypes were tested with ANOVA, and subsequent sensitivity analysis was performed by further adjusting for age, sex, education and hippocampal volume. Associations with Aβ and cognitive variables were tested with Spearman's correlation.
Results: Significant difference in hippocampal ^{11}C-UCB-J binding was present between the *APOE4* groups (p_{ANOVA}=0.016), *APOEε4ε4* showing lower SUVrs (mean 2.90, SD 0.30) compared to *APOEε3ε3* (mean 3.33, SD 0.35, p=0.013). Significant difference was also present between *APOE4* carriers and non-carriers (p=0.010), but not between Aβ-positive and Aβ-negative individuals (p=0.11). Statistically significant findings remained unchanged when adjusted for age, sex, education and hippocampal volume. Hippocampal SV2A binding did not correlate with CERAD total score (r=-0.052, p=0.74), APCC score (r=0.17, p=0.28) or global ^{11}C-PiB uptake (r=-0.10, p = 0.50) in our sample.
Conclusions: Our data suggests that hippocampal synaptic loss is an early event in the AD continuum, and measurable *in vivo* already in cognitively unimpaired at-risk individuals.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0370 / #310

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

ULTRASOUND-GUIDED DRY NEEDLING FOR VERTIGO MANAGEMENT IN A COMBAT PATIENT WITH SKULL TRAUMA: A NOVEL CASE REPORT

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Rostyslav Bubnov[1], Lev Kalika[2], Zbigniew Pilecki[3], Grzegorz Pilecki[3]
[1]Clinical hospital `Pheophania`, Ultrasound, Kyiv, Ukraine, [2]New York Dynamic Neuromuscular Rehabilitation & Physical Therapy, Rehab, New York, United States of America, [3]Center of Sport Medicine, Orthopedics, Zabrze, Poland

Aims: To investigate the efficacy of US-guided dry needling in managing vertigo symptoms associated with musculoskeletal issues following skull trauma. To explore the neurophysiological responses and potential mechanisms of action of US-guided dry needling in treating vertigo. To emphasize the importance of careful assessment and multidisciplinary collaboration in tailoring treatment for combat patients with skull trauma.
Methods: Case Diagnosis: A 30-year-old male combat patient with a history of skull trauma presenting with vertigo and neck pain. Ultrasound diagnosis revealing multiple trigger points in the neck and shoulders. Application of US-guided dry needling to suboccipital muscles, including m. rectus capitis post major and m. obliquus capitis inf., with one needle incidentally touching the dura mater. Assessment of extralong needle grasp pattern and referred pain in the occipital area.
Results: Immediate relief from vertigo symptoms and elimination of neck pain observed after US-guided dry needling. The technique's effectiveness attributed to its impact on trigger points and specific neurophysiological responses. Caution emphasized due to the complexity of the procedure, necessitating expertise and careful patient evaluation, particularly in combat patients with skull trauma.
Conclusions: US-guided dry needling demonstrates promise as a potential intervention for managing vertigo associated with musculoskeletal issues post-skull trauma. The technique's efficacy may be linked to its influence on trigger points and neurophysiological responses. In cases involving intracranial needling, only experienced practitioners should perform the procedure, with thorough patient assessment to ensure safety and suitability. A multidisciplinary approach is essential for tailoring individualized management plans, thereby enhancing treatment outcomes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0371 / #903

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

ASSOCIATIONS BETWEEN NEUROINFLAMMATION AND BRAIN BETA-AMYLOID ACCUMULATION IN AN ELDERLY POPULATION – A 5-YEAR FOLLOW-UP STUDY WITH [11C]PBR28 AND [11C]PIB PET IMAGING

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Laura Ekblad[1], Teemu Kipinoinen[1], Anniina Snellman[1], Matti Viitanen[2], Semi Helin[1], Antti Jula[3], Sini Toppala[1], Jouni Tuisku[1], Juha Rinne[1]
[1]University of Turku, Turku Pet Centre, Turku, Finland, [2]University of Turku, Department Of Geriatrics, Turku, Finland, [3]Finnish Institute for Health and Welfare, Public Health And Wellbeing, Turku, Finland

Aims: Neuroinflammation appears to participate in the Alzheimer's disease (AD) pathogenesis, but the temporal course of neuroinflammation across the disease stages remains unclear. In this 5-year follow-up study we aimed to evaluate if neuroinflammation predicts Aβ accumulation by examining dementia-free elderly individuals at baseline and at follow-up using [^{11}C]PBR28 positron emission tomography (PET) scans for TSPO availability (neuroinflammation) and [^{11}C] Pittsburgh compound B ([^{11}C]PiB)-PET scans for beta-amyloid (Aβ) accumulation.
Methods: We examined 40 volunteers (median age at follow-up 74.2, 55% women, 50% APOEε4 carriers) in 2014-2016 and 2019-2021 with [^{11}C]PBR28 and [^{11}C]PiB PET. [^{11}C]PBR28 and [^{11}C]PiB binding was quantified for a cortical composite region-of-interest using standardized uptake value ratio (SUVR) with respect to cerebellar cortex. We employed a linear regression model adjusted to age, sex and TSPO genotype to examine associations between [^{11}C]PBR28 binding and [^{11}C]PiB binding at baseline and follow-up. Associations were further evaluated based on baseline Aβ-positivity (cut-off for positivity [^{11}C]PiB SUVR = 1.5).
Results: In the model adjusted for age, sex and TSPO genotype, baseline [^{11}C]PBR28 did not predict follow-up [^{11}C]PiB binding (β=-0.59, p=0.72), and baseline Aβ status did not modify this association (β=1.01, p=0.23 for Aβ-negative; slope=3.85, p=0.072 for Aβ-positive). However, in cross-sectional analyses with Aβ-negative individuals, [^{11}C]PBR28 binding was associated with Aβ accumulation both at baseline (β=1.43, p=0.018) and at follow-up (β=0.68, p=0.032).
Conclusions: Neuroinflammation measured with [^{11}C]PBR28 PET showed no association with Aβ accumulation in prospective design. However, concurrent assessment revealed an association between neuroinflammation and amyloid accumulation at both timepoints in the participants who were still amyloid negative. Our results suggest that neuroinflammation might be important in the earliest phases of Aβ accumulation. However, baseline neuroinflammation does not predict Aβ accumulation during a 5-year follow-up.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0372 / #1446

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

UK BIOBANK IMAGING IN A MEMORY CLINIC POPULATION: ASSOCIATIONS BETWEEN IMAGING-DERIVED PHENOTYPES AND COGNITIVE DOMAINS IN THE OXFORD BRAIN HEALTH CLINIC

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Grace Gillis[1,2], Gaurav Bhalerao[1], Clare O'Donoghue[1,2], Jasmine Blane[1,2], Robert Mitchell[1,2], Lola Martos[1,2], Vanessa Raymont[1,2], Clare Mackay[1], Ludovica Griffanti[1,2]
[1]University of Oxford, Psychiatry, Oxford, United Kingdom, [2]Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, United Kingdom

Aims: The Oxford Brain Health Clinic (BHC) has seen over 200 NHS memory clinic patients. In addition to high-quality cognitive and lifestyle assessments and opportunities for research participation, patients receive a clinical MRI scan (T1-weighted, T2-FLAIR, and SWI) and can consent to additional research scans (dMRI, rfMRI, and ASL) aligned to the UK Biobank. We aimed to automatically extract imaging-derived phenotypes (IDPs) and explore associations with cognition and diagnoses in this real-world memory clinic population.
Methods: Scans from 213 BHC patients, 122 of whom completed all additional research scans, were processed using the UK Biobank pipeline with previously described modifications and supplementary quality control. Using the ACE-III, cognition was assessed across the following domains: memory, attention, language, verbal fluency, and visuospatial abilities. We performed regression analyses to test associations of IDPs with cognitive scores (N=203) and subsequent diagnoses (dementia, MCI, no dementia-related diagnosis; N=184). Results were controlled for age, sex, head size, and corrected for multiple comparisons.
Results: Out of 4100 IDPs of interest, 47 and 49 IDPs significantly associated with ACE-III scores and diagnoses, respectively (Benjamini-Yekutieli correction; Figures 1-2). While many associations align with known dementia-related atrophy patterns, others are less well-established. Memory sub-scores associated with 52 IDPs including many temporal lobe volumes, while visuospatial sub-scores associated with 10 IDPs mainly clustered in the occipital and parietal lobules. Language sub-scores associated with 16 IDPs, 13 of which were left-localised. **Fig1**: Associations between IDPs and ACE-III total scores.

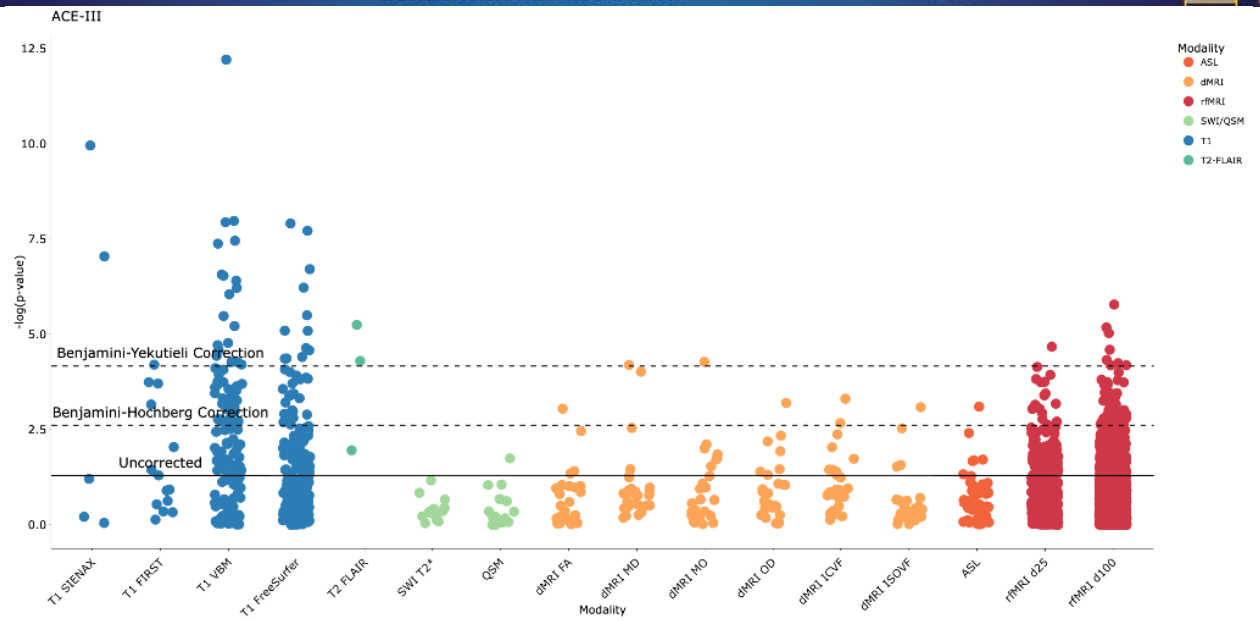
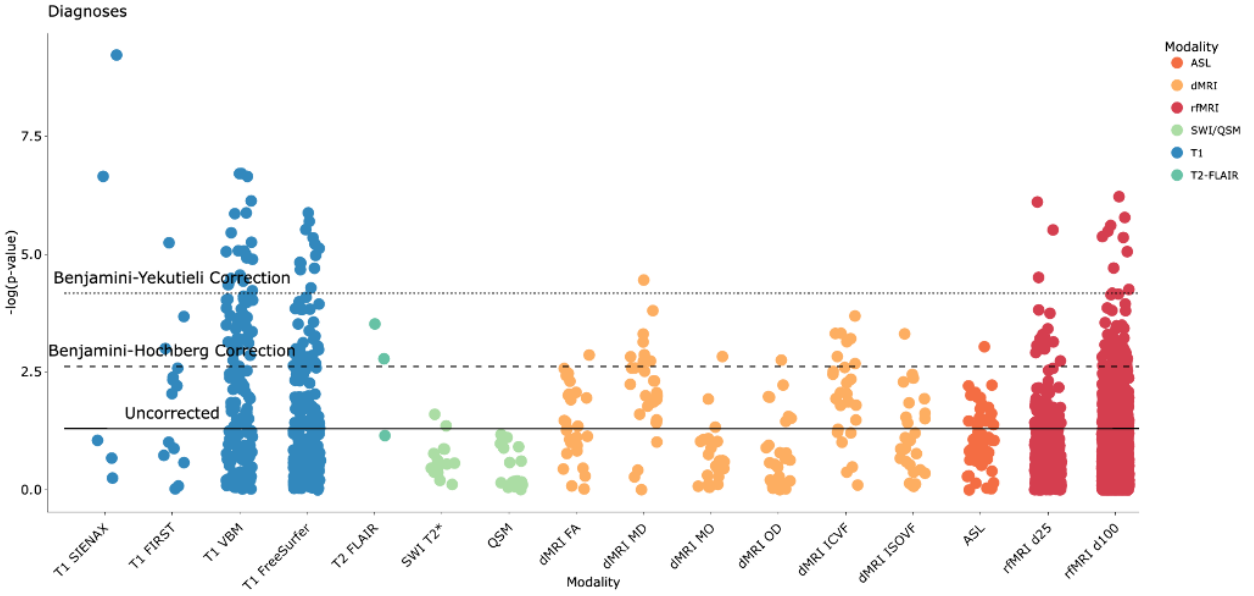


Fig2: Associations between IDPs and diagnoses.



Conclusions: By using an unselected memory clinic population, this work provides real-world validation of associations well-established in research, while also supporting specific patterns of changes associated with cognitive domains. This represents a key step towards integrating research-quality imaging in memory clinics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0373 / #823

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

EXPLORING THE ROLE OF BRAIN MRI IN THE MEMORY CLINIC PATHWAY FOR THE DEPLOYMENT OF DISEASE MODIFYING THERAPIES FOR AD

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Ludovica Griffanti[1,2], Grace Gillis[1,2], Pieter Pretorius[3], Robert Mitchell[2], Vanessa Raymont[1,2], Lola Martos[1,2], Clare Mackay[1,2]
[1]University of Oxford, Department Of Psychiatry, Oxford, United Kingdom, [2]Warneford Hospital, Oxford Health Nhs Foundation Trust, Oxford, United Kingdom, [3]Oxford University Hospitals NHS Trust, Neuroradiology, Oxford, United Kingdom

Aims: We explored the role of brain MRI for diagnosis and screening eligibility to receive monoclonal antibodies in a real-world UK memory clinic population from the Oxford Brain Health Clinic (BHC).
Methods: 237 people referred to the BHC (O'Donoghue et al., 2023 BMJOpen) received a 3T brain MRI scan which was reported using a standardised template (Griffanti et al., 2022 Neuroimage:Clinical). Information about diagnosis was obtained after the memory clinic appointment. Psychiatrists were asked to report on their confidence in diagnosis (0-5 scale, consensus of 2 clinicians) on a subset of 12 BHC patients (receiving advanced assessments including MRI) and 14 patients seen in memory clinic but who did not attend the BHC. From the MRI report, we extracted the type and amount of brain anomalies that would meet an exclusion criterion for Lecanemab or Aducanumab, according to published Appropriate Use Recommendations.
Results: Out of the 237 consecutive patients, 95 (40%) were diagnosed with MCI or mild AD (IC10 codes F06.7, F00.0, F00.1 or F00.9 and ACE-III 60-100). Psychiatrists reported increased confidence in diagnosis for BHC patients (average score 4.04 vs 3.29 for non-BHC patients) and an evaluation on a bigger sample is currently ongoing. 22 MCI/mild AD patients (23%) had one or more brain anomalies that would make them ineligible for Lecanemab or Aducanumab (N=3 with more than 4 microhemorrhages; N=10 periventricular or deep Fazekas score greater than 3; N=9 infarcts; N=1 hemorrhage; N=2 superficial siderosis or hemosiderin deposit; N=1 meningioma).
Conclusions: MRI performed in the memory clinic diagnostic pathway and reported using a standard template can increase confidence in diagnosis and be used for screening eligibility for monoclonal antibodies, potentially saving around 20% of amyloid investigations (PET or CSF).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0374 / #2352

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

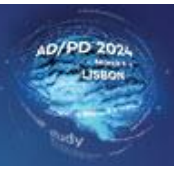
MASS SPECTROMETRY IMAGING REVEALS REGION-SPECIFIC ALTERATIONS OF BRAIN LIPIDS INDUCED BY PARKINSONISM AND L-DOPA-INDUCED DYSKINESIA

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Ibrahim Kaya[1], Theodosia Vallianatou[1], Anna Nilsson[1], Patrik Bjärterot[1], Dominika Luptáková[1], Yachao He[2], Reza Shariatgorji[1], Per Svenningsson[2], Erwan Bezard[3], Per Andrén[1]
[1]Uppsala University, Department Of Pharmaceutical Biosciences, Uppsala, Sweden, [2]Uppsala University, Department Of Clinical Neuroscience, Stockholm, Sweden, [3]Univ. de Bordeaux, CNRS, IMN, UMR 5293,, 1inst. Of Neurodegenerative Dis, Bordeaux, France

Aims: The aim of the study is to comprehensively map different molecular species (spatial omics), such as neurotransmitters, neuropeptides, and lipids in specific brain regions, using brain samples from an experimental Parkinson's disease (PD) model (MPTP, *Macaca mulatta*) with L-DOPA-induced dyskinesia (LID).
Methods: We employed matrix-assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI) methods for the visualisation of neurotransmitters, neuropeptides and lipids within several brain regions of the coronal brain tissue sections within this project. For this study, all of the MALDI-MSI experiments for lipid imaging were performed in both negative and positive ionization modes on the same tissue sections using a MALDI-FTICR (7T solariX XR-2ω, Bruker Daltonics) mass spectrometer equipped with a Smartbeam II 2 kHz laser.
Results: We previously observed abnormal elevations of L-DOPA and its metabolite, 3-O-methyldopa, in the whole brain of LID animals. This resulted in increased dopamine and downstream metabolites in all brain regions, except putamen and caudate. Furthermore, we found that the abundance of selected neuropeptides was associated with L-DOPA concentrations in the putamen, emphasizing their sensitivity to L-DOPA. In this study, we conducted extensive imaging of various lipid species, enabling the detection of specific distributions of hydroxylated and non-hydroxylated sulfatide lipids within the same individual brains. Hydroxylated sulfatides were abundant within several basal ganglia brain regions, whereas long-chain hydroxylated sulfatides were depleted in motor-related regions, with non-hydroxylated showing an elevation. When comparing individuals with LID to those without dyskinesia, we observed a decrease in plasmalogen phosphatidylcholines and an increase in polyunsaturated fatty acid-containing glycerophospholipids specifically in the internal segment of globus pallidus. These changes were significantly correlated with the LID scores of the animals.
Conclusions: This MALDI-MSI study provides valuable insights into signaling system dynamics during PD and its treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0375 / #2380

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

OPTICAL DIFFERENTIATION OF PROTEIN AGGREGATES IN DIFFERENT TYPES OF ALZHEIMER´S DISEASE AND ALPHA-SYNUCLEINOPATHIES USING THIOPHENE-BASED LIGANDS

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Therése Klingstedt[1], Linnea Björk[1], Hamid Shirani[1], Martin Ingelsson[2,3,4], Ruben Vidal[5], Bernardino Ghetti[5], Peter Nilsson[1]
[1]Linköping University, Department Of Physics, Chemistry And Biology, Linköping, Sweden, [2]Uppsala University, Department Of Public Health And Caring Sciences, Uppsala, Sweden, [3]University Health Network, Krembil Brain Institute, Toronto, Canada, [4]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [5]Indiana University School of Medicine, Department Of Pathology And Laboratory Medicine, Indianapolis, United States of America

Aims: The aim of this study was to investigate binding of a variety of thiophene-based ligands to amyloid-β (Aβ) deposits in Alzheimer´s disease (AD), as well as to α-synuclein (α-syn) inclusions in α-synucleinopathies.
Methods: For Aβ, cases of sporadic and inherited AD were included. For this study, inherited AD consisted of mutation carriers of the *APP* or *PSEN1* genes; α-synucleionopathies consisted of Parkinson's disease (PD) or multiple system atrophy (MSA). Brain tissue sections from each case were stained with combinations of thiophene-based ligands such as HS-276 and LL-1. The ligand staining patterns were compared using hyperspectral imaging and ligand specificity was confirmed by immunohistochemistry.
Results: When applying different dual staining protocols with specific thiophene-based ligands, distinct staining patterns of Aβ deposits were revealed for sporadic versus inherited AD. For example, with a combination of ligands HS-276 and LL-1, HS-276 was most prominent in sporadic AD, whereas LL-1 was most prominent in an *APP* E693G case. In addition, within the group of inherited AD, a difference in ligand staining could be seen. Differential staining patterns were also observed in the analysis of α-syn inclusions in PD versus MSA.
Conclusions: Dual staining protocols with different thiophene-based ligands allow a more precise differentiation of Aβ deposits in sporadic and inherited AD, as well as α-syn inclusions in PD and MSA. This study also highlights the importance of having a toolbox of ligands to enable detection and differentiation of the entire spectrum of disease-associated Aβ or α-syn pathologies. Hence, a variety of ligands is probably essential for an early and accurate diagnosis of different types of AD and α-synucleinopathies, as well as for monitoring disease progression and evaluating potential treatment strategies for these diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0376 / #308

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

BLOOD BIOMARKERS OF NEURODEGENERATION ASSOCIATE DIFFERENTLY WITH AMYLOID DEPOSITION, MEDIAL TEMPORAL ATROPHY, AND CEREBROVASCULAR CHANGES IN APOE E4-ENRICHED COGNITIVELY UNIMPAIRED ELDERLY

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Mikko Koivumäki[1], Laura Ekblad[2], Juan Lantero-Rodriguez[3], Nicholas Ashton[3], Thomas Karikari[4,5], Semi Helin[1], Riitta Parkkola[6], Jyrki Lötjönen[7], Henrik Zetterberg[8], Kaj Blennow[9], Juha Rinne[10], Anniina Snellman[1]
[1]University of Turku, Pet-centre, Turku, Finland, [2]Turku University Hospital, Department Of Geriatric Medicine, Turku, Finland, [3]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [4]University of Gothenburg, Psychiatry And Neurochemistry, Göteborg, Sweden, [5]Gothenburg University, Psychiatry And Neurochemistry, Gothenburg, Sweden, [6]Turku University Hospital, Department Of Radiology, Turku, Finland, [7]Combinostics Ltd, Combinostics Ltd, Tampere, Finland, [8]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [9]Gothenburg University, Psychiatry And Neurochemistry, Göteborg, Sweden, [10]Clinical Research Services Turku, Crst, Turku, Finland

Aims: We aimed to i) assess differences in blood and imaging biomarkers of neurodegeneration among cognitively unimpaired *APOE* ε4 homozygotes, heterozygotes, and non-carriers and ii) to determine how different cerebral pathologies (Aβ deposition, medial temporal atrophy, and cerebrovascular pathology) contribute to blood biomarker concentrations.
Methods: Sixty *APOE* ε4 homozygotes (n = 19), heterozygotes (n = 21), and non-carriers (n = 20) ranging from 60–75 years, were recruited. Participants underwent Aβ-PET ([^{11}C]PiB), structural brain MRI, and blood sampling for measuring neurofilament light chain (NfL), total tau (t-tau), N-terminal tau fragments (NTA-tau) and glial fibrillary acidic protein (GFAP). [^{11}C]PiB standardized uptake value ratio was calculated for different brain regions. MRI images were analysed for regional volumes, atrophy scores, and volumes of white matter hyperintensities. Differences in biomarker levels and associations between blood and imaging biomarkers were tested using uni- and multivariable linear models.
Results: NfL concentration was increased in *APOE* ε4 homozygotes compared with non-carriers (mean 21.4 pg/ml vs. 15.5 pg/ml, p = 0.013), whereas other blood biomarkers did not differ between the groups (p > 0.077 for all). Hippocampal volume was decreased in *APOE* ε4 homozygotes compared with non-carriers (6.71 ml vs. 7.2 ml, p = 0.029). In the whole sample, blood biomarker levels were differently predicted by the cerebral pathologies; NfL concentration was associated with cerebrovascular pathology and medial temporal atrophy, NTA-tau associated with medial temporal atrophy. GFAP showed significant association with both medial temporal atrophy and Aβ pathology. T-tau concentration did not associate with any of the measured pathologies.
Conclusions: Only increased NfL concentrations and decreased hippocampal volume was observed in cognitively unimpaired APOEε4 homozygotes compared to non-carriers. In the whole population the blood biomarkers were affected in distinct ways by different pathologies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0377 / #2506

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

PROBING THE MOLECULAR DIVERSITY AND CONFORMATIONAL POLYMORPHISM OF TAU PATHOLOGY IN ALZHEIMER'S DISEASE

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Srinivas Koutarapu[1], Junyue Ge[2], Wojciech Michno[3], Jörg Hanrieder[4], Henrik Zetterberg[5], Kaj Blennow[6]
[1]Sahlgrenska Academy, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [2]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [3]Stanford University School of Medicine, Stanford University, Department Of Pediatrics, Stanford, United States of America, [4]University of Gothenburg, Department Of Psychiatry & Neurochemistry, Gothenburg, Sweden, [5]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [6]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: The primary goal of this project is to combine hyperspectral confocal imaging and SIMOA to probe the chemical and structural aspects of neurofibrillary tau pathology in Alzheimer's Disease.
Methods: Herein we devised a hyperspectral chemical imaging approach to stratify Tau aggregation and biochemical Tau profiles in postmortem brain across different phases of disease progression. We further correlate those profiles with blood and CSF biomarker patterns collected antemortem in a unique paired longitudinal cohort. Using fluorescent probes and hyperspectral, fluorescent microscopy we characterized and annotated distinct stages of Tau aggregation and maturation in the brain.
Results: Correlative immunohistochemistry identified ptau 217 deposition across structurally distinct Tau aggregates including pretangles (PT), neurofibrillary tangles (NFT), ghost tangles (GT), neuropil threads (NPT) and axonal and dystrophic neurites associated with amyloid pathology. Finally, we show that pTau217 levels within hippocampal tangle pathology correlate with both pTau 217 CSF and Braak stages.
Conclusions: These results provide new insights into the continuum of polymorphic Tau aggregation and how pTau biomarkers relate to brain pathology at the microscale.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0378 / #748

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

HIPPOCAMPAL SUBFIELD VOLUMES AT 7T IN MILD COGNITIVE IMPAIRMENT

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Michela Pievani[1], Federica Ribaldi[2], Ileana Jelescu[3], Jorge Jovicich[4], Valentina Garibotto[5], Giovanni Frisoni[6]
[1]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Lab Alzheimer's Neuroimaging & Epidemiology, Brescia, Italy, [2]University of Geneve, Laboratory Of Neuroimaging Of Aging (lanvie), Geneve, Switzerland, [3]Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Dept Of Radiology, Lausanne, Switzerland, [4]University of Trento, Center For Mind/brain Sciences (cimec), Rovereto, Italy, [5]Laboratory of Neuroimaging and Innovative Molecular Tracers (NIMTlab), Geneva University Neurocentre, Faculty of Medicine, University of Geneva, Division Of Nuclear Medicine And Molecular Imaging, Geneva, Switzerland, [6]University of Geneva (UNIGE and Geneva University Hospital (HUG), Department Of Rehabilitation And Geriatrics, Geneva, Switzerland

Aims: Hippocampal subfields play a key role in memory and are affected early in Alzheimer's disease (AD). In this study, we used 7T MRI to assess hippocampal subfield volumes in patients with mild cognitive impairment (MCI) and their relationship with memory deficits and AD pathology.
Methods: Thirty-nine participants were recruited at the Geneva Memory Center: n=22 cognitively unimpaired participants (CU; MMSE: 29±1) and n=17 MCI patients (MMSE: 27±3). Participants underwent 7T MRI (Siemens), including T2-weighted and structural MRI, at the EPFL in Lausanne. A subsample of participants underwent amyloid PET and tau PET. Hippocampal subfields (subiculum, CA1, CA2, CA3, dentate gyrus (DG), hippocampal tail) and extra-hippocampal areas (entorhinal and parahippocampal cortex) were segmented using Automated Segmentation of Hippocampal Subfields (ASHS) package. Differences between groups in hippocampal subfields were assessed with analysis of variance adjusting for age, sex and education. Correlations between hippocampal subfields, memory, amyloid and tau were assessed with Spearman's correlation test.
Results: MCI showed smaller volumes than CU in all hippocampal subfields ($p<0.05$), except for the DG that showed a trend ($p=0.087$). CA1, DG, and hippocampal tail volumes were positively associated with episodic memory in MCI (FCSRT immediate and delayed recall, $p<0.05$), while CU showed a significant association between memory and DG volume ($p=0.03$). In the whole sample, tau uptake in the hippocampus showed a negative correlation with CA1 volume ($p=0.05$), tau uptake in the inferior temporal cortex with parahippocampal volume ($p=0.02$), and tau uptake in the parahippocampus with DG volume ($p=0.03$). Amyloid levels were not associated with hippocampal subfield volumes.
Conclusions: These results suggest that hippocampal subfield markers may be sensitive to cognitive deficits in MCI, and confirm that tau but not amyloid pathology is associated with subfields neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0379 / #2167

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

NOVEL DUAL MODALITY IMAGING AGENTS FOR DIAGNOSTIC APPLICATIONS IN ALZHEIMER'S DISEASE

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Liviu Mirica
University of Illinois, Chemistry, Urbana, United States of America

Aims: Metal radiotracers exhibit beneficial properties that can improve *in vivo* positron emission tomography (PET) imaging over traditional radionuclides, such as longer half-lives, facile last-stage radiolabeling steps, and the potential for dual imaging-therapy applications. Among such radionuclides, ^{64}Cu exhibits a longer half-life ($t_{1/2}$ = 12.7 h) that allows for later PET imaging times and the ability to distribute ^{64}Cu imaging agents to facilities that do not have an on-site cyclotron.
Methods: The employed approach uses a bifunctional chelator with two Aβ-interacting fragments that dramatically improves the Aβ-binding affinity and lipophilicity for favorable blood-brain barrier (BBB) penetration, while the use of optimized-length spacers between the Cu-chelating group and the Aβ-interacting fragments further improves the *in vivo* Aβ-binding specificity and brain uptake of the corresponding ^{64}Cu PET imaging agent.
Results: Herein, we report to the best of our knowledge the first ^{64}Cu PET imaging agent that shows appreciable *in vivo* brain uptake and exhibits high specific affinity for beta-amyloid aggregates, leading to the successful PET imaging of amyloid plaques in the brains of 5xFAD mice versus those of WT mice.
Conclusions: ^{64}Cu PET imaging agents can be used for *in vivo* imaging of beta-amyloid aggregates.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0380 / #669

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

A VISUAL SCALE TO RATE AMYGDALAR ATROPHY ON MRI

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Francesca Benedetta Pizzini[1], Federica Ribaldi[2], Valerio Natale[3], Giovanni Frisoni[2,4], Max Scheffler[5]
[1]University of Verona, Department Of Engineering For Innovation Medicine, Verona, Italy, [2]University of Geneve, Laboratory Of Neuroimaging Of Aging (lanvie), Geneve, Switzerland, [3]Radiology, University of Verona, Dept. Of Diagnostic And Public Health, Verona, Italy, [4]University of Geneva (UNIGE and Geneva University Hospital (HUG), Department Of Rehabilitation And Geriatrics, Geneva, Switzerland, [5]University of Geneve, Radiology And Medical Informatics, Geneve, Switzerland

Aims: Visual scales are routinely used in clinical radiology to assess brain atrophy, but no scoring system specifically addresses amygdala atrophy. Recently, a highly prevalent neurodegenerative condition called TDP-43 age-related predominant limbic encephalopathy (LATE), characterized by early and severe atrophy of the amygdala, has been described. The purpose of this study is to develop and validate a visual assessment scale of amygdalar atrophy (AAS).
Methods: We evaluated: inter/intra-rater reliability (Hypothesis 1-H1), convergent validity of AAS versus volumetry (H2) and its association with autopsy-confirmed LATE neuropathologic change (LATE-NC–H3) For *H1,* we randomly selected 100 patients from Geneva Memory Centre (GMC) cohort stratified by medial temporal atrophy based on Scheltens' scale (MTA 0-1, 1.5-2, 2.5-3, 3.5-4) to represent the variability observed in clinical cohorts. AAS criteria were operationalized for no, mild/moderate, and severe amygdalar atrophy. AAS was scored by three independent expert neuroradiologists (R1, R2, R3) on 3D T1 acquisitions. Weighted Cohen's Kappa (wK) assessed intra- and inter- rater reliability.
For *H2,* we used the entire GMC cohort (N=2008) with available 3D T1 scans. We assessed the association of AAS scores with amygdalar volumes with a Kruskal–Wallis test. For *H3* we used ADNI cohort (N=96) and assessed the association of LATE-NC with AAS score with a test for trend.
Results: Intra- and inter- rater agreement for AAS demonstrated very good reliability (mean wK 0.79, range 0.71-0.93). Significant amygdalar volume differences were observed between individuals with no atrophy, mild atrophy and severe atrophy, regardless of the rater ($p \leq 0.0001$). There was a trend towards increasing percentage of LATE-NC in the amygdala with severity of amygdalar atrophy ($p=0.057$).
Conclusions: AAS scale proves to be a reliable and valid tool to assess amygdalar atrophy in clinical routine.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0381 / #406

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

RELATIVE POWER FOR LONGITUDINAL CHANGES OF CORTICAL MICROSTRUCTURE, CORTICAL THICKNESS, TAU PET AND COGNITION IN MILD COGNITIVE IMPAIRMENT

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Ged Ridgway[1], Ritobrato Datta[2], Mario Torso[1], Michele Valotti[1], Ziad Saad[2], Hartmuth Kolb[2], Steven Chance[1], Adni Alzheimer'S Disease Neuroimaging Initiative[1]
[1]Oxford Brain Diagnostics Ltd, Obd, Oxford, United Kingdom, [2]Janssen R&D, Johnson & Johnson, Neuroscience Biomarkers And Global Imaging, La Jolla, United States of America

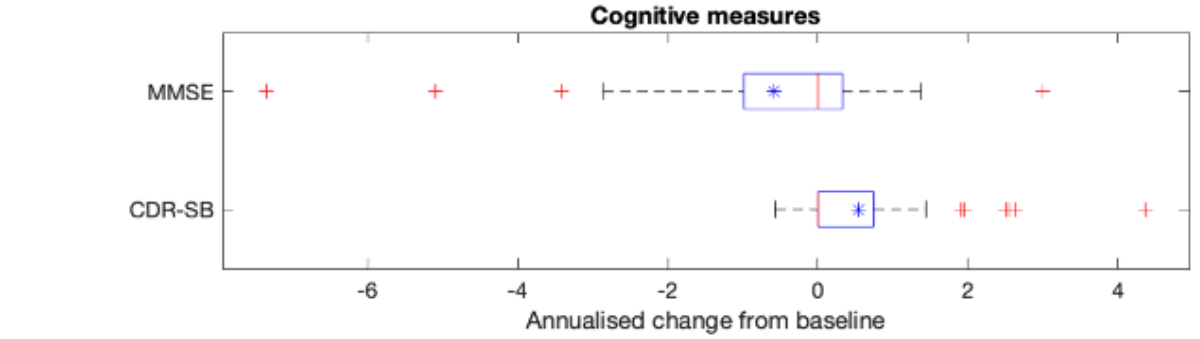
Aims: To compare longitudinal rates of decline in cognition and function, microstructural and macrostructural neurodegeneration, and tau pathology, in the Mild Cognitive Impairment (MCI) stage of Alzheimer's Disease (AD).
Methods: Data comprised all available ADNI diffusion MRI and tau PET scans acquired within 100 days of each other, having two or more time-points on the same MRI scanner model, diagnosed as MCI at time of first scan, yielding 99 scans from 43 subjects (19 female), summarised in Table 1. Cortical thickness was derived using FreeSurfer; dMRI were processed using FSL, and proprietary software produced a minicolumn-associated measure of cortical microstructure (PerpPD^{+}; Torso et al., 2022; PMID:36281682). Measures were averaged over all cortical regions (whole-brain [WB]) and over AD signature regions (Ridgway et al., CTAD2022). Tau PET SUVR (using cerebellar gray reference region) was averaged over all cortical regions (WB) and a Braak4 meta-ROI (Therriault et al., 2022; PMID:37118445). Longitudinal imaging data were summarised by annualised percentage change from baseline, alongside absolute annualised change for MMSE and CDR-SB.

Table 1 Clinical and demographic characteristics

	Mean	SD
Age at first scan (years)	73.398	7.651
MMSE at first scan	27.698	2.435
CDR at first scan	0.477	0.106
CDR-SB at first scan	1.291	0.861
MRI timespan (years)	1.996	0.723
PET timespan (years)	1.916	0.731

Results: Longitudinal changes are summarised in Figure 1. Following Wang et al., (2016; PMID:27010616), we report mean-to-standard deviation ratio (MSDR) and relative sample size (RelSS, proportional to inverse square MSDR) compared to the best method (Table 2). PerpPD+ signature performed best, followed by Tau PET Braak4 (9% higher RelSS), followed by cortical thickness signature (approx. twice as many subjects). These three best imaging metrics are related to MMSE and CDR-SB in Figure 2; the strongest association is between MMSE and PerpPD+ signature.

Figure 1


Cognitive measures
MMSE
CDR-SB
-6
-4
-2
0
2
4
Annualised change from baseline

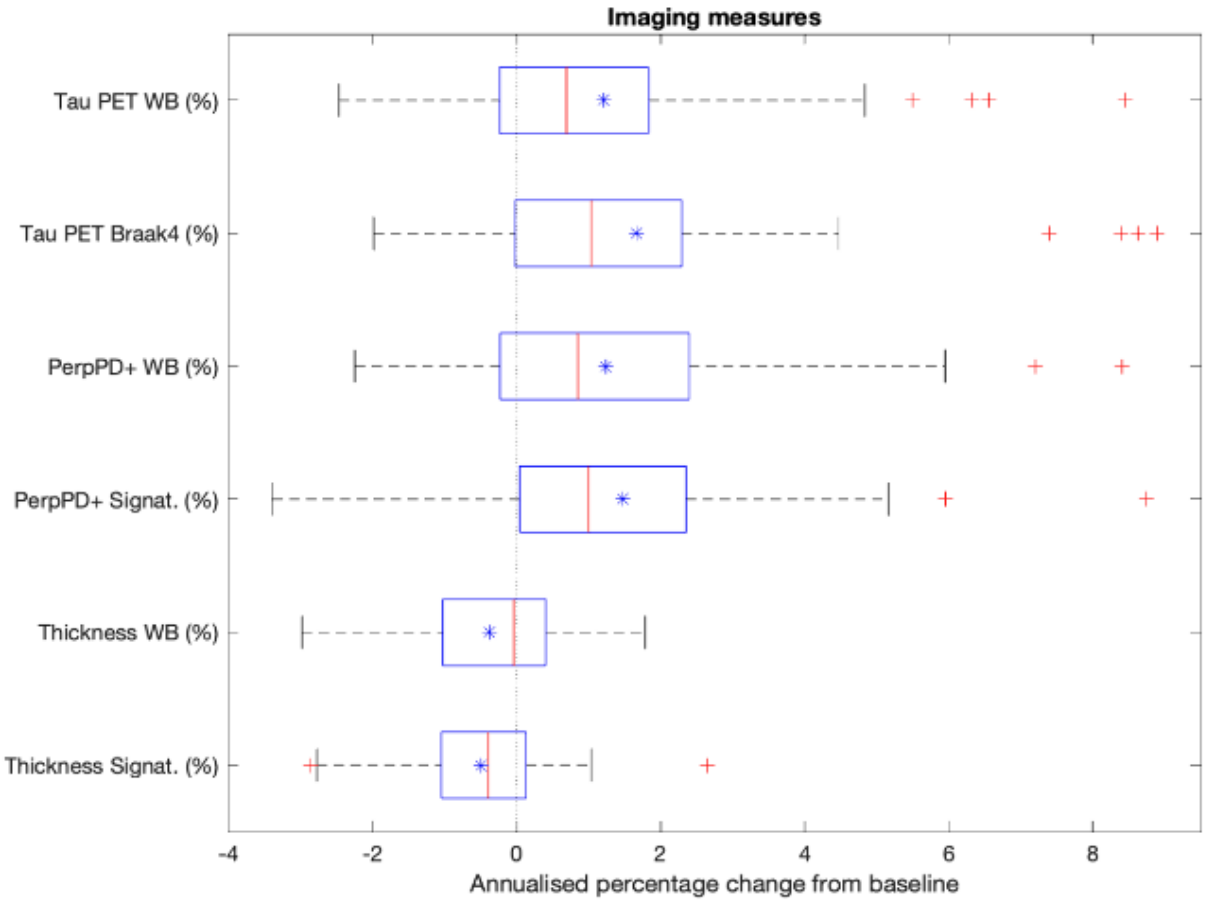
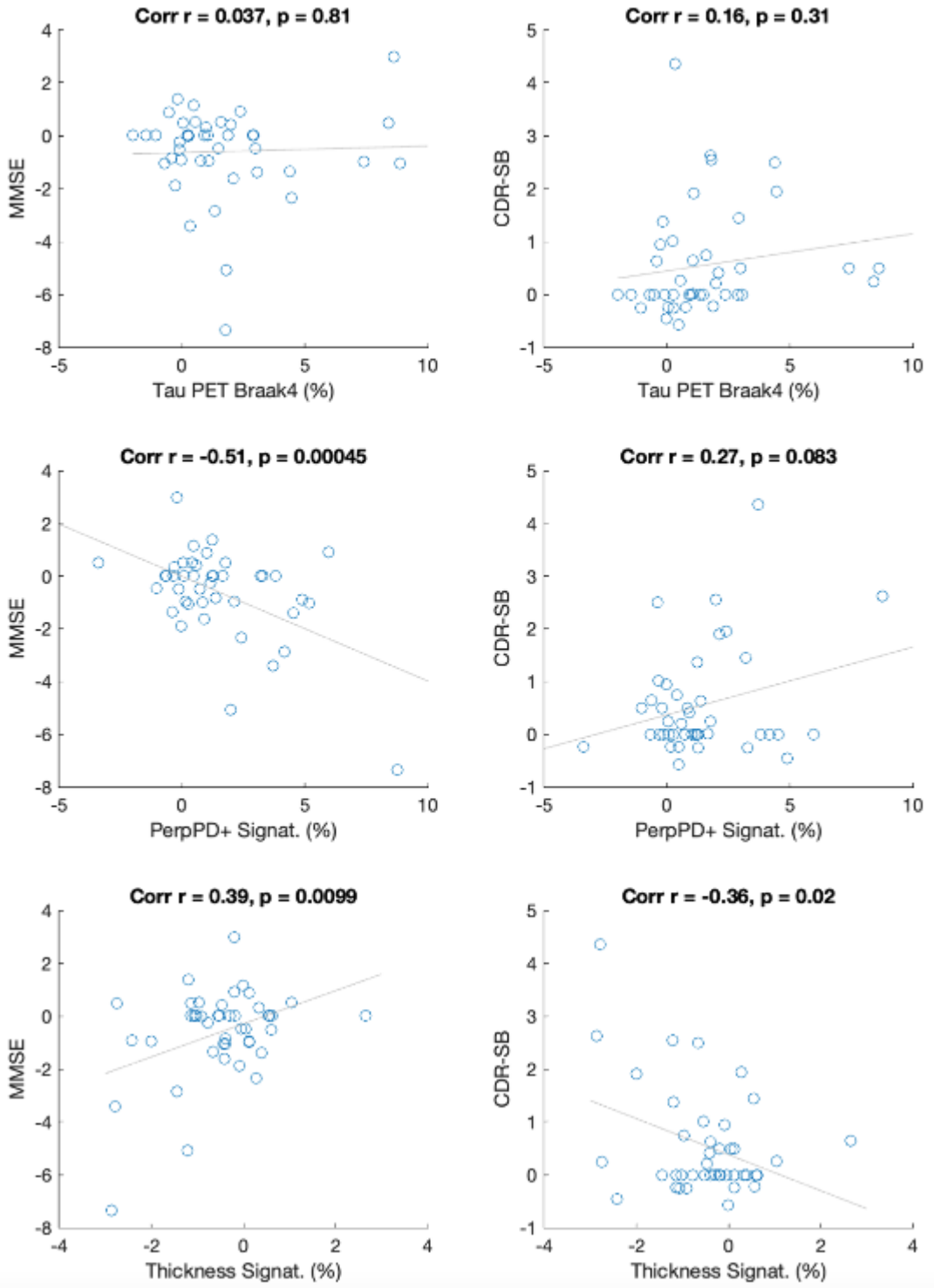

Imaging measures
Tau PET WB (%)
Tau PET Braak4 (%)
PerpPD+ WB (%)
PerpPD+ Signat. (%)
Thickness WB (%)
Thickness Signat. (%)
-4
-2
0
2
4
6
8
Annualised percentage change from baseline

Table 2 Annualised longitudinal change from baseline (percentage where indicated)

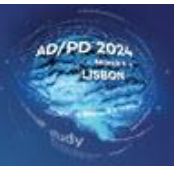
Metric	Mean	SD	MSDR	RelSS
MMSE	-0.599	1.704	-0.351	3.657
CDR-SB	0.547	1.019	0.537	1.563
Tau PET WB (%)	1.215	2.262	0.537	1.564
Tau PET Braak4 (%)	1.658	2.581	0.642	1.094
PerpPD+ WB (%)	1.238	2.469	0.502	1.792
PerpPD+ Signat. (%)	1.477	2.199	0.672	1
Thickness WB (%)	-0.373	1.088	-0.343	3.839
Thickness Signat. (%)	-0.490	1.058	-0.463	2.101

Figure 2



Conclusions: Cortical microstructure assessed using dMRI can quantify longitudinal change in MCI, better than cortical macrostructure, and similarly to tau PET. Future work will explore additional cortical microstructural measures, tau PET measures, and their interrelations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0382 / #2150

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

EXPLORING THE FEASIBILITY OF DETECTING PROTEIN AGGREGATIONS IN SPINAL CORDS OF ALZHEIMER'S DISEASE MOUSE MODELS THROUGH MULTIMODAL HIGH-RESOLUTION IMAGING

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Valeriia Skoryk[1], Pablo De Castro Mínguez[1], Stephen Hall[2], Oxana Klementieva[1]
[1]Faculty of Medicine, Lund University, Experimental Medical Science, Lund, Sweden, [2]Faculty of Engineering, Lund University, Solid Mechanics, Lund, Sweden

Aims: Early detection of amyloid plaque is an important task to be resolved for early Alzhiemer's desease (AD) diagnosis. High-resolution X-ray tomography (HR-XT) can reveal protein aggregates in tissue based on density variations, yet the exact composition and structure of these aggregates remain elusive.
Methods: To validate HR-XT as label free tool for early plaque detection, we performed three-dimensional HR-XT imaging and immunolabeling of amyloid plaques in spinal cords of two AD mouse models, 5xFAD and hAPP^{NL-G-F}knock-in. The comprehensive approach involved visualizing various protein epitopes using different antibodies, followed by three-dimensional reconstruction. These methods enabled us to visualize components like amyloid-β and α-synuclein within protein aggregations in a three-dimensional context.
Results: We acquired HR-XT data through two techniques: 1) laboratory X-ray microtomography, 4D Imaging Lab, Lund University; 2) synchrotron X-ray phase-contrast tomography, Anatomix beamline, SOLEIL. After reconstructing the data into 3D representations, we identified small, condensed areas in the second dataset. Comparison between the tomography- and immunolabeling-based 3D-models revealed a partial overlap between the condensed areas and amyloid-β. This is significant result, suggesting the presence of components within the aggregates missed by immunolabeling.
Conclusions: Therefore, to have a greater understanding of protein aggregation related to AD pathology the use of multimodal imaging approach is an imperative. Furthermore, to augment our methodology we are incorporating another label-free technique: structure sensitive high-resolution optical infrared spectroscopy, as a downstream imaging procedure, followed by multiplex immunolabeling. This provides a 3D depiction of small protein aggregates, elucidating their structure and composition. The following comparison of the 3D models from the different approaches may help us to characterise better the components within the aggregates missed by immunolabeling and to, thus, identify potential proteins depositions even at an early stage.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0383 / #1088

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

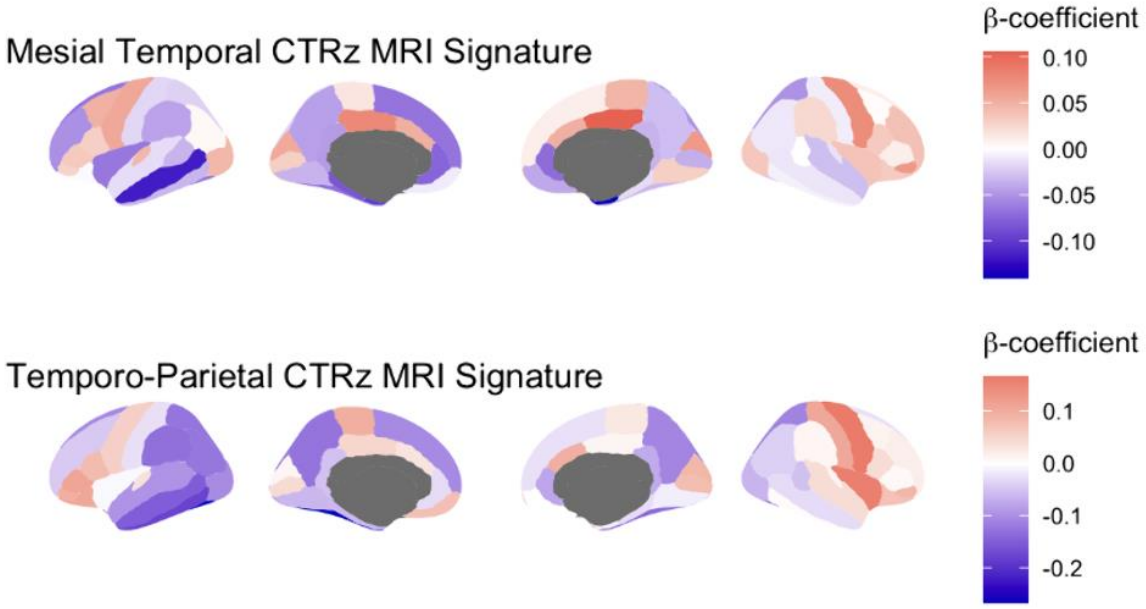
STRUCTURAL CONNECTOME-INFORMED MRI-BASED SIGNATURES PREDICT TAU BIOLOGICAL STAGES OF ALZHEIMER'S DISEASE

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Clara Sorensen, Duygu Tosun
University of California - San Francisco, Radiology And Biomedical Imaging, San Francisco, United States of America

Aims: In light of recent clinical trials for Alzheimer's disease (AD), the newly proposed NIA-AA staging has extended biological stratification by including tau proteinopathy stages. Our goal was to develop predictive models for tau stages in the absence of tau positron emission tomography (PET). To accomplish this, we analyzed demographic, clinical, and imaging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study.
Methods: Structural magnetic resonance imaging (MRI) signatures were trained on a cohort of 469 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to identify patterns of atrophy associated with tau PET burden ($CenTauR_z$ values) in mesial temporal (MTL) and temporo-parietal (TP) regions separately, using regularized linear regression constrained by the average structural connectome of 80 healthy controls. Tau positivity for MTL and TP stages were defined at $CenTauR_z>2$. Nested ordinal logistic regression models were trained on an independent cohort of 118 ADNI subjects to predict the MTL and TP tau stage positivity. These models incorporated independent variables of demographic and clinical data, amyloid centiloid, and MTL and TP MRI signatures, both separately and jointly.
Results: MRI signatures associated with MTL and TP tau burden (R^2 of 0.44 and 0.40, respectively) are shown in Fig1. Employing 5-fold cross validation, the top-performing model achieved a multiclass AUC of 0.76, incorporating both MTL and TP MRI signatures, CDR-SOB, MMSE, APOE e4 status, and amyloid centiloid value. In contrast, using demographic data as predictors alone yielded an AUC of 0.5, while combining demographic and clinical data resulted in an AUC of 0.67.

Fig. 1 Structural MRI Signatures



Conclusions: Our study highlights the potential of leveraging intrinsic brain properties to construct MRI signatures as a promising and effective approach to significantly improve the accuracy of tau staging in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0384 / #962

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

APOE4-RELATED WHITE MATTER IMPAIRMENT CORRELATES WITH INCREASED BETA-AMYLOID DEPOSITION IN HEALTHY ELDERLY ADULTS

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Claudia Tato-Fernández[1], Laura Ekblad[1], Elina Pietilä[1], Virva Saunavaara[1], Semi Helin[1], Riitta Parkkola[2], Juha Rinne[1,3], Anniina Snellman[1,4]
[1]University of Turku, Turku Pet Centre, Turku, Finland, [2]Turku University Hospital, Department Of Radiology, Turku, Finland, [3]University of Turku, Inflames Research Flagship Center, Turku, Finland, [4]Institute of Neuroscience & Physiology, The Sahlgrenska Academy, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden

Aims: *APOE4* is a genetic risk factor for late-onset Alzheimer's disease. In this study, we evaluated whether i) white matter impairment measured by DTI differs between healthy individuals with different number of *APOE4* alleles; ii) white matter impairment associates with Aβ load measured by positron emission tomography (PET).
Methods: Our sample included 96 participants (*APOE4/4*, *N* = 20; *APOE4/3*, *N* = 39; *APOE3/3*, *N* = 37), with mean (SD) 68 (8) years, 64.9% females. All underwent magnetic resonance imaging, including diffusion tensor imaging sequences, and ^{11}C-PiB amyloid PET. We conducted hypothesis-driven region-of-interest (ROI) analysis in the cingulum, corpus callosum and uncinate fasciculus. Fractional anisotropy (FA) and mean diffusivity (MD) were calculated within each ROI and compared between the *APOE* groups using ANCOVA, with sex and age as covariates. A voxel-weighted average of FA and MD was calculated for each subject to evaluate correlation with Aβ load, estimated as ^{11}C-PiB composite standardized uptake value ratio, using Spearman's rank correlation.
Results: A significant difference between groups in regional MD was present in the body of corpus callosum ($p = 0.039$, ANCOVA) where *APOE4/4* carriers exhibited higher MD than *APOE4/3* ($p = 0.0053$) and *APOE3/3* ($p = 0.026$). On the contrary, no regional differences were detected for FA ($p > 0.13$ for all). High brain Aβ load was associated with elevated MD ($r = 0.29$, $p = 0.0063$) in the whole sample, driven by *APOE4/3* carriers ($r = 0.42$, $p = 0.011$).
Conclusions: Cognitively unimpaired *APOE4/4* carriers showed increased MD in the body of corpus callosum. This indicator for neurodegeneration positively correlated with ^{11}C-PiB uptake, suggesting that Aβ deposition and white matter damage are related in subjects with high risk for Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0385 / #2736

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

A MULTIMODAL STRATEGY FOR PREDICTING COGNITIVE AND FUNCTIONAL IMPAIRMENTS THROUGH WHITE MATTER DATA

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Nishant Chauhan[1], Hyun Woong Roh[2], Sang Son[2], Chang Hyung Hong[2], Dongha Lee[1]
[1]Korea Brain Research Institute, Cognitive Science Research Group, Daegu Metropolitan City, Korea, Republic of, [2]Ajou University School of Medicine, Psychiatry, Suwon, Korea, Republic of

Aims: Neurodegenerative disorders, marked by the accumulation of pathological proteins in the brain, often lead to cognitive impairment and disability. Accurate diagnosis of cognitive decline and functional independence in these conditions poses clinical challenges. White matter, housing vital neural circuits and glial cells, can sustain damage, resulting in clinical symptoms that affect daily life independence. Recent advances in imaging have made brain MRI and amyloid PET examinations more accessible. While these tests traditionally focused on grey matter, this study highlights the significance and potential of white matter in neurodegenerative disease diagnosis.
Methods: This study examined data from 455 participants in the Biobank Innovations for Chronic Cerebrovascular Disease with Alzheimer's Disease Study (BICWALZS), encompassing individuals with subjective cognitive decline (SCD), mild cognitive impairment (MCI), Alzheimer's disease (AD), and vascular dementia (VD). The dataset was categorized into two groups: cognitive impairment (SCD vs. MCI, AD, VD), which involves individuals experiencing cognitive deficits, and functional disability (SCD, MCI vs. AD, VD), which pertains to individuals facing limitations in their daily functioning. Amyloid PET and MRI data were collected, and white matter information from these scans was integrated to create an ensemble dataset.
Results: The classification was performed using a support vector machine (SVM) on multimodal datasets, which included T2-FLAIR, amyloid PET, and ensemble data. The ensemble model achieved significantly higher accuracy in classifying cognitive impairment (89.25%) compared to individual T2-FLAIR (85.29%) and amyloid PET models (84.20%). In the classification of functional disability, the ensemble model (77.58%) outperformed T2-FLAIR (70.77%) and amyloid PET models (73.17%), with no significant difference between T2-FLAIR and amyloid PET models.
Conclusions: This study showcases the potential of white matter data to enhance diagnostic accuracy in neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0386 / #679

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

HORMONE THERAPY MITIGATES ALZHEIMER'S DISEASE TAU BIOMARKERS IN POST-MENOPAUSAL FEMALES: EVIDENCE FROM 2 INDEPENDENT COHORTS

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

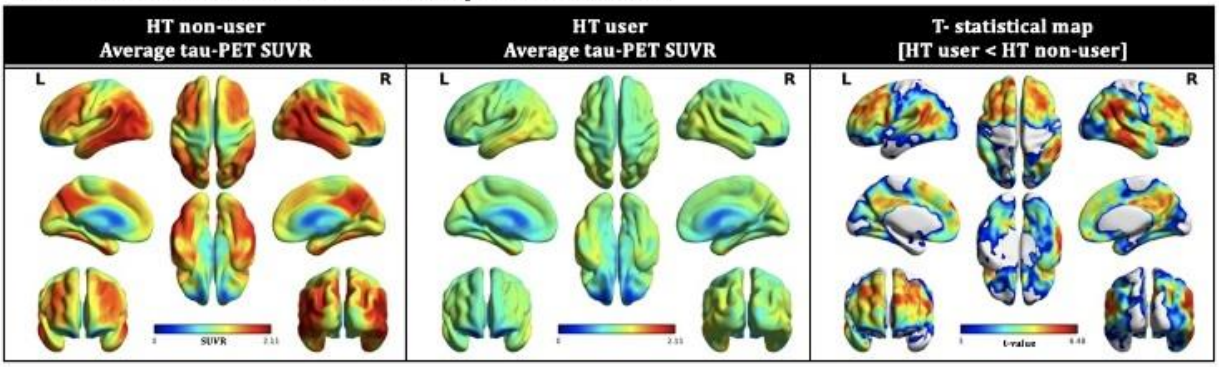
Yi-Ting Wang[1,2], Joseph Therriault[2], Cécile Tissot[2], Stijn Servaes[2], Nesrine Rahmouni[1,2], Arthur Macedo[1,2], Sulantha Sanjeewa[2], Andréa L. Benedet[3], Jenna Stevenson[2], Nicholas Ashton[3], Tharick A Pascoal[4], Firoza Lussier[4], Henrik Zetterberg[5], Kaj Blennow[5], Serge Gauthier[2], Pedro Rosa-Neto[1,2]
[1]McGill University, Neurology And Neurosurgery, Montreal, Canada, [2]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [3]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [4]Department of Neurology and Psychiatry, University Of Pittsburgh School Of Medicine, Pittsburgh, United States of America, [5]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: Postmenopausal females represent approximately 70% of the Alzheimer's disease (AD) cases. Previous literature proposes a connection between the decreased estrogen levels during menopause and an increased risk of dementia. However, the outcomes of administrating hormone therapy (HT) as a preventive strategy against AD in peri/post-menopausal females have been inconclusive. The goal of the present study was to examine the impacts of HT on AD biomarker-informed pathologies.
Methods: This cross-sectional study assessed post-menopausal female individuals from two cohorts: the TRIAD cohort and the ADNI cohort. Participants underwent magnetic resonance imaging (MRI), amyloid-β (Aβ) and tau positron emission tomography (PET), and biofluid collection. Voxel-based t-tests were performed to assess the differences in Aβ and tau neurofibrillary tangles (NFTs) loads between post-menopausal females without HT history (HT-) and post-menopausal females who were using HT (HT+). Linear regression models with interaction terms were conducted to examine the effects of the interaction between HT and Aβ-PET on regional tau-PET and tau fluid biomarkers.
Results: HT+ females demonstrated significantly lower tau-PET standardized uptake value ratio (SUVR) in Braak I-II ROIs ($P < 0.05$, Hedges' $g = 0.73$), Braak III-IV ROIs ($P < 0.0001$, Hedges' $g = 0.74$) and Braak V-VI ROIs ($P < 0.0001$, Hedges' $g = 0.69$) compared to HT- females (Fig 1). HT+ females also showed significantly lower CSF p-tau$_{181}$ ($P < 0.001$) and plasma p-tau$_{181}$ ($P < 0.0001$) concentrations. Additionally, results from linear regression models indicated that HT use interacts with cortical Aβ and mitigates regional NFT formation (Table
1).

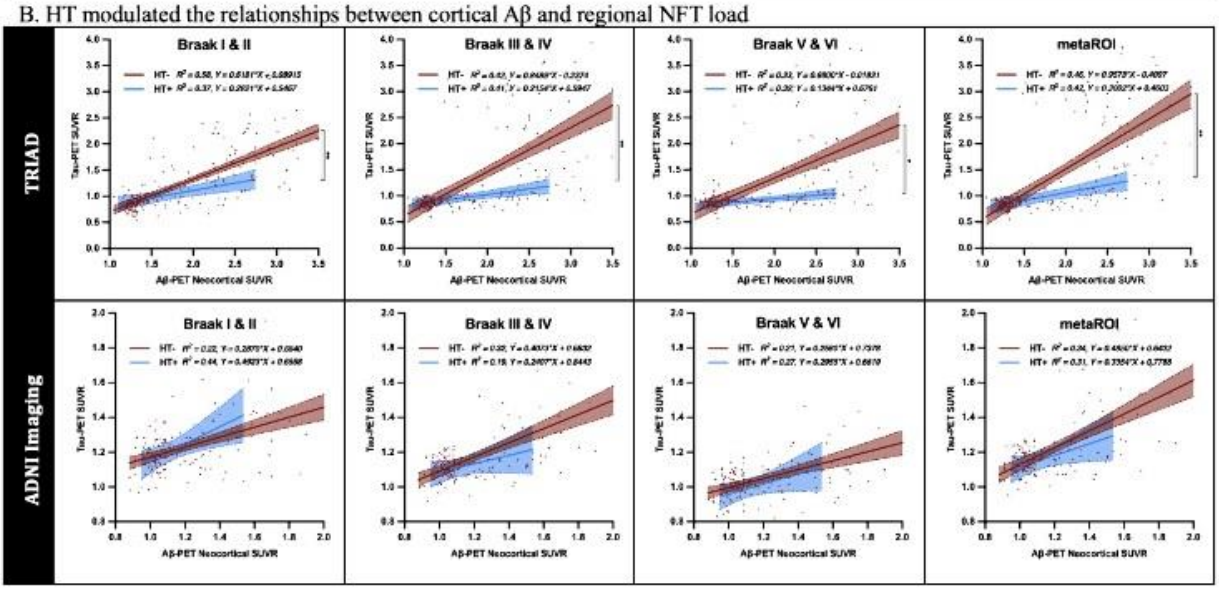
Figure 1. Hormone therapy mitigates tau tangle aggregation in post-menopausal females

A) Results from voxel-based Welch's t-test showed that HT+ females presented significantly lower tau-PET SUVR in multiple brain regions as demonstrated in the t-statistical map. B) ROI-based linear regression models showed that with similar Aβ load, HT+ females demonstrated less NFT aggregation compared to HT- females, suggesting HT use modulated the relationship between cortical Aβ and regional NFT load.

A. HT+ females had lower tau-PET SUVR compared to HT- females



B. HT modulated the relationships between cortical Aβ and regional NFT load



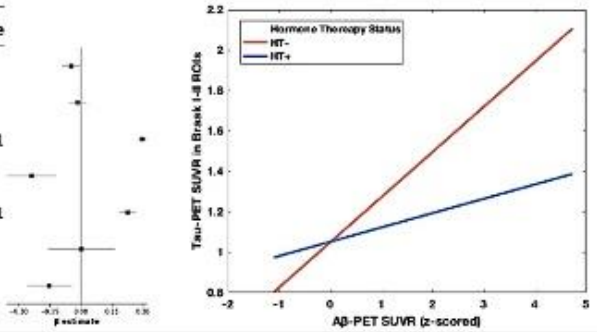
AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

Table 1. Hormone therapy interacts with cortical Aβ and mitigates regional tau-PET load

Multivariate linear regression models were performed to understand how the interaction between Aβ and HT influenced regional tau-PET. The results showed that HT interacted with neocortical Aβ-PET and predicted lower tau-PET in Braak ROIs. The findings remained significant after correcting for age, education, *APOE ε4* carriage status and clinical diagnosis. Interaction plots are demonstrated on the right side of the table.

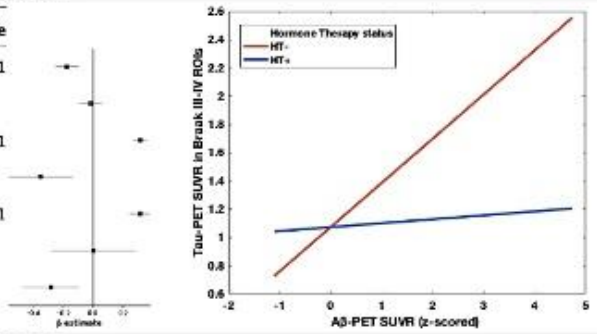
Braak I - II

Variable	Est. (95% Conf. Int.)	t-stat	P-value
Age	-0.05(-0.09 to -0.00)	-2.151	0.033
Education	-0.02(-0.06 to 0.03)	-0.741	0.459
APOE4	0.30(0.27 to 0.32)	22.072	<0.0001
Clinical Diagnosis (CU)	-0.24(-0.36 to -0.12)	-3.86	0.0002
Aβ-PET SUVR	0.22(0.18 to 0.26)	11.289	<0.0001
Hormone Therapy (HT+)	0.00(-0.16 to 0.16)	0.041	0.967
Interaction (Aβ-PET*HT+)	-0.15(-0.26 to -0.04)	-2.785	0.0059



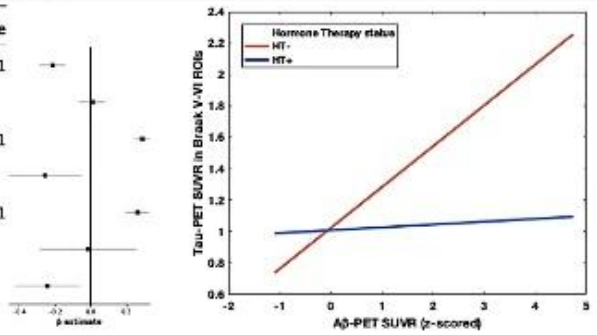
Braak III - IV

Variable	Est. (95% Conf. Int.)	t-stat	P-value
Age	-0.18(-0.25 to -0.10)	-4.469	<0.0001
Education	-0.02(-0.09 to 0.06)	-0.397	0.692
APOE4	0.31(0.27 to 0.36)	13.283	<0.0001
Clinical Diagnosis (CU)	-0.35(-0.56 to -0.14)	-3.228	0.0015
Aβ-PET SUVR	0.31(0.24 to 0.38)	8.939	<0.0001
Hormone Therapy (HT+)	0.00(-0.29 to 0.29)	0.004	0.997
Interaction (Aβ-PET*HT+)	-0.29(-0.48 to -0.09)	-2.941	0.0037



Braak V -VI

Variable	Est. (95% Conf. Int.)	t-stat	P-value
Age	-0.21(-0.29 to -0.14)	-5.746	<0.0001
Education	0.01(-0.07 to 0.08)	0.226	0.821
APOE4	0.29(0.24 to 0.33)	12.784	<0.0001
Clinical Diagnosis (CU)	-0.25(-0.46 to -0.05)	-2.465	0.015
Aβ-PET SUVR	0.26(0.19 to 0.33)	7.818	<0.0001
Hormone Therapy (HT+)	-0.01(-0.29 to 0.26)	-0.103	0.918
Interaction (Aβ-PET*HT+)	-0.24(-0.42 to -0.06)	-2.628	0.009



Conclusions: Overall, findings from this study suggest that HT mitigates tau pathology in postmenopausal females. Due to the close association between tau pathology and clinical symptoms, these findings present significant clinical implications for the management and prevention of AD dementia in middle-aged females.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0387 / #2237

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

VALIDATING THE ACCURACY OF PLASMA P-TAU217 FOR DETECTING ALZHEIMER'S PATHOLOGY

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Anna Mammel[1], Pankaj Kumar[2,3], Don Biehl[1], Mary Encarnacion[2], Ryan Fortna[1], Ali Mousavi[2,3], Anna Cruz[2], Michelle Zaharic[2], Hans Frykman[1,2,3]
[1]Neurocode USA Inc., Neurology, Bellingham, United States of America, [2]BC Neuroimmunology Lab., Neurodegenerative, Vancouver, Canada, [3]University of British Columbia, Medicine, Canada, Canada

Aims: Plasma p-tau217 can differentiate Alzheimer's disease (AD) cases with significant brain pathology from non-AD cases. In addition, plasma p-tau217 starts to increase earlier than other p-tau variants and shows an increase during preclinical AD. Data strongly suggests that while both plasma p-tau181 and p-tau217 are accurate markers to predict the future development of AD in symptomatic patients with either MCI or subjective cognitive decline (SCD), plasma p-tau217 is slightly better for AD diagnosis due to its sizable increase in the earlier stage of AD. In this study, we validated the diagnostic accuracy of p-tau217 in differentiating AD from non-AD pathology.
Methods: In this study, we conducted diagnostic validation to assess the analytical performance of plasma p-tau217 using EDTA plasma samples from individuals with β amyloid PET-positive (n=121) and β amyloid PET-negative (n=35) status. Plasma p-tau217 levels were quantified using an innovative commercial plasma-based Simoa assay developed by ALZpath, employing an exclusive proprietary monoclonal p-tau217 capture antibody.
Results: The mean plasma p-tau217 levels were 1.25 ± 0.54 ng/L in PET+ cases and 0.49 ± 0.42 ng/L in PET-negative cases. ROC analysis demonstrated an AUC of 0.92, with a Youden's Index of 0.73 pg/mL, indicating a specificity of 92.9% and a sensitivity of 86.4%. Notably, when considering an upper limit cut-off of 0.63 pg/mL, specificity remained at 82% while sensitivity increased to 92.2%. Conversely, employing a lower limit cut-off of 0.40 pg/mL resulted in a specificity of 53.6% but a notably higher sensitivity of 99%.
Conclusions: The specific analytic findings of plasma p-tau 217 validation showed good promise. However, establishing a potentially practical clinical cut-off for the AD diagnosis, particularly as a clinical screening tool, requires further validations through clinical studies conducted within memory clinics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0388 / #1375

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PORTRAYING ALZHEIMER'S DISEASE BLOOD BIOMARKERS IN URINE AS A NON-INVASIVE APPROACH TO MONITOR NEURO-GLIAL DAMAGE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Burak Arslan[1], Andréa L. Benedet[1], Ilaria Pola[1], Joseph Therriault[2,3], Nesrine Rahmouni[3], Jenna Stevenson[3], Stijn Servaes[2,3], Cécile Tissot[2,3], Kaj Blennow[1,4], Henrik Zetterberg[1,5,6,7,8], Pedro Rosa-Neto[2,3], Nicholas Ashton[1,9,10,11]
[1]The Sahlgrenska Academy at the University of Gothenburg, Institute Of Neuroscience And Physiology, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [2]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [3]McGill University, Neurology And Neurosurgery, Montreal, Canada, [4]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [5]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [6]UK Dementia Research Institute, University College London, London, United Kingdom, [7]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China, [8]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America, [9]Stavanger University Hospital, Centre For Age-related Medicine, Stavanger, Norway, [10]King's College London, Institute Of Psychiatry, Psychology And Neuroscience, Maurice Wohl Institute Clinical Neuroscience Institute, London, United Kingdom, [11]NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia, South London And Maudsley Nhs Foundation, London, United Kingdom

Aims: In the last decade, biomarker research in the field of Alzheimer's Disease(AD)using body fluids has moved toward the blood-based biomarker concept to ease sample handling decrease cost and facilitate disease management.In this regard, measurements of AD biomarkers in urine matrix would be even more patient-friendly practical,and cost-effective.Therefore we aimed to profile Aβ40Aβ42 GFAP NfL and p-tau231 in the paired spot urine and plasma samples of AD patients along the AD continuum in a proof-of-concept approach.
Methods: We included 634 longitudinally collected urine samples from the TRIAD,which was representative of the AD continuum.All paired plasma and urine samples were measured for Aβ42 Aβ40 GFAP and NfL with a commercial Simoa N4PE kit and p-tau231 using in-house Simoa technology at the University of Gothenburg.Plasma and urine creatinine and urine albumin concentrations were determined using a Cobas c501.Glomerular barrier function was assessed based on albumin-creatinine ratio(ACR) and eGFR calculation.
Results:

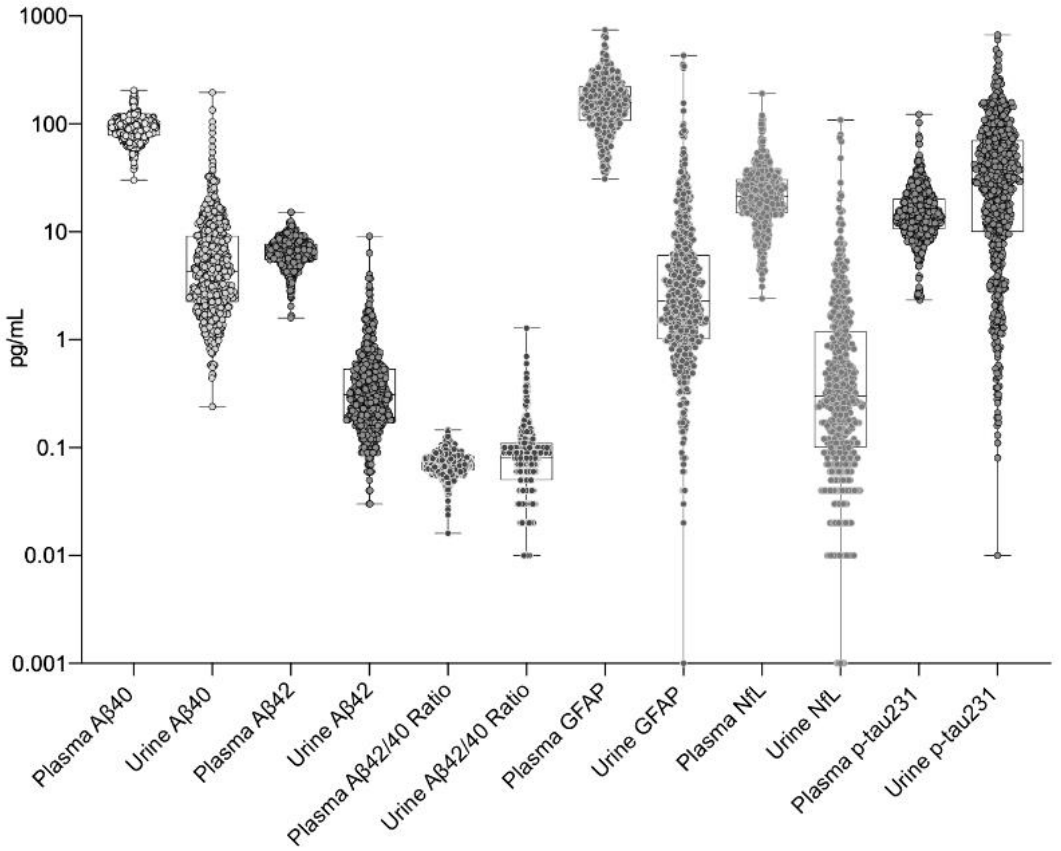


Figure 1. The box-and-whisker plots show plasma vs. urine concentrations of biomarkers. For the box-and-whisker plots, the horizontal bar shows the median, and the upper and lower boundaries show the 25th and 75th percentiles, respectively.

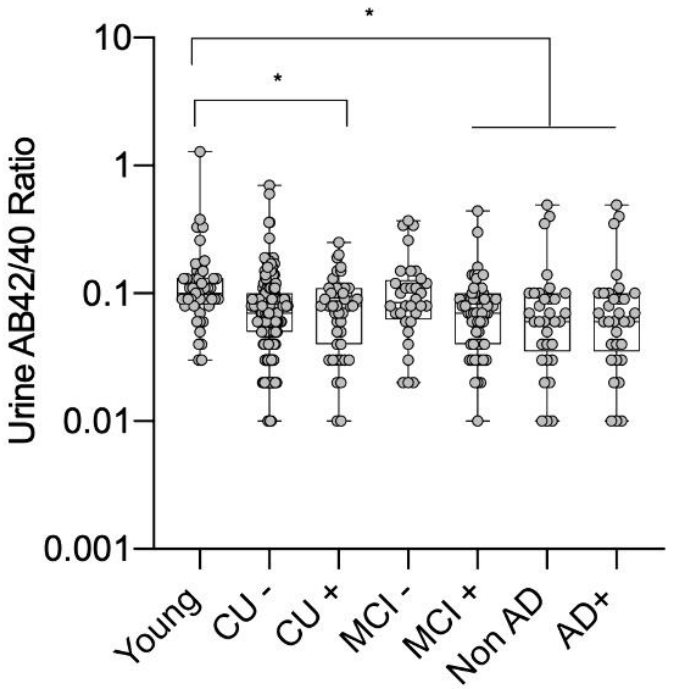


Figure 2. The box-and-whisker plots show urine Aβ42/40 ratio across groups. For the box-and-whisker plots, the horizontal bar shows the median, and the upper and lower boundaries show the 25th and 75th percentiles, respectively. *p <0.001

The quantitative measurability of urine biomarkers(n,%),respectively,were Aβ40(623 98.26%)Aβ42(611 96.37%)GFAP(618 97.47%)NfL(521 82.17%)p-tau231(626 98.73%).The median absolute concentrations of biomarkers in plasma samples were significantly higher than urine concentrations,except for p-tau231 which was higher in urine(Figure1).Across groups along the ADcontinuum only urine Aβ42/40 was significantly higher in young participants(Figure2).

Conclusions: In contrast to few publications a large percentage of five investigated AD blood biomarkers were detectable in the urine matrix.While urine biomarkers correlated between themselves we found no significant change of AD markers in urine across the ADcontinuum.We also did not find a relationship between plasma and urine in patients with impaired glomerular barrier.As a result of this study urine seems not to be a reliable matrix for the determination of AD pathology.However the wide range of values of such biomarkers in urine warrants further investigate for mechanistic understanding.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0389 / #825

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

MAPPING THE TEMPORAL COURSE OF CSF GAP-43 IN ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Prithvi Arunachalam[1], Alexis Moscoso[1], Nicolai Franzmeier[1,2,3], Michael Schöll[1,4,5]
[1]1University of Gothenburg, The Sahlgrenska Academy, Institute of Neuroscience and Physiology, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [2]LMU Munich, Institute For Stroke And Dementia Research, Munich, Germany, [3]LMU Munich, Munich Cluster For Systems Neurology (synergy), Munich, Germany, [4]University of Gothenburg, Wallenberg Centre For Molecular And Translational Medicine, Gothenburg, Sweden, [5]Institute of Neurology, University College London, Dementia Research Centre, London, United Kingdom

Aims: Synaptic dysfunction has been proposed as one of the earliest events in Alzheimer's Disease (AD) pathogenesis, strongly correlating with cognitive decline. Changes in the pre-synaptic protein Growth-associated protein 43 (GAP-43) in the cerebrospinal fluid (CSF), which plays a crucial role in synaptogenesis, have been linked to the detection of cognitive impairment. Several studies have further linked changes in CSF GAP-43 to pathological changes in markers of AD. However, the biomarker lacks longitudinal validation. In this work, we have mapped the temporal trajectory of CSF GAP-43 across the AD spectrum and investigated, when in the disease course, its levels turn abnormal.
Methods: We included longitudinal Ab PET scan (either with [^{18}F]Florbetapir; FBB, [^{18}F]Florbetaben) from 1480 ADNI participants, baseline CSF GAP-43 from 673 ADNI subjects (i.e., cognitively normal (CN) Ab-, n=138; CN Ab+=77; cognitively impaired (CI) Ab-=164; CI Ab+=294). To estimate the population-based shape of AD-specific timeline of Ab accumulation, we fitted a nonlinear mixed effects model based on longitudinal Ab PET measures. Similar models were used to model baseline and longitudinal levels of available biomarkers (including CSF GAP-43) as a function of time since Ab positivity.
Results: The findings indicated an increase in CSF GAP-43 levels in the presence of Ab pathology at baseline (**Figure 1**). The longitudinal analysis demonstrated a consistent upward trend with the earliest CSF GAP-43 changes manifesting ~6.5 years before the onset of Ab pathology. Finally, it was estimated that CSF GAP-43 is the first AD biomarker to reach abnormal levels (**Figure 2**).

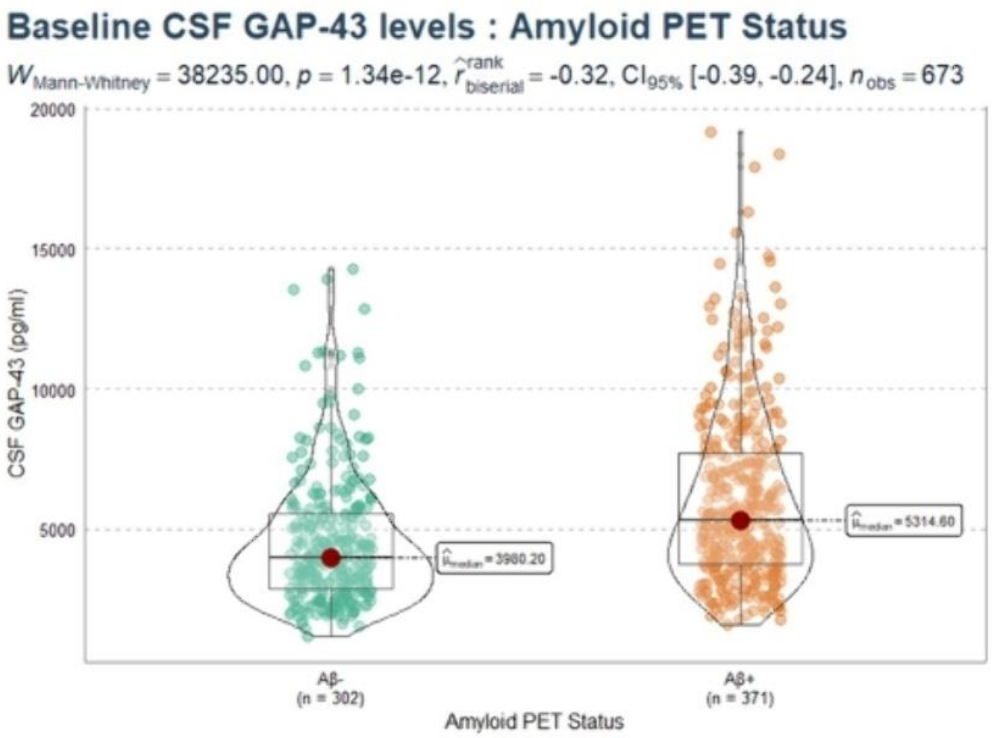


Figure 1. Group comparisons represented by violin plots for baseline CSF GAP-43 levels based on Ab positivity. The CSF GAP-43 concentration in Ab+ was higher than in Ab-. Boxes show the median and first and third quartiles. Dots represent individual observations. Abbreviations: Ab-, Ab PET negative group; Ab+, Ab PET positive group.

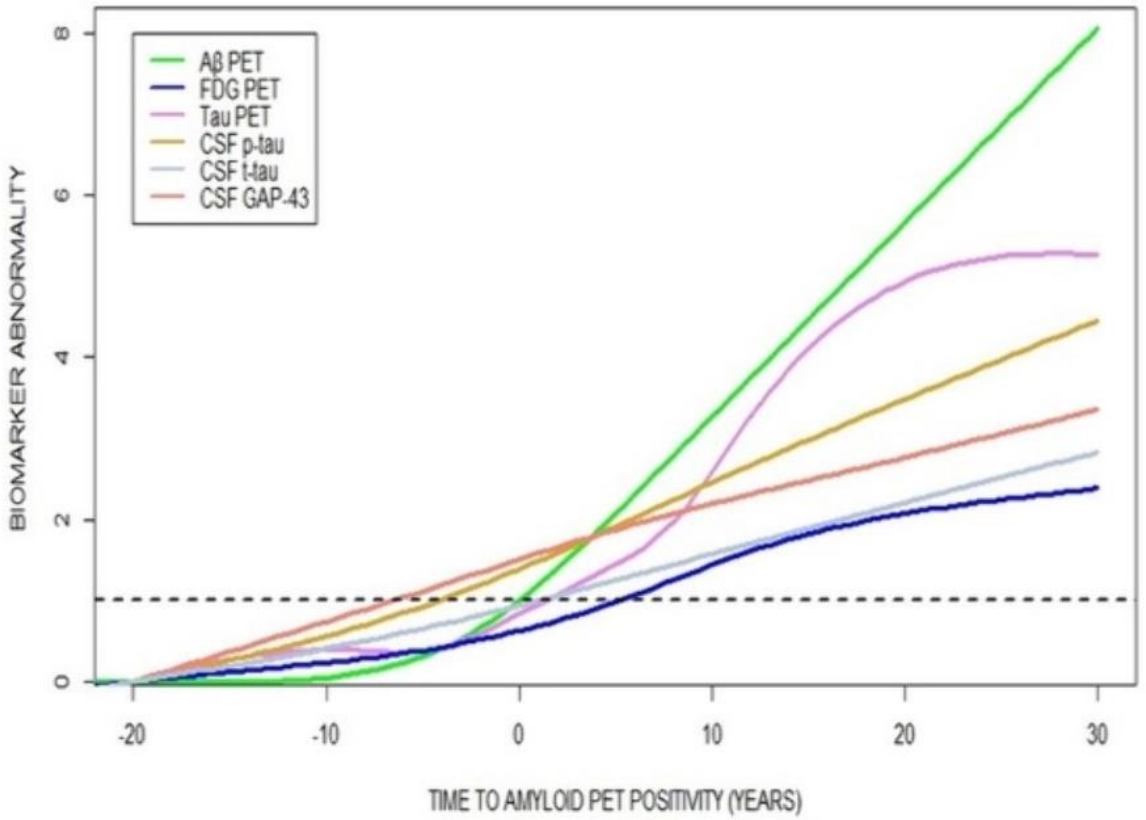


Figure 2. Combined biomarker trajectories of CSF GAP-43, Ab PET, Tau PET, FDG, and other CSF biomarkers as a function of time since Ab PET positivity in AD. The different biomarkers analyzed are color-coded as per the legend. Each biomarker measurement was normalized to its cut-off value to represent all biomarkers on a common scale where biomarker abnormality was recorded when the biomarker trajectory crosses the horizontal dashed line anchored at one (*i.e.*, cut-off value) on the y-axis.

Conclusions: These findings indicate that CSF GAP-43 increases before other investigated pathologic AD biomarkers, suggesting its potential significance for the early detection of aberrant synaptic activity in response to initial events during AD pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0390 / #630

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

THE ROLE OF YRNAS AND YRNA FRAGMENTATION IN THE DEVELOPMENT AND PROGRESSION OF ALZHEIMER'S DISEASE (AD)

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ingrid Lovise Augestad, Ingrun Alseth
Oslo University Hospital, Department Of Microbiology, Oslo, Norway

Aims: Despite intense research efforts over the past decades, the exact causes underlying AD is unknown and there is still no effective treatment or cure. In order to develop AD therapies, we need reliable and non-invasive biomarkers for diagnosis and disease progression. Therefore, it is crucial to investigate underlying pathophysiological mechanisms. The role of exosomes, a subgroup of extracellular vesicles, has recently gained a lot of attention for their potential as diagnostic biomarkers. Most cells in the body release exosomes, which are important for maintaining cell homeostasis and in cell-to-cell communication. We are interested in cytoplasmic (y) RNA, that are found enriched in exosomes. The fact that yRNAs are found in higher levels in exosomes suggest a highly selective packaging process. Our main hypothesis is that AD has a specific exosomal yRNA profile that can be used as biomarker. Further, we hypothesize that EndoV is instrumental for exosomal packaging of yRNAs and is involved in regulating inflammation.
Methods: Blood plasma will be collected from wildtype, AD mice (5XFAD), *EndoV*$^{-/-}$ and 5XFAD/*EndoV*$^{-/-}$ mice at different timepoints before (1-month- old) and during (2.5-, 4.5- and 9-month-old) the progression of AD. Exosomes will be isolated using size exclusion chromatography columns and exosomal yRNA levels and fragmentation will be analyzed with RT-qPCR. Neuronal and glial markers will be used to analyze brain tissue for neurodegeneration and inflammation.
Results: Previous work from our group has shown that yRNA bind to the human ribonuclease Endonuclease V (EndoV) and that deletion of EndoV in mice leads to milder disease in three different disease models.
Conclusions: We expect to generate new knowledge about AD and to our knowledge this is the first time yRNAs and EndoV in AD will be studied.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0391 / #577

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

THE ROLE OF PLASMA NEUROFILAMENT LIGHT CHAIN AND GLIAL FIBRILLARY ACIDIC PROTEIN IN SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Silvia Bagnoli[1], Assunta Ingannato[1], Salvatore Mazzeo[1], Giulia Giacomucci[1], Arianna Cavaliere[1], Valentina Moschini[1], Juri Balestrini[1], Carmen Morinelli[1], Giulia Galdo[1], Filippo Emiliani[1], Diletta Piazzesi[1], Chiara Crucitti[1], Daniele Frigerio[1], Cristina Polito[1], Valentina Berti[2], Sonia Padiglioni[3], Sandro Sorbi[1], Valentina Bessi[3], Benedetta Nacmias[1]
[1]University of Florence, Department Of Neuroscience, Psychology, Drug Research And Child Health, Firenze, Italy, [2]University of Florence, Department Of Biomedical, Experimental And Clinical Sciences "mario Serio", University Of Florence, Florence, 50134, Italy, Firenze, Italy, [3]Azienda Ospedaliero-Universitaria Careggi, Florence, Italy, 2research And Innovation Centre For Dementia-cridem, Firenze, Italy

Aims: NfL and GFAP are promising blood-based biomarkers for Alzheimer's disease. However, few studies have explored plasma GFAP in the prodromal and preclinical stages of AD. In our cross-sectional study, our aim is to investigate the role of these biomarkers in the earliest stages of AD.
Methods: We enrolled 40 patients (11 SCD, 21 MCI, 8 AD dementia). All patients underwent neurological and neuropsychological examinations, analysis of CSF biomarkers ($A\beta_{42}$, $A\beta_{42}/A\beta_{40}$, p-tau, t-tau), Apolipoprotein E (*APOE*) genotype analysis and measurement of plasma GFAP and NfL concentrations. Patients were categorized according to the ATN system as follows: normal AD biomarkers (NB), carriers of non-Alzheimer's pathology (non-AD), prodromal AD, or AD with dementia (AD-D).
Results: GFAP was lower in NB compared to prodromal AD (p=0.003, d=1.463) and AD-D (p=0.002, d=1.695). NfL was lower in NB patients than in AD-D (p=0.011, d=1.474). NfL demonstrated fair accuracy (AUC=0.718) in differentiating between NB and prodromal AD, with a cut-off value of 11.65 pg/mL. GFAP showed excellent accuracy in differentiating NB from prodromal AD (AUC=0.901) with a cut-off level of 198.13 pg/mL.
Conclusions: GFAP exhibited excellent accuracy in distinguishing patients with normal CSF biomarkers from those with prodromal AD. Our results support the use of this peripheral biomarker for detecting AD in patients with subjective and objective cognitive decline.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0392 / #1801

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ASSOCIATION BETWEEN CEREBROSPINAL PHOSPHORYLATED-TAU181 AND BETA-AMYLOID1-42/1-40 RATIO VALUES AND ALZHEIMER'S PHENOTYPE: A SINGLE-LABORATORY CROSS-SECTIONAL STUDY

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Simone Baiardi[1], Michelangelo Stanzani-Maserati[2], Marcello Rossi[2], Angela Mammana[2], Luisa Sambati[2], Sabina Capellari[1], Piero Parchi[1]
[1]University of Bologna, Department Of Biomedical And Neuromotor Sciences, Bologna, Italy, [2]IRCCS Istituto delle Scienze Neurologiche di Bologna, Ausl Bologna, Bologna, Italy

Aims: To define whether a quantitative assessment of amyloid (A+) and tau (T+) cerebrospinal fluid (CSF) biomarkers can predict Alzheimer's (AD) phenotype and severity. To assess the effect of Lewy body (LB) co-pathology on AD presentation.
Methods: We evaluated 420 consecutive subjects with documented cognitive decline and CSF profile A+/T+ (Aβ42/40 ratio <0.68; phospho-tau181 >57 pg/ml). Participants were stratified twice in tertile groups according to Aβ42/40 ratio and phospho-tau values. Additionally, all cases were tested for the alpha-synuclein seeding activity by the real-time-quaking induced conversion assay in the CSF.
Results: CSF phospho-tau181 and Aβ42/40 ratio were negatively correlated (rho=-0.489). Higher phospho-tau181 levels were associated with younger age at onset (highest tertile 67.4±8.5 vs. lowest 71.0±9.3 years, p=0.0004; onset <65 years 48.9% vs. 29.8%, p=0.001), higher CSF total-tau (1049 [871-1334] vs. 466 [412-563] pg/ml, p<0.0001) and NfL (1513 [1140-1871] vs. 1039 [798-1700] pg/ml, p=0.003) levels, and a trend toward lower MMSE scores (19.8±6.4 vs. 21.4±5.7). By contrast, no significant differences were detected by comparing A+ tertiles. NfL levels in CSF and plasma, but not phospho-tau181, were significantly correlated (rho=0.514). LB co-pathology was found in 17.8% of patients; it was associated with a higher frequency of at least one clinical core feature of dementia with LB (28.6% vs. 12.5%, p<0.001), later onset (>65 years, 70.4% vs. 58.4%, p=0.04) and older age at CSF collection (71.2±9.4 vs. 68.9±9.0 years, p=0.03).
Conclusions: Higher CSF phospho-tau181 but no lower Aβ42/40 ratio levels are associated with a more severe AD phenotype, because of the younger age at onset, the worse performance at neuropsychological testing, and the significant increase of CSF biomarkers of neurodegeneration (N+). LB co-pathology influences the clinical presentation independently from phospho-tau181 and Aβ42/40 ratio levels.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0393 / #1816

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

OLIGOMERS COUNT.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Oliver Bannach[1], Marlene Pils[1], Fabian Rehn[1], Sandra Kienast[1], Dieter Willbold[1,2]
[1]attyloid GmbH, Research And Development, Düsseldorf, Germany, [2]Forschungszentrum Jülich, Ibi-7, Jülich, Germany

Aims:

re in neurodegenerative diseases is the formation of toxic protein oligomers, which include amyloid-beta, alpha-synuclein, and Tau proteins ut also potent biomarkers for early diagnosis and drug development. However, accurately measuring these oligomers in biological fluids lik technical challenge, requiring extreme sensitivity and specificity.

Methods: We have introduced a technology called surface-based Fluorescence Intensity Distribution Analysis (sFIDA), which offers unparalleled sensitivity and specificity for quantitative detection of oligomers and other soluble aggregates. By integrating the precision of immunoassays with digital fluorescence microscopy, sFIDA enables the counting of individual oligomers.

Results: This presentation will offer an updated overview of our most recent findings, including novel data on quantifying oligomers in blood samples from the DELCODE cohort as well as in fecal samples. These insights are valuable not only for diagnostic applications but also for enhancing our understanding of key disease mechanisms, such as the clearance of oligomers from the brain.

Conclusions: In the realm of drug development, sFIDA serves as a crucial tool for validating the efficacy of drugs designed to dismantle oligomers. This technique can be applied in vitro, in animal models, and in ex vivo tissue samples. Furthermore, sFIDA proves invaluable as a biomarker assay for patient selection, stratification, and monitoring, as well as for evaluating drug-target engagement and therapeutic efficacy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0394 / #1535

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DAY-TO-DAY SLEEP VARIABILITY AND HIGHER PLASMA P-TAU231: INTERACTION BY MILD COGNITIVE IMPAIRMENT CONVERTING STATUS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Andrée-Ann Baril[1], Cynthia Picard[2], Anne Labonté[2], Erlan Sanchez[3], Bery Mohammediyan[2], Catherine Duclos[1], Nicholas Ashton[4], Henrik Zetterberg[5], Kaj Blennow[5], John Breitner[2], Sylvia Villeneuve[2], Judes Poirier[2]
[1]Université de Montréal, Medecine, Montreal, Canada, [2]Douglas Mental Healthy University Institute, Stop-ad, Montreal, Canada, [3]Sunnybrook Research Institute, Research Center, Toronto, Canada, [4]University of Gothenburg, Neurochemistry, Gothenburg, Sweden, [5]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: Day-to-day variability might reveal unstable sleep-wake cycles reflecting neurodegenerative processes. Elevated plasma p-tau231 is an early event when correlated with AD post-mortem neuropathology, and may increase already at subtle levels of Ab deposition prior to amyloid positivity. We evaluated the association between plasma p-tau231 with sleep day-to-day variability.
Methods: In the PREVENT-AD cohort, 203 dementia-free participants (age:68.3±5.4, 78M) with a parental history of sporadic AD were tested with actigraphy, plasma p-tau231 (Simoa) and $A\beta_{42}$ (LC-MS) assays, as well as with longitudinal RBANS cognitive testing for mild cognitive impairment (MCI) adjudication. Day-to-day variability (standard deviations in sleep metrics over a week of actigraphy) was assessed for sleep midpoint, duration, efficiency, and nighttime activity count.
Results: Higher plasma p-tau231/$A\beta_{42}$ was associated with higher day-to-day variability of sleep duration and nighttime activity count (b=0.221, FDR p=0.020; b=0.333, FDR p<0.001). These associations were still significant when adjusting for body mass index, retirement status, and psychoactive medications. The exact same finding was observed when looking at higher plasma p-tau231 alone (and not in a ratio with $A\beta_{42}$) with higher sleep duration variability and nighttime activity count variability (p=0.002; p<0.001). MCI converter status significantly interacted with plasma p-tau231/$A\beta_{42}$ (p=0.037), where higher plasma p-tau231/$A\beta_{42}$ was associated with higher sleep duration variability only in those that converted to MCI (b=0.662, p<0.001).
Conclusions: Sleep day-to-day variability was associated with the novel plasma p-tau231 in at-risk individuals, suggesting that unstable sleep promotes neurodegeneration or, conversely, that AD neuropathology disrupts sleep-wake cycles.

P0395 / #798

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

TRACING CHANGES IN BLOOD CELL TRANSCRIPTOMIC LANDSCAPE DURING THE ALZHEIMER'S DISEASE CONTINUUM

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Viktoriia Bavykina, Mariano Avino, Adrien Zimmer, Hugo Parent-Roberge, Usma Munawara, Mohammed Amir Husain, Abdelouahed Khalil, Marie A. Brunet, Tamas Fülöp, Benoit Laurent
Université de Sherbrooke, Department Of Biochemistry And Functional Genomics, Sherbrooke, Canada

Aims: Alzheimer's disease (AD) is the most common form of dementia with the symptoms gradually worsening over the years, ultimately leading to death. However, the driving pathological processes occur well before the appearance of symptoms. It has been observed that AD patients display signs of systemic inflammation, suggesting that it could precede well-established AD hallmarks such as the deposit of Aβ plaques and neurofibrillary tangles. Our goal is to characterize changes in gene expression in monocytes and lymphocytes isolated from patients' blood at different stages of AD progression and validate potential RNA biomarkers for a better AD prognosis and diagnosis.
Methods: We collected blood from three groups of patients: healthy subjects, Mild Cognitive Impairment (MCI) and AD patients n=9 for each group). We purified monocytes and lymphocytes from each sample and performed a whole transcriptome analysis by RNA-seq. We established differentially expressed genes (DEGs) per cell type of AD patients compared to those of healthy individuals and cross-correlated them to identify universal biomarkers across blood cells.
Results: We observed that the majority of DEGs are mainly involved in chemokine activity and cytokine-mediated signaling pathways. We further confirmed several RNA biomarkers by quantitative PCR and showed that they are often deregulated at pre-clinical stages of the disease (MCI stage). We finally confirmed the alteration of these candidates at the protein level, opening the possibility of detecting these biomarkers via different diagnostic methodologies.
Conclusions: Our findings provide evidence that we can detect the pre-clinical stage of AD in blood cells using a specific set of RNA biomarkers, highlighting the importance of studying the early immune response in neurodegenerative diseases. Blood-based RNA biomarkers have the potential to revolutionize AD diagnostic and prognostic.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0396 / #1544

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EVALUATION OF NOVEL MID-REGION AND C-TERMINAL-SPECIFIC CSF B-SYNUCLEIN ELISAS FOR ALZHEIMER'S DISEASE DIAGNOSIS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Sherif Bayoumy[1], Julie Goossens[2], Charlotte De Rocker[2], Wiesje Van Der Flier[3,4], Inge Verberk[1], Charlotte Teunissen[1], Eugeen Vanmechelen[2]
[1]Amsterdam UMC, Laboratory Medicine, Amsterdam, Netherlands, [2]ADx Neurosciences, Neurosciences, Ghent, Belgium, [3]Amsterdam UMC, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [4]Neurodegeneration, Amsterdam Neuroscience, Amsterdam, Netherlands

Aims: Elevated cerebrospinal fluid (CSF) β-synuclein levels measured with an N-terminal-targeted ELISA has emerged as a potential specific biomarker for Alzheimer's disease (AD) [1, 2]. The N-terminus is more conserved across synuclein variants, potentially leading to assay cross-reactivity [3]. This suggests potential improved diagnostic efficacy of assays targeting the more β-synuclein-specific mid and C-terminal regions, which we aimed to assess here.
Methods: We developed two novel CSF ELISAs targeting mid and C-terminal β-synuclein independently, and set-up the N-terminal assay previously described [2]. We validated the precision, sensitivity and selectivity of the ELISAs. Next, we validated the diagnostic performance of the ELISAs by analyzing 44 routine CSF samples (22 AD and 22 control with CSF Aβ42 and p-tau181 profiles).
Results: All three assays detected β-synuclein in all clinical samples with mean intra-assay precisions below 10%CV (Figure 1). The β-specific-synuclein capture-antibody used for both the mid-region and C-terminal assays did not react with recombinant α-synuclein. In contrast, the capture antibody of the N-terminus assay did show reactivity with α-synuclein protein. CSF β-synuclein levels measured with all three ELISAs significantly discriminated AD from controls (Figure 2, all: $p<0.05$). Fold-change differences in median values were 2.3 (N-terminus), 1.6 (mid-region), and 2.2 (C-terminus). Age and sex-corrected ROC analyses showed comparable diagnostic performance across the assays (AUCs: N-terminus: 0.75 (95%CI: 0.60-0.90), mid-region: 0.69 (95%CI: 0.51-0.86) and C-terminus: 0.81 (95%CI: 0.67-0.95).
Conclusions: The novel β-synuclein-specific ELISAs have robust analytical performance, and promising diagnostic accuracy to reliably distinguish AD from control CSF samples. Further validation of these ELISAs across various clinical AD stages is underway to assess their full diagnostic and prognostic utility and to determine if our specific assays have improved diagnostic accuracy compared to the N-terminal assay.

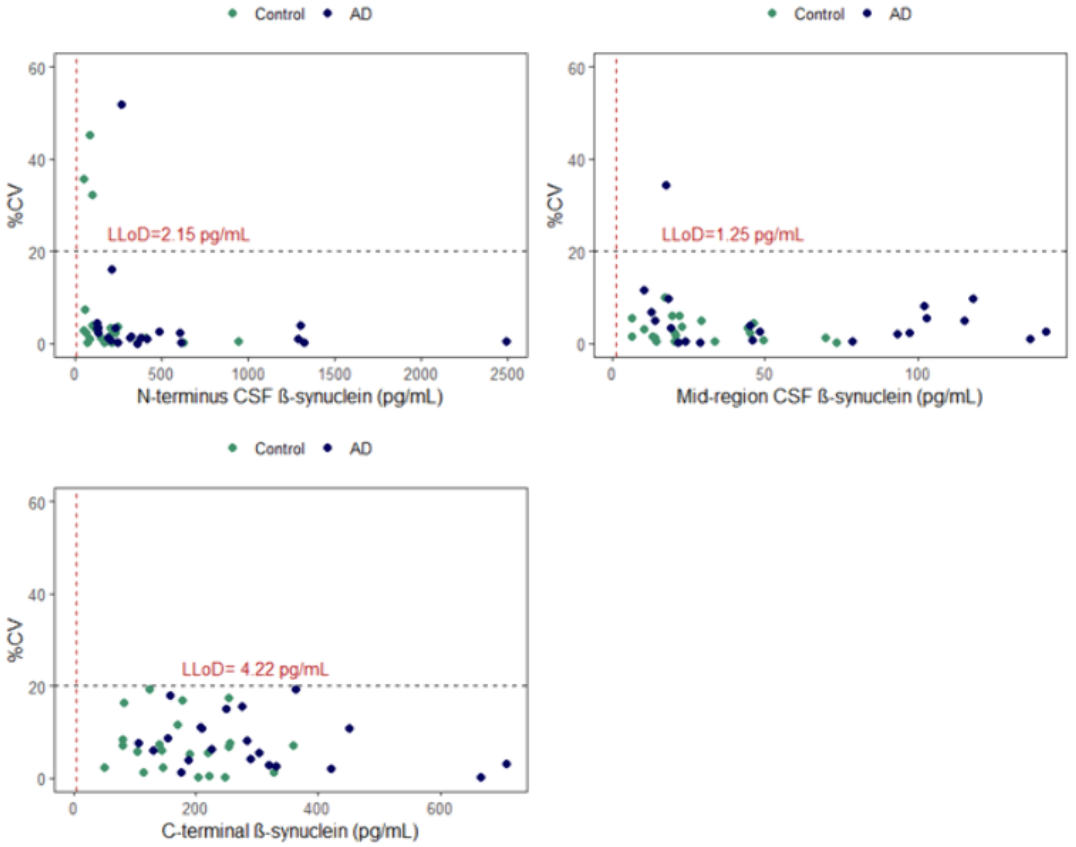


Figure 1. Precision plots of the novel CSF β-synuclein ELISAs. The plots demonstrate β-synuclein concentrations for each assay on the x-axis against the variation of duplicate measurements as percentage coefficient of variation (%CV) on the y-axis. The clinical samples were color-coded per group as AD (mean age 69.8±7.1 years: 55% F) and control (68.8 ±7.4 years: 20%F). The vertical dashed lines represent the lowest limit of detection (LLoD) (i.e., mean of 16 blanks*10x standard deviation of the blanks), and the horizontal dashed lines represent a CV of 20% for each assay.

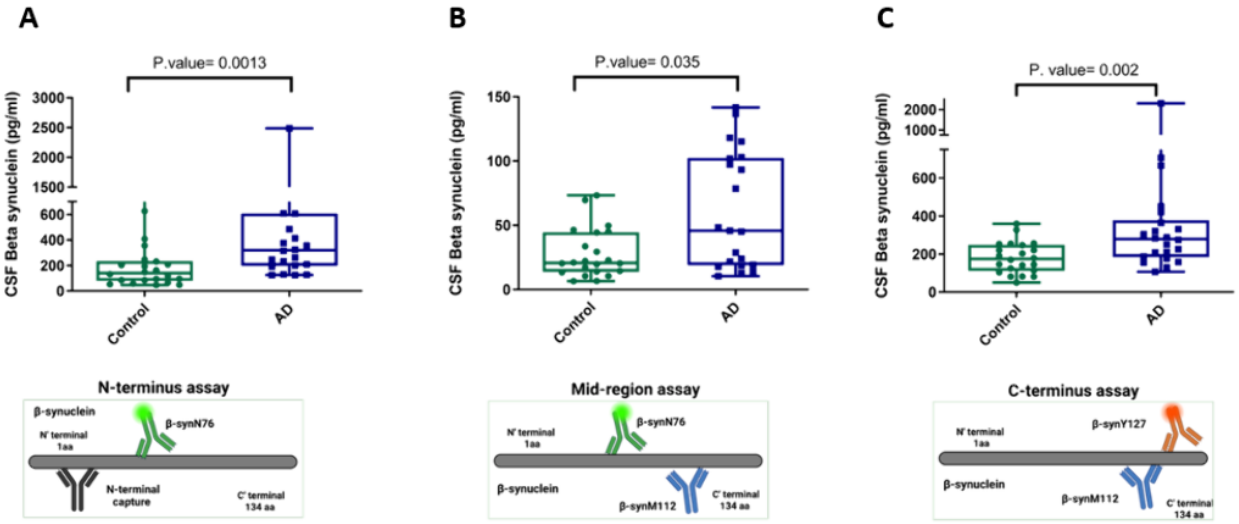


Figure 2. A) Box plots of the novel CSF β-synuclein ELISAs. A) N-terminal-β-synuclein ELISA, B) mid-β-specific-synuclein ELISA, C) C-terminal-β-specific-synuclein ELISA. Group differences were calculated using non-parametric Mann-Whitney U Tests, and results are shown with p-values within the boxplots. All assays showed significant differences between the groups with p-values of <0.05.

Reference

1. Barba, L., et al., *Cerebrospinal fluid ß-synuclein as a synaptic biomarker for preclinical Alzheimer's disease.* J Neurol Neurosurg Psychiatry, 2023. **94**(1): p. 83-86.
2. Halbgebauer, S., et al., *Beta-synuclein in cerebrospinal fluid as an early diagnostic marker of Alzheimer's disease.* J Neurol Neurosurg Psychiatry, 2021. **92**(4): p. 349-356.
3. Oeckl, P., et al., *Alpha-, Beta-, and Gamma-synuclein Quantification in Cerebrospinal Fluid by Multiple Reaction Monitoring Reveals Increased Concentrations in Alzheimer's and Creutzfeldt-Jakob Disease but No Alteration in Synucleinopathies.* Mol Cell Proteomics, 2016. **15**(10): p. 3126-3138.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0397 / #2342

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

FULLY AUTOMATED MEASUREMENT OF PLASMA AB42/40 AND P-TAU181: ANALYTICAL ROBUSTNESS AND CONCORDANCE WITH CSF PROFILE ALONG THE AD CONTINUUM IN TWO INDEPENDENT COHORTS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Giovanni Bellomo[1], Sherif Bayoumy[2], Alfredo Megaro[1], Andrea Toja[1], Giovanna Nardi[1], Lorenzo Gaetani[1], Elena Raluca Blujdea[2], Federico Paolini Paoletti[1], Anna Lidia Wojdała[1], Davide Chiasserini[3], Wiesje Van Der Flier[4], Inge Verberk[2], Charlotte Teunissen[2,5], Lucilla Parnetti[1]
[1]University of Perugia, Laboratory Of Clinical Neurochemistry, Section Of Neurology, Department Of Medicine And Surgery, Perugia, Italy, [2]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Laboratory Medicine, Neurochemistry Laboratory, Amsterdam, Netherlands, [3]University of Perugia, Section Of Physiology And Biochemistry, Department Of Medicine And Surgery, Perugia, Italy, [4]Amsterdam UMC, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [5]Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands

Aims: Fully-automated platforms offer standardized and cost-effective plasma biomarker measurements for the molecular diagnosis of Alzheimer's disease (AD). Analyzing the concordance between plasma and CSF biomarkers can expedite their clinical implementation.
Methods: Two independent cohorts (UNIPG and AMS) were included. UNIPG cohort consisted of n=450 paired CSF/plasma samples with a CSF biomarker profile of A-/T- (n=126), A-/T+ (n=50), A+/T- (n=48), and A+/T+ (n=226). This cohort considered subjects belonging to the whole AD continuum, controls, and patients affected by other neurodegenerative diseases. AMS cohort was composed of n=40 paired CSF/plasma AD samples (A+/T+) and plasma of n=40 controls. Plasma and CSF Aβ1-42, Aβ1-40, and p-tau181 levels were measured with Lumipulse® assays. For these assays we evaluated analytical performance, impact of renal dysfunction and blood-brain-barrier permeability, and diagnostic performance.
Results: High plasma p-tau181 values optimally reflected CSF A+/T+ profile in AD dementia and prodromal AD, but not in asymptomatic AD. Plasma Aβ42/40 showed similar sensitivities and specificities in all clinical stages, well reflecting the CSF A status. Cutoffs and probability-based classification models (Figure 1) for A+ and A+T+ obtained in UNIPG well performed in

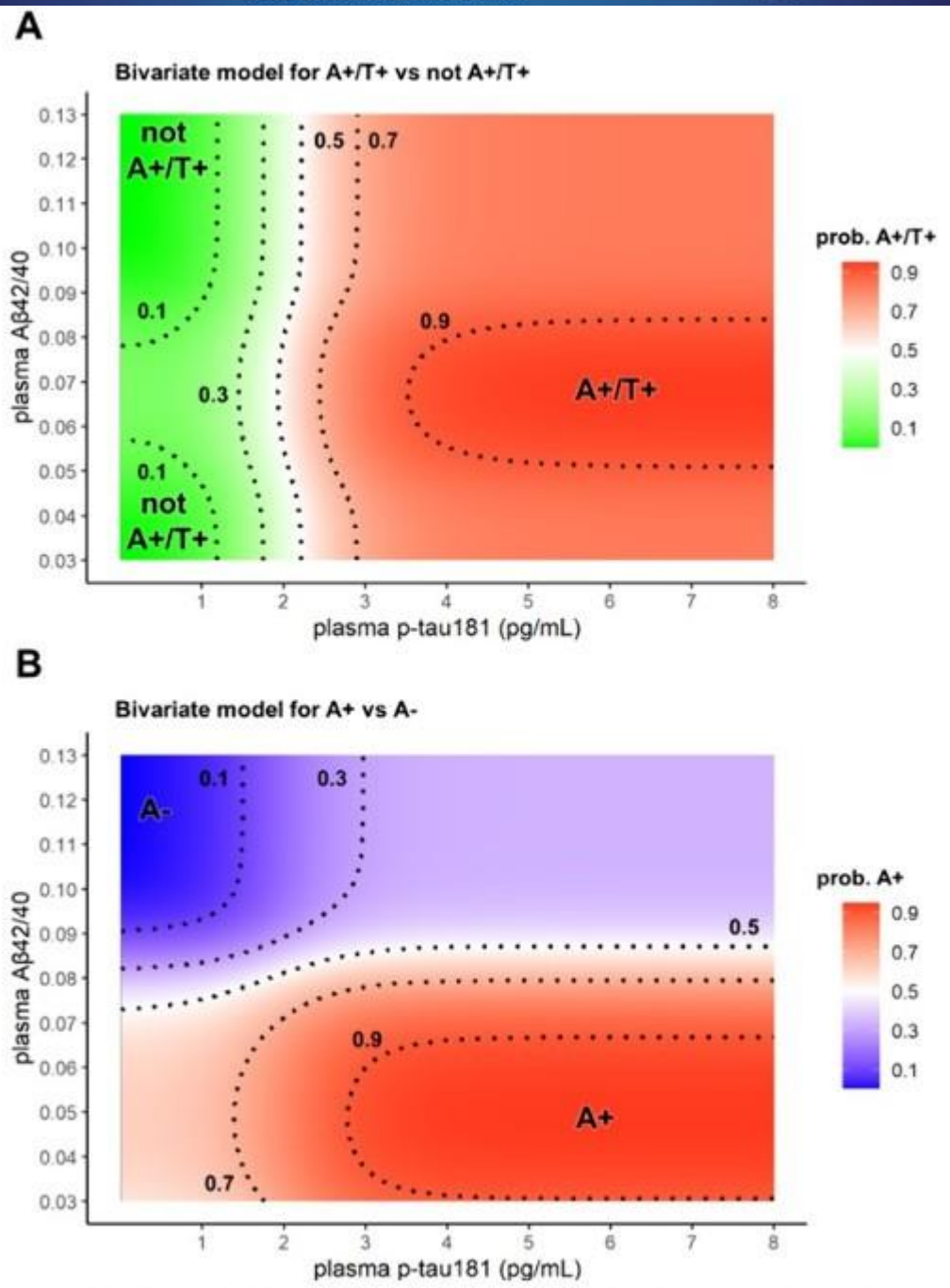


Figure 1. Bivariate probability models. The 2D probability plots for A+ vs A- (A) and for A+/T+ vs not A+/T+ (B) were built by combining 1D probabilities calculated for plasma Aβ42/40 and p-tau181. The optimal combination constant for each of the two models was chosen by maximizing the average accuracy on the training set by 100-fold cross-validation. Isoprobability dotted lines for $p = 0.1, 0.3, 0.5, 0.5$ and 0.9 are displayed.

AMS.

Conclusions: Automated plasma Aβ42/40 and p-tau181 assays showed high concordance with CSF AD biomarkers. Here we propose cutoff values and algorithms that may allow to bypass CSF collection in presence of cognitive deficits and in absence of kidney dysfunction

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0398 / #2444

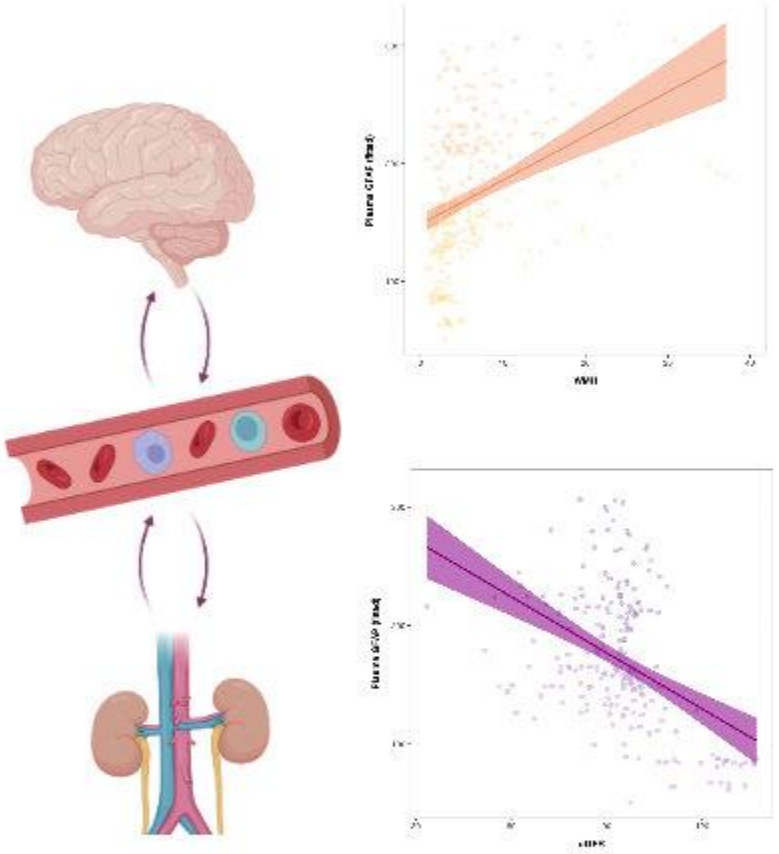
Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA GFAP AND THE KIDNEY-BRAIN AXIS.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Andréa L. Benedet[1], Burak Arslan[1], Ilaria Pola[2], Stijn Servaes[3], Wagner Brum[4], Joseph Therriault[3], Nesrine Rahmouni[3], Guglielmo Di Molfetta[5], Cécile Tissot[3], Eduardo R Zimmer[6], Tharick A Pascoal[7], Andreas Jeromin[8], Henrik Zetterberg[9], Kaj Blennow[9], Nicholas Ashton[1], Pedro Rosa-Neto[3]
[1]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [2]Sahlgrenska University Hospital/Mölndal, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [3]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [4]Universidade Federal do Rio Grande do Sul (UFRGS), Graduate Program In Biological Sciences: Biochemistry, Porto Alegre, Brazil, [5]The Sahlgrenska Academy at the University of Gothenburg, Institute Of Neuroscience And Physiology, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [6]Department of Pharmacology, Graduate Program in Biological Sciences: Biochemistry (PPGBioq) and Phamarcology and Therapeutics (PPGFT), Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil, [7]Department of Neurology and Psychiatry, University Of Pittsburgh School Of Medicine, Pittsburgh, United States of America, [8]ALZPath, Inc, Alzpath, Inc, Carlsbad, United States of America, [9]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: It is increasingly recognized the association between kidney function and brain health. Studies investigating the "Kidney-Brain Axis" suggest that poor renal function is linked to cerebrovascular changes and cognitive decline. Several mechanisms for that are being suggested, including vascular damage, inflammation and others. Given that the blood is the main pathway linking the kidney and the brain, it is important to evaluate how protein concentrations in the peripheral circulation affect/are affected by these factors. Thus, we aimed at investigating the association between brain vascular damage, renal function and plasma biomarkers.
Methods: Cross-sectional data from the TRIAD cohort was available for 370 participants classified according to clinical and amyloid status (Young=35, CU-=140, CU+=38, MCI-=28, MCI+=50, AD=50, Non-AD dementia=29) who had quantified white matter hyperintensities (WMH) as well as plasma biomarkers (GFAP, NfL, pTau217, sTREM2). Renal function was measured by estimated Glomerular Filtration Rate (eGFR). Amyloid status was indexed by [^{18}F]AZD469 PET. Spearman correlations and linear models tested the association between plasma biomarkers and WMH or eGFR, adjusting for age, sex and diagnostic groups.
Results: All plasma biomarkers correlated with WMH and eGFR. When linear regression models accounted for covariates, only plasma GFAP was associated with both WMH (P=0.04) and eGFR (P=0.02). No other plasma biomarker was associated with WMH. Higher NfL levels were associated with reduced eGFR (P=0.0001), but no association was found between eGFR and pTau217 (P=0.37) or sTREM2 (P=0.05).



Conclusions: Preliminary results suggest that plasma GFAP levels might be specifically linking kidney function and brain vascular damage, which was not observed for other biomarkers. Coming analysis should further investigate these associations and suggest possible mechanisms connecting these findings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0399 / #742

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DISENTANGLING THE RELATIONSHIP BETWEEN PLASMA BIOMARKERS, AMYLOID PET, AND CSF PTAU IN MEMORY CLINIC PATIENTS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Marina Bluma[1], Konstantinos Chiotis[1], Marco Bucci[1], Irina Savitcheva[2], Anna Matton[1], Miia Kivipelto[1], Andreas Jeromin[3], Giovanni De Santis[4], Guglielmo Di Molfetta[4], Nicholas Ashton[4], Kaj Blennow[4], Henrik Zetterberg[4], Agneta Nordberg[1,5]
[1]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, Division Of Clinical Geriatrics, Center Of Alzheimer Research, Stockholm, Sweden, [2]Karolinska University Hospital, Medical Radiation Physics And Nuclear Medicine, Stockholm, Sweden, [3]ALZPath, Inc, Alzpath, Inc, Carlsbad, United States of America, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [5]Karolinska University Hospital, Theme Inflammation And Aging, Stockholm, Sweden

Aims: Plasma biomarkers are on the verge of being introduced into screening of individuals at risk for Alzheimer's disease (AD). Yet, previous studies yielded contradictory results regarding their association with established biomarkers of AD pathology. This study aims to investigate the specific relationship between core AD biomarkers, such as amyloid PET and CSF pTau, and the novel plasma biomarkers.
Methods: We analyzed plasma pTau181, pTau217, pTau231 and GFAP, CSF pTau181, and Aβ-PET scans in a cohort of memory clinic patients (N=139) who underwent a comprehensive clinical assessment at the the Memory Clinic, Karolinska University Hospital, Stockholm,Sweden. We utilized methods based on multiple linear regression to model and evaluate the distinct contributions of Aβ-PET and CSF pTau in explaining the variance of plasma biomarkers, while also considering demographic variables.
Results: We found significant positive associations between Aβ-PET and all plasma biomarkers (R^2=0.14-0.56); highest associations were observed for pTau217. Similarly, significant positive associations of lower magnitude were observed between plasma biomarkers and CSF pTau(R^2=0.09-0.26). After accounting for the influence of Aβ-PET on plasma biomarkers and CSF pTau, only pTau217(R^2=.049) and pTau231(R^2=.024) remained significantly associated with CSF pTau. Dominance analysis showed that Aβ-PET had the highest relative importance in predicting plasma biomarkers values, followed by CSF pTau. Aβ-PET and CSF pTau explained the larger portion of variance in plasma pTau217 levels(~60%) compared to that explained in plasma GFAP (~30%),pTau181(~17%), and pTau231(~18%) levels.
Conclusions: Amyloid burden was the main predictor of levels of all plasma biomarkers. The effect of CSF pTau on GFAP and pTau181 was attenuated by the effect of Aβ-PET, while pTau231 and pTau217 also reflected subtle effects of CSF pTau. Variance in plasma pTau217 levels appeared to be well explained by AD-related pathological changes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0400 / #2151

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EVALUATION OF PLASMA PTAU181 TO PREDICT ALZHEIMER'S DISEASE DEMENTIA RISK IN A REAL WORLD COHORT OF A MEMORY CLINIC

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Amanda Cano[1], María Capdevila[1], Raquel Puerta[2], Laura Montrreal-Navarro[1], Raúl Núñez-Llaves[1], Itziar De Rojas[1], Pablo Garcia-Gonzalez[1], Clàudia Olivé[1], Adelina Orellana[1], Maitee Rosende-Roca[1], Vanesa Pytel[1], Montserrat Alegret[1], Lluís Tárraga Mestre[1], Marta Marquié[1], Merce Boada Rovira[1], Agustín Ruiz Laza[1]
[1]Ace Alzheimer Center Barcelona, Research Center And Memory Clinic, Barcelona, Spain, [2]Ace Alzheimer Center Barcelona, Molecular Biology & Biomarkers, Barcelona, Spain

Aims: Background & Objective: Plasma biomarkers need of further research to translate them as a realistic option in the clinical practice. However, many studies to date have assessed them in research cohorts. Here we evaluated the clinical value of plasma pTau181 as a predictive marker of AD dementia risk in a real-world memory clinic cohort.
Methods: Methods: The ACE cohort encompass 1649 patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI), AD dementia and other dementias, with paired CSF and plasma samples. CSF Aβ42, Aβ40, pTau181 and tTau, and plasma pTau181 were measured using the Lumipulse G1200 automatic platform (Fujirebio Inc.). Complete cohort were divided in the Testing cohort (n=1000) and Validation cohort (n=649).
Results: Results: plasma pTau181 significantly correlated (P<0.0001) with CSF pTau181 in MCI, AD dementia and other dementias, but not in SCD. Specifically for MCI patients, ROC curve of MCI A+T+ *vs* MCI A-T- showed and AUC=0.8874 and P<0.0001. A cut off value of 1.300 pg/ml exhibited a 93.6% sensibility and only 8.3% of false negatives in MCI patients. Hazard ratio of survival of conversion analysis showed that MCI patients above to this cut off value exhibited a 7.3 higher risk to convert to AD dementia than MCI under the cut off value. Validation cohort confirmed these findings.
Conclusions: Conclusion: plasma pTau181 could be useful as a pre-screening biomarker of MCI patients with high risk to progress to dementia. Positive patients will also require a confirmatory test. Plasma pTau181 by itself does not present a suitable biomarker for SCD. Another biomarker or a combination of biomarkers would be needed to this population. Further studies are need to obtain more clinical data and improve the knowledge to finally substitute CSF/PET biomarkers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0401 / #1967

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

BIOSENSOR FOR DETECTION OF AN ALZHEIMER'S DISEASE BIOMARKER

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Pedro Carneiro[1,2], Joana Loureiro[1], Simone Morais[2], Maria Carmo Pereira[1]
[1]Faculty of Engineering, University of Porto, Lepabe, Department Of Chemical Engineering, Porto, Portugal, [2]Instituto Superior de Engenharia do Porto, Instituto Politécnico do Porto, Requimte-laqv, Chemical Engineering, Porto, Portugal

Aims: The identification and detection of cerebrospinal fluid (CSF) and blood biomarkers has been gaining increasing relevance in the clinical diagnosis of Alzheimer's disease (AD). Although, pathophysiological hallmarks of AD can be identified through CSF or imaging techniques, its early diagnosis is still challenging due to the invasiveness and high cost associated with these methods. This way, the goal of this work was to develop a more cost-effective immunosensor for the sensitive detection of amyloid beta 42 in plasma samples by electrochemical sensing.
Methods: The proposed immunosensor consists of an indirect sandwich assay with a screen-printed carbon electrode (SPCE) modified with graphene oxide (GO) as the electrochemical transducer. The detection process is generated through an enzymatic degradation of H_2O_2 by horseradish peroxidase (HRP) converting the TMB substrate into its oxidative state. The capture antibodies specific for amyloid beta 42 were immobilized on the GO modified SPCE surface through covalent bonding to ensure the formation of a stable layer of the biorecognition elements. Moreover, this stage was accompanied with the addition of bovine serum albumin to minimize the occurrence of non-specific bindings. To conclude the detection process, a monoclonal antibody specific to amino acids 1-17 of human Aβ followed by a secondary antibody labelled with HRP were sequentially added.
Results: The electrochemical signal was generated by chronoamperometry, where under optimal conditions an analytical curve was attained using the current increase (%) observed after exposure of the developed immunosensor to different concentrations of amyloid beta 42.
Conclusions: The developed immunosensor enables a successful and highly sensitive detection of amyloid beta 42.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0402 / #638

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

SALIVARY DISTURBANCES IN INFLAMMATORY, IMMUNOLOGICAL AND ANTIMICROBIAL DEFENSE RESPONSES IN PATIENTS WITH ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Eva Carro, Desiree Antequera, Laura Carrero, Cristina Municio
Carlos III Health Institute (ISCIII), Neurobiology Of Alzheimer's Disease Unit, Majadahonda, Spain

Aims: Lactoferrin is an antimicrobial protein present in saliva and associated with host defense against oral pathogens. Salivary lactoferrin plays an important role in regulating the oral microbiota and the inflammatory state of the oral mucosa contributing to the maintenance of oral symbiosis. In our previous studies, we found that salivary lactoferrin correlates with AD status. Saliva samples from mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients showed decreased levels of lactoferrin when compared with controls. Since lactoferrin displayed proteinase inhibitory activity against oral bacteria including *Porphyromonas gingivalis* (*P. gingivalis*), we propose that low salivary levels of lactoferrin, as seen in AD patients, lead *P. gingivalis* proliferation and subsequently, and infection-mediated inflammatory responses. Our study aimed to evaluate components of oral dysbiosis, including *P. gingivalis*-related manifestations, lactoferrin levels, and inflammatory profile, in the saliva of AD patients.
Methods: We performed a cross-sectional study including patients with (MCI) and AD, comparing with healthy controls. Diagnosis was based on detailed clinical assessment, neuropsychological study, neuroimaging and amyloid-Positron-Emission Tomography (PET) scan results. Non-stimulated saliva samples were collected and processed from all subjects as described previously, and biochemical analysis were performed to determine lactoferrin levels, inflammatory profile and gingipain expression.
Results: As we expected, we found significant reduction in salivary lactoferrin levels in MCI and AD patients, as well as in anti-inflammatory cytokines such as IL-1ra, IL-10. On the contrary, pro-inflammatory cytokines such as IL-6, IL-7, and IL-23 were up expressed in MCI and AD patients. We also found reduced levels of SDF-1α, MIP-1β, IP-10 and VEGF in saliva of AD patients compared to healthy control subjects.
Conclusions: Taken together, these finding suggest an inflammatory condition, compatible with oral dysbiosis, in the saliva of AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0403 / #2375

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

NEURODEGENE: A GENETIC PANEL FOR THE PROGNOSIS AND EARLY-DETECTION OF MULTIPLE FORMS OF NEURODEGENERATIVE DISEASES

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Miguel Casanova, Swann Ruyter, Seval Kul, Louis Chauvière, Ramiro Magno, Dany Mukesha, Lucas Pham-Van, Stéphanie Boutillier, Hüseyin Firat
Firalis, Amoneta, Huningue, France

Aims: Current diagnostic solutions for neurodegenerative disorders (NDs) are insufficient. We developed a novel target enrichment genetic panel, as an aid for early and differential diagnosis of NDs, their prognosis and better characterization of these patients, and of target populations enrichment for drug development studies.
Methods: Using multiple genetic disease and proprietary databases, we selected the most relevant coding and non-coding gene variants associated with NDs. These variants were used to create a target enrichment capture panel, NeuroDeGene, which was used to sequence 963 whole blood samples from the ADDIA (NCT03030586) and ADDKIT cohorts using the Illumina NovaSeq 6000 DX platform. The genomic data was analyzed with interdependent approaches: polygenic risk score to quantify individual susceptibility to disease; unsupervised analysis to stratify and extract patterns from the population; and machine learning to predict disease diagnosis.
Results: Using AD as a case study, we confirm that variants in *APOE* are amongst those with the strongest genetic risk. Interestingly, we identify other variants showing either an increased or decreased association with AD. Harnessing the genotyping information from these variants, we are able to cluster AD patients subjects into genomic profiles. Finally, our modelling approach allows predicting disease group with high performance (AUC ~0.80).
Conclusions: NeuroDeGene is an innovative precision medicine tool aiming to develop a clinically applicable, single risk prediction test for multiple NDs. It provides a panel of genetic variants covering many essential genes, but also many non-coding functional regions that are often overlooked. It will prove an invaluable tool to aid on the diagnosis of neurodegenerative disorders, prognostic applications and for supporting clinical trials in early dementia populations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0404 / #1699

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

A SENSITIVE DIGITAL BIOASSAY FOR SERUM-BASED DIAGNOSIS OF NEURODEGENERATIVE DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Matthew Cheetham[1], Dorothea Böken[1], Emre Fertan[1], Zengjie Xia[1], Jeff Lam[1], Elizabeth English[1], Henrik Zetterberg[2], David Klenerman[1]
[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: To develop an aggregate-specific assay that is compatible with the SIMOA platform, and sufficiently sensitive to detect the presence of amyloid-beta and alpha-synuclein aggregates in serum samples and other biofluids.
Methods: The SIMOA platform uses antibody coated magnetic beads to capture biomarkers from the sample. A biotinylated detector antibody, and streptavidin conjugated enzyme are added to form an immunocomplex on the beads, which are then loaded into an array of microwells large enough to fit only a single bead. Resorufin conjugates are then added to this array, and any wells containing an immunocomplex exhibit fluorescence. The analyte concentration is then obtained from the fraction of beads in the "on" state, giving a significantly higher sensitivity than a typical ELISA. The standard use of SIMOA is to detect monomers, however since we are specifically interested in aggregates as biomarkers of disease, we developed our assays using the same antibody (6E10 or SC211) for both the capture and detection – that way monomeric amyloid-beta and alpha-synuclein are excluded as they only have single epitopes.
Results: The assays were highly sensitive, with limits of detection seen for in-vitro aggregates ~100 fM. The assays were also shown to be highly specific, not detecting monomers or other proteins. We also tested a cohort of serum and CSF samples and demonstrated that the assays are capable of detecting aggregates in these samples.
Conclusions: We have developed an ultra-sensitive and highly specific assay for amyloid-beta and alpha-synuclein aggregates. Further studies of early-onset disease vs control groups will enable us to explore the use of this assay to distinguish between the two, with the potential to offer early diagnosis to the patient based on the results of a routine blood test.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0405 / #1378

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

MULTIOMIC ANALYSES OF PLASMA PROTEOMIC BIOMARKERS OF DEMENTIA SUGGESTS A DIVERGENT BRAIN AGING TRAJECTORY

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Loet Coenen[1,2], Elga De Vries[1], Jinte Middeldorp[2]
[1]Amsterdam UMC location Vrije Universiteit Amsterdam, Molecular Cell Biology And Immunology, Amsterdam, Netherlands, [2]Biomedical Primate Research Centre, Neurobiology & Aging, Rijswijk, Netherlands

Aims: Aging is the main risk factor for neurodegenerative diseases such as Alzheimer's disease and other dementias (ADOD). Both aging and dementia leave a molecular signature in the plasma proteome. Understanding how the Dementia Plasma Proteome (DPP) diverges from the Aging Plasma Proteome provides insights in pathological changes in dementia patients, or resilience mechanisms in cognitive healthy individuals.
Methods: Using publicly available datasets such as the Human Protein Atlas, GTEx, and the Aging, Dementia and TBI study, we link changes observed in the plasma to age-associated changes in the brain. We provide a broad overview and evidence across multiple biological levels using methods such as Mendelian Randomization (MR), enrichment analysis, linear modeling and permutation tests.
Results: We compiled a DPP of 712 proteins shown to be changed in the plasma of ADOD patients with their corresponding protein quantitative trait loci (pQTLs). These pQTLs are enriched in brain-related phenotypes and phenotypes linked to dementia such as soluble TREM2 levels and lipoprotein levels. MR prioritizes proteins enriched with functions related to peripheral inflammation in ADOD. Proteins mostly expressed in the brain are shown to reflect a strong cortical signature and are more expressed in brain regions known to be vulnerable to ADOD. Permutation tests across brain regions show that DPP genes are more subjective to age-associated transcriptional changes than other genes. Comparing transcriptomic changes between ADOD patients and non-demented controls indicate both age-associated and pathology-associated differences in the brain transcriptome.
Conclusions: These results contribute to understanding the molecular signature of dementia in blood plasma and to the identification of novel biomarkers of brain pathology. Further validation in tissue is needed to link results from the DPP to pathology in the brain.

P0406 / #874

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ALZHEIMER'S DISEASE PLASMA BIOMARKERS FOLLOW AGE-RELATED TRAJECTORIES IN COGNITIVELY HEALTHY OLDEST OLD

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Jennifer Cooper[1], Sophie Stukas[1], Mohammad Ghodsi[1], Stephen Leach[2], Angela Brooks-Wilson[2], Cheryl Wellington[1]
[1]University of British Columbia, Pathology And Laboratory Medicine, Vancouver, Canada, [2]BC Cancer, Canada's Michael Smith Genome Sciences Centre, Vancouver, Canada

Aims: To investigate how ageing modifies plasma levels of amyloid beta 42/40 (Aβ42/40), phosphorylated tau-181 (p-tau-181), neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) in a normative, epidemiologically representative Canadian population and in cognitively healthy seniors over 80 years of age.
Methods: Biomarkers were analysed on the Quanterix Simoa HD-X analyzer using Neurology 4-plex E and p-tau-181 assays. N=900 Canadian Health Measures Survey plasma specimens were analyzed as a normative population. Using smoothed quantile regression, the 5th, 50th and 95th percentiles from ages 3-79 years were determined. N=480 plasma specimens were analyzed from cognitively healthy Super Seniors Study participants with a median age of 88 years old (IQR= 87-90y), who had never been diagnosed with dementia, cancer, diabetes, cardiovascular or major pulmonary disease.
Results:

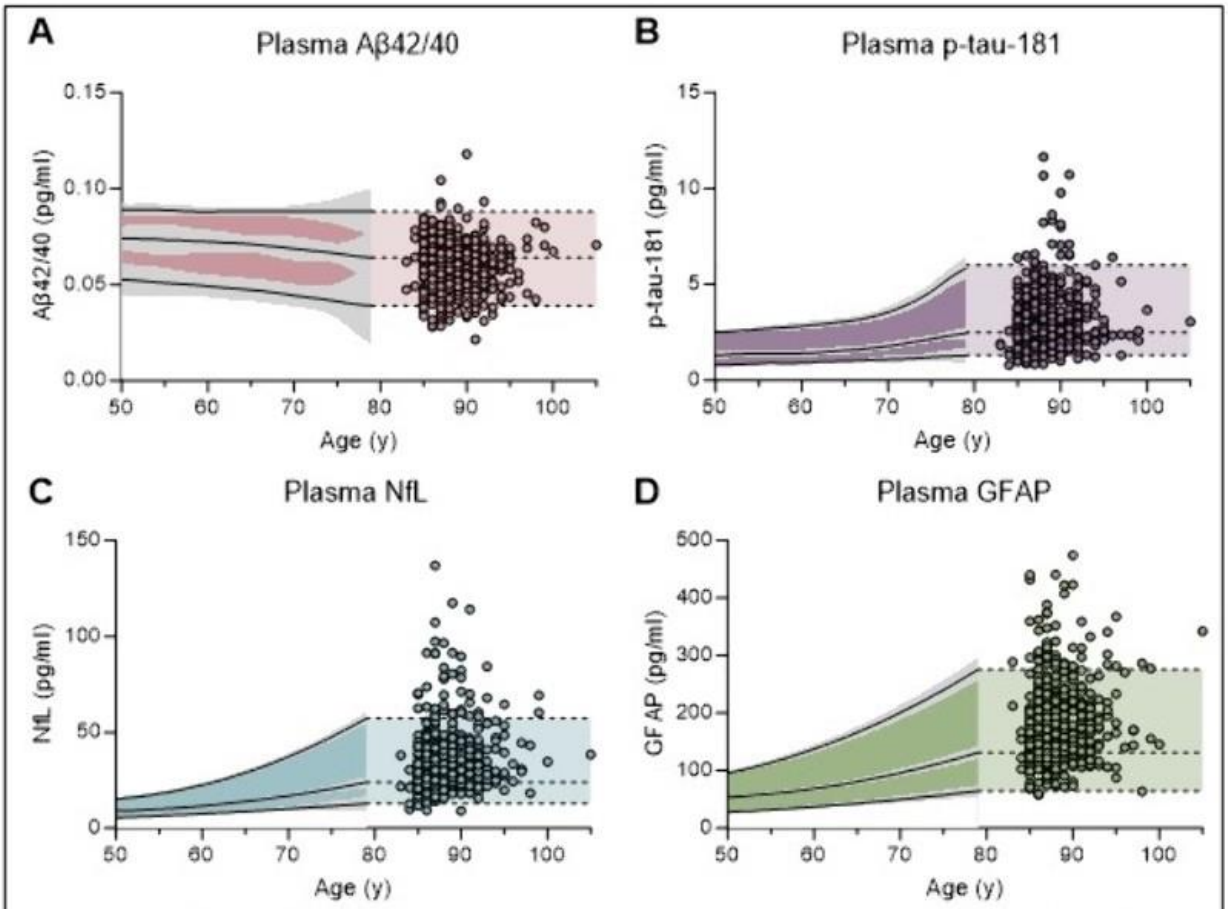


Figure 1. Plasma Aβ42/40 (A), p-tau-181 (B), NfL (C), and GFAP (D) in normative and healthy populations. N=243 specimens from normative participants from age 50 to 79 years old were used to generate percentiles of population normal concentrations. The 95th, 50th, and 5th percentiles are indicated by the solid black lines. The gray shaded regions indicate the 95% CI of each percentile. Dark shaded regions indicate the reference ranges (5th to 95th percentiles) for each biomarker form the age of 50 to 79 years old. Beyond 80 years old, the dashed black lines indicate the 95th, 50th, and 5th percentiles of 79-year-olds, with the light shaded region indicating the corresponding reference range. Coloured circles represent data from N=480 cognitively normal, Super Seniors.

In the normative population, the 50th percentiles of p-tau-181, NfL, and GFAP increased by 3-4% per year and the 95th percentile increased by 4-5% per year between 60-80 years of age. For Aβ42/40, both the 5th and 50th percentiles decreased by 1% per year. After age 80, biomarker levels in Super Seniors mimicked the levels of normative 79-year-olds. In Super Seniors, 93% of Aβ42/40, 90% of p-tau-181, 89% of NfL, and 87% of GFAP data points fell within the 5th and 95th percentiles of normative 79-year-olds. Within this reference range, a higher proportion of Super Seniors fell above the 50th percentile for p-tau-181 (59%), NfL (78%), and GFAP (75%), or below the 50th percentile for AB42/40 (60%), indicating a continuation of the trajectories observed in the normative population.

Conclusions: Cognitively healthy seniors over 80 years have similar plasma biomarker distributions as normative 79-year-olds, indicating that age, regardless of cognitive status, modifies biomarker concentrations over the age of 80 years.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0407 / #1872

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

BIOMARKER CHANGES IN THE AGED BEAGLE DOG MODEL OF ALZHEIMER'S DISEASE PROGRESSION

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Christina De Rivera[1], Roisin Winters[2], Jack Prenderville[2], Joseph Araujo[3]
[1]Transpharmation Ltd., Companion Animal Department, Fergus, Canada, [2]Transpharmation Ireland Ltd., Neuropharmacology, Dublin, Ireland, [3]Transpharmation Ltd., Business Development, Fergus, Canada

Aims: In humans, neuroinflammation is thought to be a contributing factor to Alzheimer's Disease. We have previously shown that canine aging is linked to several biomarker changes, including age-related increases in NfL chain levels in CSF of Beagle dogs and decreases in %Aβ42 with age. The current study sought to further characterize inflammatory biomarker changes in the aged dog by investigating whether concentrations in CSF and plasma of the cytokines, TNFα, IL-2, IL-6, and IL-8, varied by age and with amyloid fluid biomarkers.
Methods: Concentrations of the biomarkers in CSF and plasma from three age groups of dogs were quantified using a commercially available canine multiplex cytokine kit and analyzed by the MESO QuickPlex SQ. Data were analyzed using the GraphPad Prism 9 statistical software.
Results: There was a significant effect of age group on concentrations of IL-2 and IL-6 but no significant differences in TNFα and IL-8 levels in CSF. Similar results were found in plasma. Increases in IL-2 and IL-6 were negatively correlated with %Aβ42.
Conclusions: The current results support the hypothesis of increased neuroinflammation in the aged dog and suggests that increased inflammatory biomarkers are correlated with increased brain amyloid load. Additional studies will need to be conducted to determine how these changes affect cognitive function and other clinically relevant biomarker changes previously reported in the aged Beagle dog.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0408 / #2687

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA AND CEREBROSPINAL FLUID PROTEOMIC ANALYSIS USING NULISASEQ CNS PANEL IN ALZHEIMER'S DISEASE PATIENTS.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Guglielmo Di Molfetta[1], Ashvini Keshavan[2], Ishara Ariyapala[3], Sean Kim[3], Xiaolei Qiu[3], Bingqing Zhang[3], Xiao-Jun Ma[3], Kaj Blennow[1,4], Jonathan Schott[2], Nicholas Ashton[1,5,6,7], Henrik Zetterberg[1,4,8,9,10,11]
[1]The Sahlgrenska Academy at the University of Gothenburg, Institute Of Neuroscience And Physiology, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [2]UCL Queen Square Institute of Neurology, Dementia Research Centre, Department Of Neurodegenerative Disease, London, United Kingdom, [3]Alamar Biosciences, Inc., Fremont, United States of America, [4]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [5]King's College London, Department Of Old Age Psychiatry, Institute Of Psychiatry, Psychology And Neuroscience, London, United Kingdom, [6]Stavanger University Hospital, Centre For Age-related Medicine, Stavanger, Norway, [7]NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia, South London And Maudsley Nhs Foundation, London, United Kingdom, [8]UCL London, Uk Dementia Research Institute, London, United Kingdom, [9]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China, [10]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America, [11]Department of Neurodegenerative Disease, Ucl Institute Of Neurology, London, United Kingdom

Aims: Ultra-sensitive immunoassays allowed the development of blood biomarkers for Alzheimer's disease (AD). However, current methods are often limited by their ability to measure only few analytes simultaneously. Here we report the results from the novel nucleic acid linked immunoassay (NULISA) platform, which offers attomolar sensitivity and high multiplexing abilities, through which we measured and compared 100+ proteins in plasma and CSF of AD patients and controls.
Methods: The NULISA platform implements a proximity ligation (PL) assay concept using oligonucelotides conjugated to antibodies and, through sequential capture and wash steps, it minimizes background noise. A PL creates a library of DNA barcodes that can be sequenced and relatively quantified on a next-generation sequencer (Fig.1). We utilised the NULISAseq CNS Disease Panel in plasma and CSF from 40 patients (n=25 AD; n=15 non-AD) provided by University College London. Presence of AD pathology was assessed by CSF Aβ42/40 and p-tau181 on the LUMIPULSE-G1200.

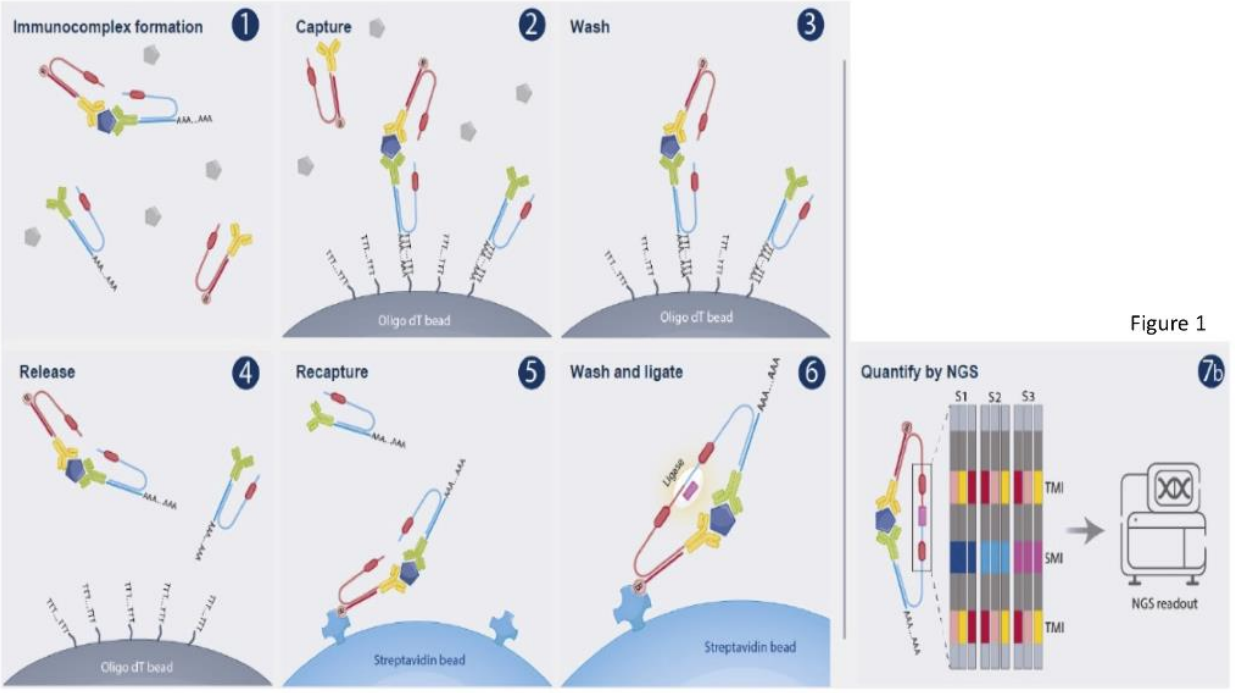


Figure 1

Results: Overall, 114/116 (98.4%) targets in the panel were detectable in plasma and 102/116 (87.9%) in CSF. FDR adjusted p-values from linear model analysis demonstrated 12 upregulated and 1 downregulated protein in CSF of AD patients (Fig.2). In plasma, 3 upregulated targets in AD were observed (Fig.3) and further targets were identified with more relaxed statistical thresholds (Fig.3) (e.g., BACE-1, BASP1,
CCL2).

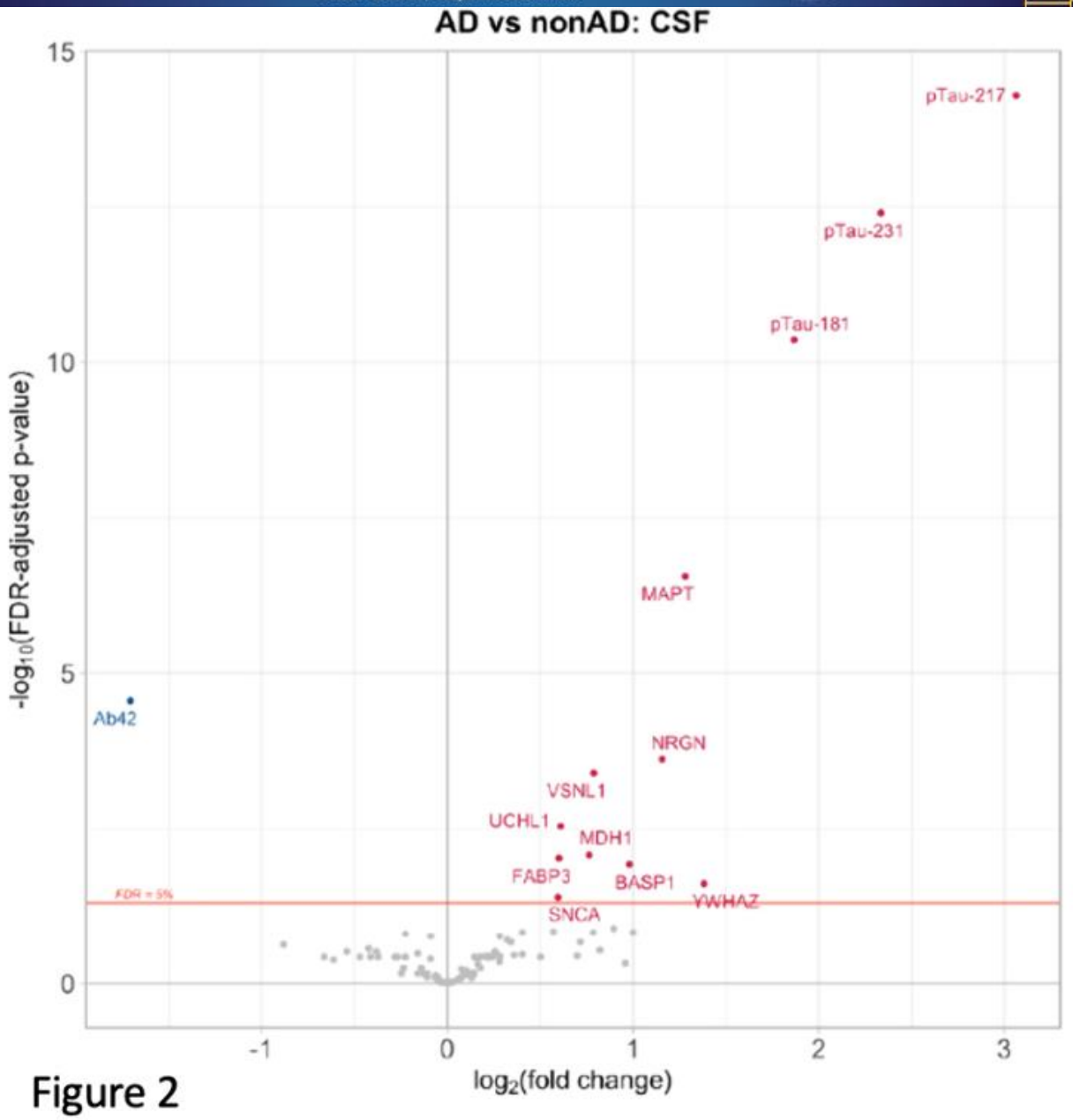

AD vs nonAD: CSF
pTau-217
pTau-231
pTau-181
MAPT
Ab42
NRGN
VSNL1
UCHL1
MDH1
FABP3
BASP1
YWHAZ
SNCA
FDR = 5%
-log10(FDR-adjusted p-value)
log2(fold change)
15
10
5
0
-1
0
1
2
3

Figure 2

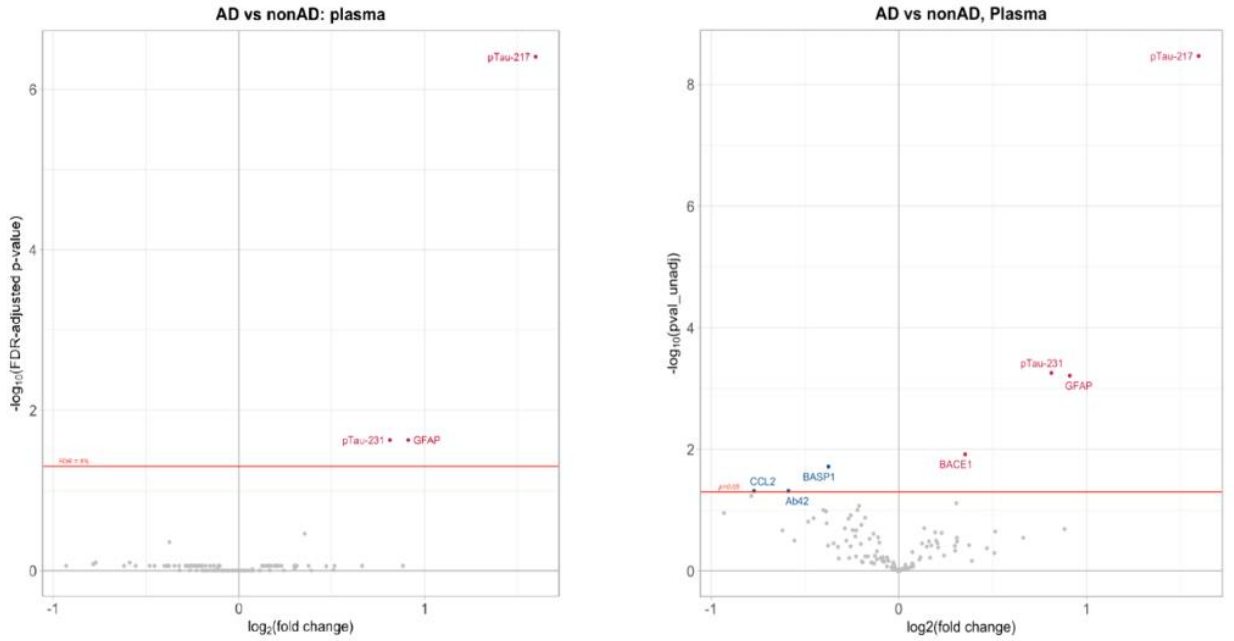


Figure 3

Conclusions: In this pilot study, the NULISA CNS Disease panel was demonstrated to be a powerful tool to profile blood and CSF proteome. In the context of AD, this combines detection of known targets (e.g., p-tau217), along with an array of exploratory targets that can all be measured with ultra-high sensitivity. This approach will be fundamental in assessing response after anti-amyloid removal therapies and exploring novel complementary drug targets for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0409 / #2633

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

M6A MODIFIED RNA TARGETS AS NOVEL BIOMARKERS FOR AD

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Sophie Van Der Spek[1], Alejandro Rondón Ortiz[2,3,4], Sambhavi Puri[1], Jenna Libera[4], Benjamin Wolozin[4,5,6,7,8]
[1]Boston University, Anatomy And Neurobiology, Boston, United States of America, [2]Boston, Biology, Boston, United States of America, [3]Boston University, Center For Network Systems Biology, Boston, United States of America, [4]Boston University, Pharmacology And Experimental Therapeutics, Boston, United States of America, [5]Boston University, Center For Systems Neuroscience, Boston, United States of America, [6]Boston University, Center For Neurophotonics, Boston, United States of America, [7]Boston University, Department Of Neurology, Boston, United States of America, [8]Boston University School of Medicine, Anatomy & Neurobiology, Boston, United States of America

Aims: The study of methylated RNA has offered a wide range of biomarkers and therapeutic avenues in the field of oncology, and holds similar potential to the field of neurodegeneration. Our lab recently discovered increased levels of methylated RNA (m6A) of about 4-fold in brains of Alzheimer's disease (AD) patients, in a stage dependent manner. This suggests the possibility that m6A-RNA may also be increased in human CSF. Here we aimed to determine abundance of specific m6A-RNA transcripts in CSF of AD patients.
Methods: To test our hypothesis, we developed a RIP-qPCR assay (termed M6RA): RNA is pulled down from CSF with anti-m6A antibody, then specific transcripts are amplified using Taqman probe-based qPCR. We first focused on m6A S18 ribosomal RNA (rRNA) because it is highly abundant and known to be methylated. We opted to target particular transcripts (rather than measuring total m6A) because we felt that quantifying particular RNA species would be more informative, this strategy has proven successful.
Results: Using U2OS human cells, we observed successful pull-down and detection of m6A-rRNA from <100 pg of total RNA. We proceeded with m6A-RNA capture from CSF. To compensate for low rRNA abundance in ante-mortem CSF we used 400 pg total RNA as assay input. The M6RA assay revealed a 4.2-fold increase in AD samples compared to healthy controls ($p<0.02$).
Conclusions: This first study shows great promise for M6RA to determine differential m6A-rRNA levels in CSF. M6RA is currently being validated and optimized towards a plate assay using avi-tagged YTH domain protein for m6A-capture. Future work includes extension of the assay to other transcripts based on m6A-transcriptomics. Together we anticipate the assay to be a powerful diagnostic platform for AD (and ADRDs in future studies).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0410 / #1046

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

AQUAPORIN-4 AS A NOVEL CANDIDATE BLOOD-BRAIN BARRIER INTEGRITY MARKER

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Giovanni De Santis[1], Kaj Blennow[1,2], Henrik Zetterberg[1,2,3,4,5,6], Nicholas Ashton[1,7,8]
[1]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg, Mölndal, Sweden, Molndal, Sweden, [2]University of Gothenburg, Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, Molndal, Sweden, [3]Department of Neurodegenerative Disease, Ucl Institute Of Neurology, London, United Kingdom, [4]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China, [5]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America, [6]UCL London, Uk Dementia Research Institute, London, United Kingdom, [7]King's College London, Institute Of Psychiatry, Psychology And Neuroscience, Maurice Wohl Institute Clinical Neuroscience Institute, London, United Kingdom, [8]King's College London, Department Of Old Age Psychiatry, Institute Of Psychiatry, Psychology And Neuroscience, London, United Kingdom

Aims: Blood-brain barrier (BBB) integrity is crucial for brain homeostasis and maintenance. Aquaporin-4 (AQP4) has been implicated in BBB maintenance. Therefore, in this pilot study, we investigated the levels of cerebrospinal fluid (CSF) AQP4 for assessing BBB integrity.
Methods: CSF samples were collected from 56 participants (20 [35.71%] female and 36 males [64.28%]; mean [SD] age, 71 [10.8] years). Participants were stratified according to their CSF/serum albumin concentration ratio (Q-Alb); intact BBB (Q-Alb <9, n = 15), mild BBB damage (Q-Alb 9-14, n = 15), modest BBB damage (Q-Alb 14-30, n = 14), and severe BBB damage (Q-Alb >30, n = 12). AD CSF biomarkers (p-Tau181, total-Tau, Aβ42/40 ratio) was assessed by LUMIPULSE G1200. AQP4 levels were quantified using Cusabio ELISA Kit. Correlation analyses were conducted between AQP4 levels and albumin CSF/serum ratios with GraphPad Prism 9 (one-way ANOVA test was performed).
Results: CSF AQP4 was significantly higher in individuals with severe BBB damage (Fig.1). No significant difference between modest and mild BBB damage was observed. A positive correlation between AQP4 and Q-Alb (r = 0.6697, P <0,0001) was found, while none with AD and neurodegeneration biomarkers was
observed.

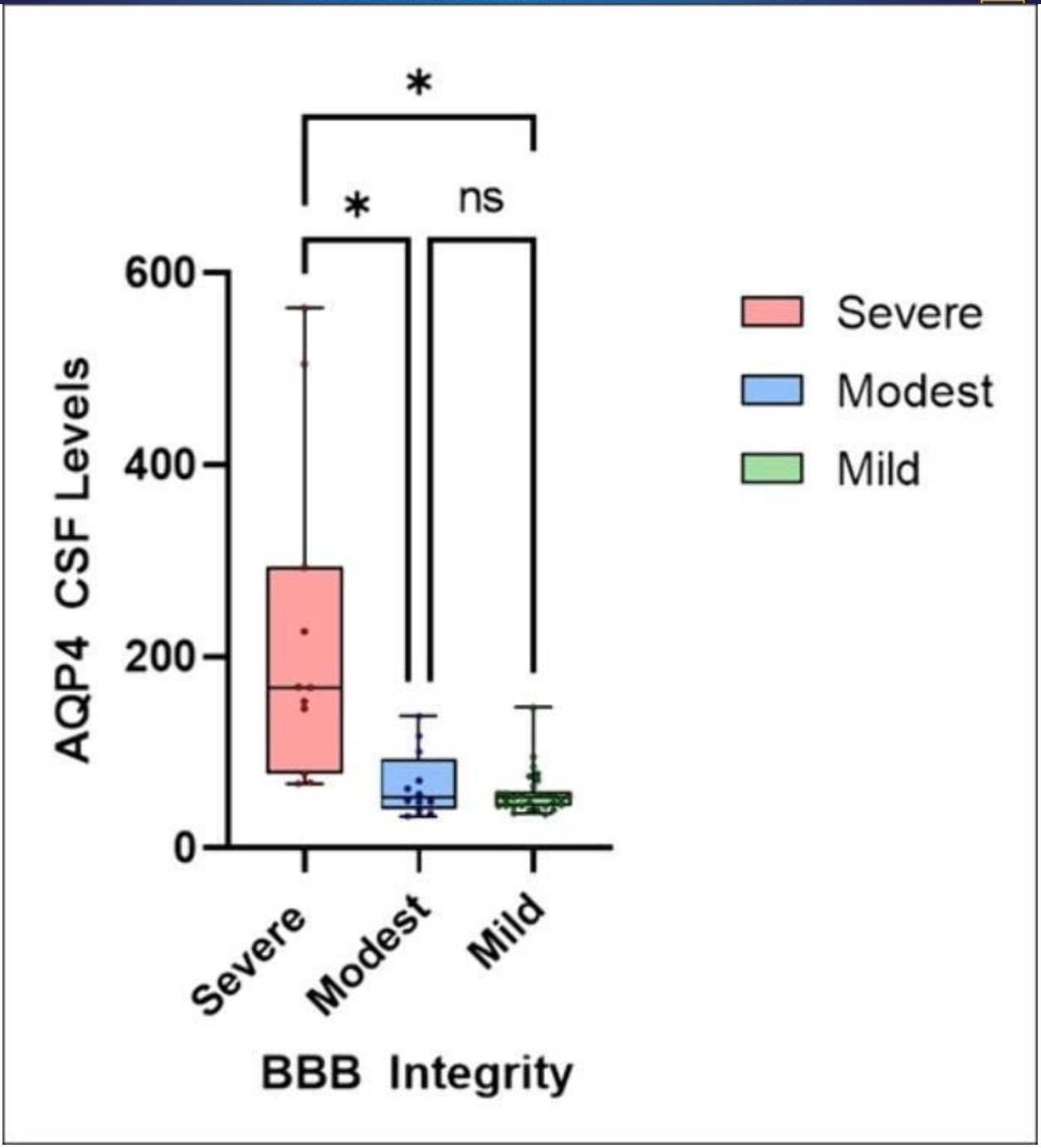


Figure 1. CSF Aquaporin-4 (AQP4) levels in individuals with severe, modest and mild blood-brain barrier damage.

Conclusions: In this pilot study, we show that CSF AQP4 concentration increases with severity of BBB damage. This highlights the potential of AQP4 as a novel biomarker for monitoring BBB integrity. Importantly, AQP4 may offer insights into a broader spectrum of neurodegenerative processes characterized by BBB dysfunction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0411 / #1439

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CEREBROSPINAL FLUID GLIAL FIBRILLARY ACIDIC PROTEIN PROVIDES DIFFERENTIAL DIAGNOSTIC VALUE IN SOME FORMS OF DEMENTIAS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Pontus Erickson[1], Tobias Skillbäck[1], Silke Kern[1,2], Linus Jönsson[3], Kaj Blennow[1,2,4], Maria Eriksdotter[1,2,3], Henrik Zetterberg[1,2,5,6,7,8]
[1]Institution for Neuroscience and Physiology, Department Of Neurochemistry And Psychiatry, Gothenburg, Sweden, [2]University of Gothenburg, Wallenberg Centre For Molecular And Translational Medicine, Gothenburg, Sweden, [3]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, STOCKHOLM, Sweden, [4]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [5]UCL London, Uk Dementia Research Institute, London, United Kingdom, [6]Clear Water Bay, Hong Kong Center For Neurodegenerative Diseases, Hong Kong, China, [7]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America, [8]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden

Aims: Glial fibrillary acidic protein (GFAP) is a marker of cerebral astrogliosis and occasionally elevated in patients with dementia. GFAP in cerebrospinal fluid (CSF), is routinely requested in referrals to neurochemistry laboratories; however, its ability to differentiate dementias and diagnostic capability is unclear. Our aim was to elucidate this, using two large datasets.
Methods: First, GFAP data measured since 2015 was retrieved from the database of the Clinical Neurochemistry Laboratory at the Sahlgrenska University hospital. We then cross-referenced with the Swedish dementia registry (SveDem). Here, information on ten different diagnoses such as early onset AD (EAD [<65 years]), late onset AD (LAD [≥65 years]), Parkinson disease with dementia (PDD), vascular dementia (VaD) and frontotemporal dementia (FTD), each with specific diagnostic criteria, were retrieved. The GFAP data was log_{10}-transformed, followed by an analysis of covariance (ANCOVA) and a subsequent post-hoc Tukey's test, with GFAP as dependent variable, diagnosis as independent variable and sex and age as covariates.
Results: In total, 1912 individuals (mean [SD] age, 71.9 [8.2] years; 52% male), were included. Lower log_{10}-transformed GFAP concentrations were seen in PDD (mean [SD], 2.68, [0.28] pg/mL), than in EAD, LAD, VaD and FTD; here, mean concentrations of 2.76 (0.24), 2.89 (0.23), 2.88 (0.32) and 2.76 (0.25) pg/mL were observed, respectively. In the post hoc analysis, GFAP differentiated VaD from EAD ($p<0.001$). PDD concentrations were significantly different from VaD ($p<0.001$) and LAD ($p<0.001$). Further, it also differentiated FTD from VaD ($p=0.006$) and LAD ($p=0.001$).
Conclusions: CSF GFAP could on a group level help differentiate VaD from EAD, FTD and PDD. Also, it could differentiate PDD from LAD. These results bear potential clinical relevance, where clinicians in some uncertain cases could use this marker as a differential tool.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0412 / #268

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

IDENTIFICATION OF CANDIDATE PREDICTIVE BIOMARKERS OF PLASMA EXCHANGE WITH ALBUMIN REPLACEMENT TREATMENT EFFICACY IN MILD-TO-MODERATE ALZHEIMER'S DISEASES

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Chunmiao Feng[1], Ricardo Gonzalo[2], Carla Minguet[2], Isabel Bravo[2], Scott Lohr[1], Merce Boada Rovira[3], Oscar Lopez[4], Antonio Paez[2], Steven Braithwaite[1], Montserrat Costa[2], Benoit Lehallier[1]
[1]Alkahest, Sio, San Carlos, United States of America, [2]Grifols, Sio, Barcelona, Spain, [3]Ace Alzheimer Center Barcelona, Research Center And Memory Clinic, Barcelona, Spain, [4]University of Pittsburgh School of Medicine, Department Of Neurology, Pittsburgh, United States of America

Aims: Alzheimer's disease (AD) is a highly heterogenous disease, requiring precision treatment for individual patients. Here we aim to identify plasma proteins that will predict patients who will benefit the most from PE-Alb treatment (Plasma exchange with albumin replacement) based on the AMBAR clinical trial (Alzheimer's Management By Albumin Replacement), where PE-Alb significantly improved cognitive functions in patients with mild-to-moderate AD, especially based on CDR-sb measurement (Clinical Dementia Rating Sum of Boxes)
Methods: Baseline levels of plasma proteins were measured using the SomaScan assay (SomaLogic, Boulder, CO, USA) and were examined using Spearman correlation (rho) to identify single protein and/or protein ratios with strong association with CDR-sb changes in the treated group at end-of-study (n=88). ROC (Receiving Operating Characteristics) curves and AUC (Area Under the Curve) were calculated to estimate the predictive powers of these identified candidate biomarkers.
Results: One single protein and 4 protein ratios at baseline plasma were identified with significant and strong association with CDR-sb change at end-of-study (rho=-0.552 for single protein and ranging from -0.606 to -0.645 for protein ratios, adjusted p-values<0.05), with mean AUC>77% for single protein and mean AUCs ranging from 80% to 87% for 4 protein ratios. The relevance of these proteins was further supported by results in randomly selected samples of AMBAR study and by significant associations with ADAS-Cog (AD Assessment Scale-Cognitive Subscale) in AMBAR study. Interestingly, this single protein was a Notch ligand and found in two of the four protein ratios identified.
Conclusions: One plasma protein and 4 protein ratios were identified with high prediction power of CDR-sb improvement after PE-Alb treatment in mild-to-moderate AD patients. They deserve further investigation and validation for developing AD precision medicine.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0413 / #1884

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EXPLORING ANGIOGENIC FACTORS IN PATIENTS WITH MANIFEST DEMENTIA

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Francesco Locatelli[1,2], Emir Basic[1,2], Sasha Hobson[3], Erik Erhardt[4], Johan Svensson[5], Gary Rosenberg[3], Anders Wallin[1,2], Petronella Kettunen[1,2]
[1]University of Gothenburg, Neuroscience And Physiology, Gothenburg, Sweden, [2]Sahlgrenska University Hospital, Psychiatry, Cognition And Old-age Psychiatry, Mölndal, Sweden, [3]University of New Mexico, Nm Center For Memory And Aging, Albuquerque, United States of America, [4]University of New Mexico, Mathematics And Statistics, Albuquerque, United States of America, [5]Sahlgrenska University Hospital, Internal Medicine And Clinical Nutrition, Gothenburg, Sweden

Aims: Alzheimer's disease (AD), subcortical small-vessel disease (SSVD) and mixed AD/SSVD (MIX) represent the most prevalent cognitive disorders, although limited knowledge exists about the involvement of angiogenic processes in their pathology. Consequently, this study aimed at assessing the contribution of angiogenic factors to the development of various dementia diagnoses. To this end, we investigated a panel of angiogenesis biomarkers in participants from the Gothenburg Mild Cognitive Impairment study, i.e. a longitudinal mono-center study of patients seeking help for cognitive complaints at the memory clinic at Sahlgrenska University Hospital.
Methods: First, we divided our subjects into 40 AD, 45 MIX, 25 SSVD and 41 controls according to the clinical diagnosis. Second, we re-diagnosed or confirmed all the patients' diagnoses using the International Working Group (IWG) for New Research Criteria for the Diagnosis of AD (IWG-2). The applied cut-offs indicating AD pathology were t-tau > 350 ng/L, p-tau181 > 59 ng/L, and Aβ1-42 < 530 ng/L. The proteins Flt1, PlGF, Tie-2, VEGF-D were analysed using the MSD Angiogenesis Panel 1 in both CSF and plasma.
Results: Our preliminary analysis showed that the endothelial growth factor Flt-1 appeared to be higher in AD and MIX than in SSVD and controls in CSF. The CSF placental growth factor PlGF was higher in MIX and SSVD compared to AD and controls. Levels of plasma angiogenesis factorsTie-2 and VEGF-D were lower in AD and SSVD compared to MIX and controls.
Conclusions: Our findings suggest that angiogenic processes play a significant role in the pathology of cognitive diseases, especially in individuals with the dual amyloid and vascular pathology, i.e. in mixed AD/SSVD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0414 / #1156

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

MULTIOMIC BLOOD-BASED BIOMARKERS EXHIBIT HIGH SPECIFICITY IN PREDICTING ALZHEIMER'S DISEASE FROM PREDEMENTIA

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Benoit Souchet[1], Alkéos Michail[1], Maud Heuillet[2], Aude Dupuy-Gayral[2], Eloi Haudebourg[2], Catherine Pech[2], Antoine Berthemy[2], François Autelitano[2], Baptiste Billoir[1], Kimiko Domoto-Reilly[3], Christopher Fowler[4], Thomas Grabowski[3], Suman Jayadev[3], Colin Masters[4], Jerome Braudeau[1]
[1]AgenT, Paris, France, [2]Evotec, Toulouse, France, [3]University of Washington, Uw Adrc, Seattle, United States of America, [4]The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Clinical Research Group, Melbourne, Australia

Aims: Diagnosing prodromal or demented Alzheimer's patients relies on cognitive assessments and amyloid plaques presence. However, these criteria have demonstrated an high sensitivity but a low specificity (Ritchie et al., 2014; Kokkinou et al., 2021; Martinez et al., 2017), leading to up to 25% false positives. **The aim of this study was to address this specificity limitation.**
Methods: We developed mass spectrometry assays for 81 blood-based biomarkers (45 proteins, 36 metabolites) identified in AAV-AD rats (Audrain et al, 2018). We analyzed samples from 345 cognitively impaired participants (193 MCI, 152 dementia), at blood draw and clinically followed for up to 13 years. The participants' diagnoses, either AD or another brain disorder, were clinically determined at their last clinical assessments. 82.9% had baseline amyloid data. We developed predictive machine learning (ML) models with high specificity for identifying AD participants (including 123 with prodromal AD and 126 with AD dementia) within the group of patients with non-AD brain disorders (comprising 96 participants). The training dataset (70%) was used to select the biomarkers, trained the algorithm, and set the cutoff, while the test dataset (30%) validated the model robustness.
Results: Combining 19 blood biomarkers and age, the ML model distinguished AD patients (41 prodromal AD and 43 AD dementia) from non-AD patients (25 individuals) with **92% specificity** and 52.4% sensitivity **on the test dataset** (AUROC=71.8%, p=0.001). When the ML model was associated with the amyloid status, we achieved **100% specificity** along with 39.7% sensitivity.
Conclusions: Our multiomics blood-based biomarkers exhibited an high specificity in identifying AD patients within the cognitively impaired population, minimizing false positives. They have the potential to not only enable earlier diagnosis but also **facilitate swift therapeutic interventions** and more effective clinical trials monitoring.

P0415 / #2303

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

A NOVEL LIQUID BIOPSY PLATFORM FOR DEMENTIA PATIENTS USING CIRCULATING CELL FREE DNA AND CHIMERIC RNAS AS BIOMARKERS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Milana Frenkel-Morgenstern[1], Eitan Okun[2]
[1]Bar-Ilan University, Azrieli Faculty Of Medicine, Safed, Israel, [2]Bar-Ilan University, The Mina And Everard Goodman Faculty Of Life Sciences, Ramat Gan, Israel

Aims: Alzheimer's Disease (AD), the most common age-associated neurodegenerative disorder, is a polygenic disease, is characterized by the presence of extracellular aggregates of amyloid plaques and intracellular tangles comprised of the Tau protein. The aim of this study was to establish a novel liquid biopsy approach that comprises a simple blood test and genomic analysis of cell-free RNA (cfRNA) and cell-free DNA (cfDNA) from tissues and liquid biopsies from patients with an early stage of mild-cognitive impairment (MCI) or AD.
Methods: Blood samples from 30 patients and 30 healthy controls, as well as 10 brain samples from AD patients and 10 samples from non-AD postmortem brains were obtained. The samples were subjected to deep sequencing and analyzed for genomic RNA (gRNA) and DNA (gDNA) data.
Results: We observed unique chimeric RNAs that have not been found in the gDNA data, particularly, sense-antisense chimeras (SAS) of *apolipoprotein E (APOE)* and *amyloid-precursor protein (APP)* genes. Moreover, we have uncovered more than 200 chimeric RNAs that are expressed in post-mortem brains as well as identified in the cfRNA of individuals with AD due to trans-splicing production. For the identification of cfDNA we mapped them specifically to the chimeric junction sites pre-computed by us from a previously developed database (ChiTaRS). Interestingly, the transcriptional chimeras of APOE and APP were associated uniquely with AD as they have not been found in the non-AD cohorts. We observed unique copy number variations on chromosomes 5 and 8. Finally, all the genes involved in chimeric transcripts tangled in cellular pathways connected to the release of dopamine and/or serotonin as well as to the function of acetylcholine.
Conclusions: These results indicate that chimeric RNAs might serve as biomarkers for the AD early diagnostics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0416 / #2273

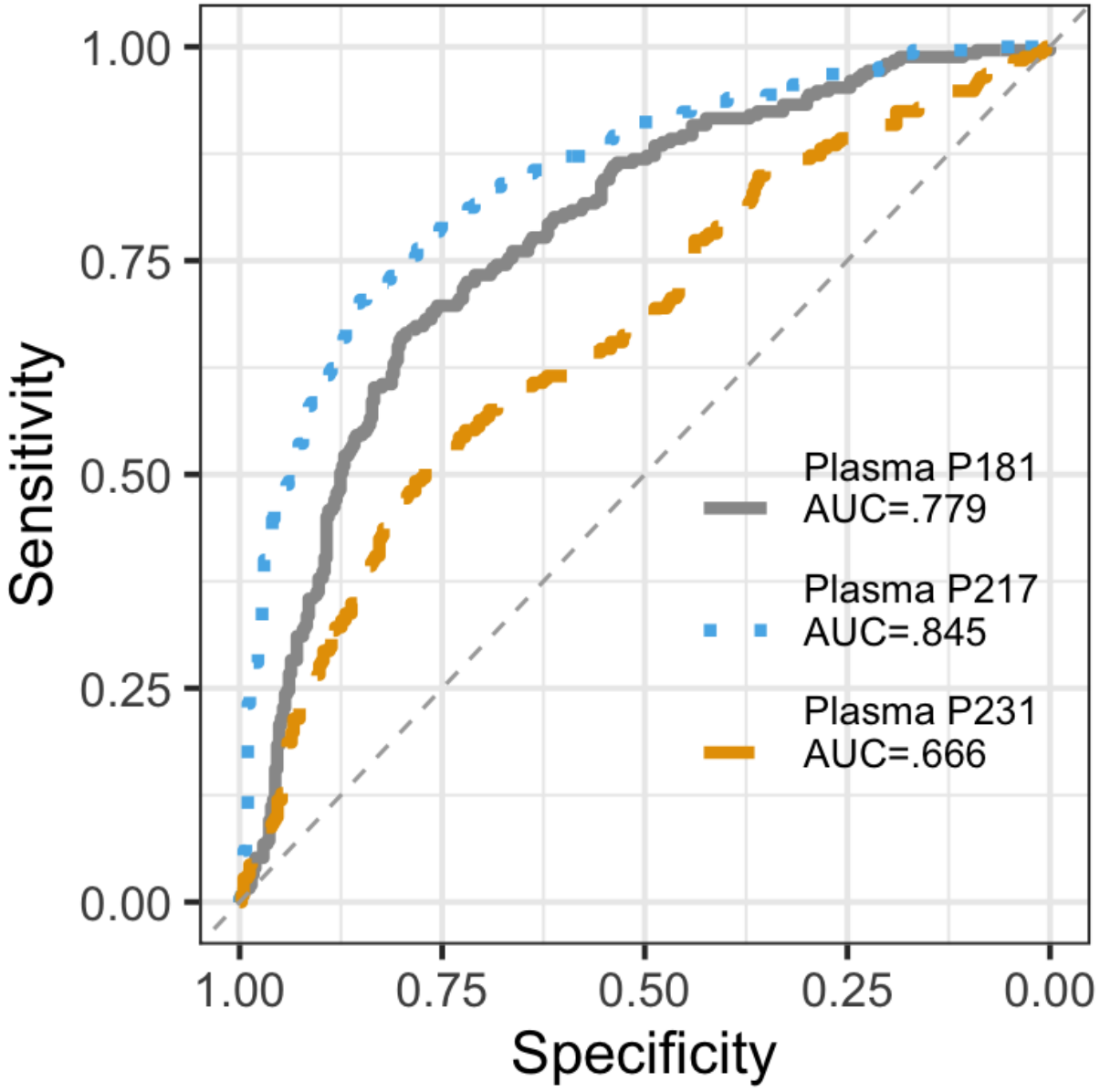
Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA P-TAU217 PREDICTS COGNITIVE DECLINE AND MRI CHANGES IN COGNITIVELY UNIMPAIRED INDIVIDUALS AND EARLY ALZHEIMER'S DISEASE

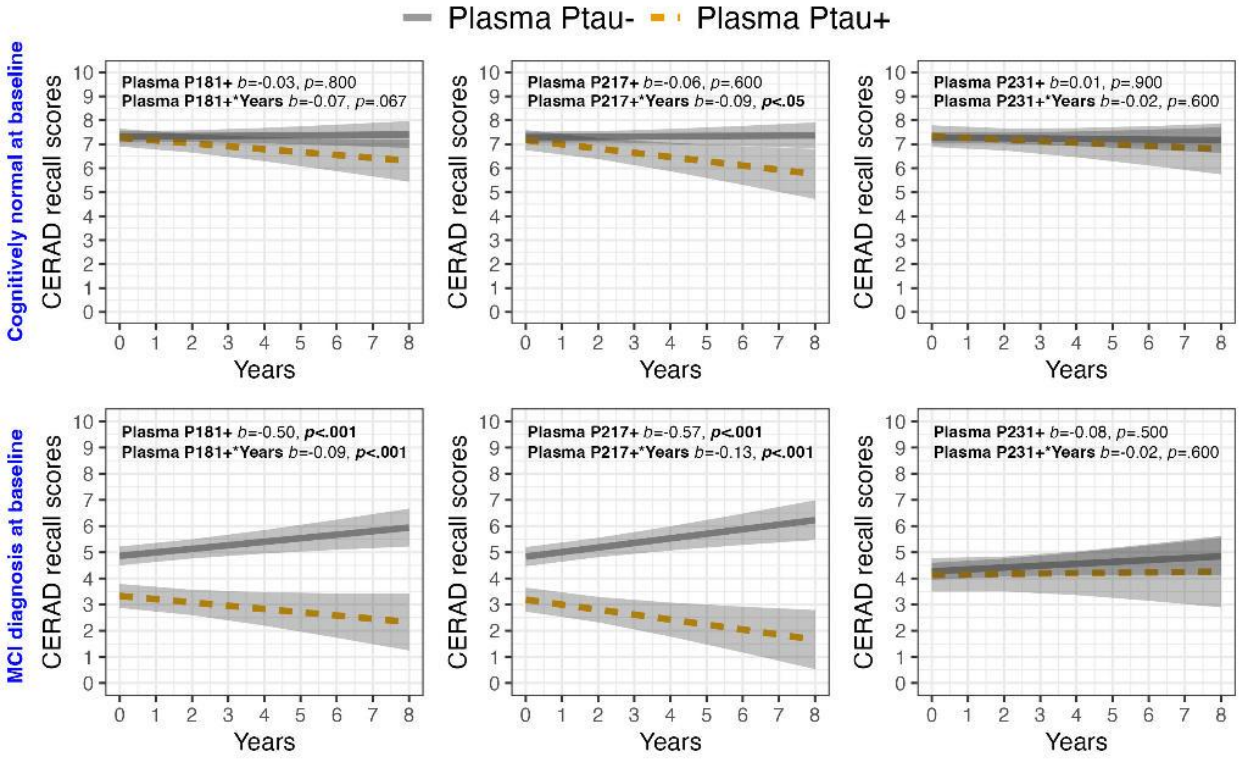
POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Fernando Gonzalez-Ortiz[1], Bjørn-Eivind Kirsebom[2], Sandra Tecelão[2], Thomas Karikari[3], Kaj Blennow[1], Tormod Fladby[4]
[1]Gothenburg University, Psychiatry And Neurochemistry, Göteborg, Sweden, [2]Akerhus University Hospital, Neurology, Lørenskog, Norway, Norway, [3]University of Gothenburg, Psychiatry And Neurochemistry, Göteborg, Sweden, [4]Akerhus University Hospital, Neurology, Oslo, Norway

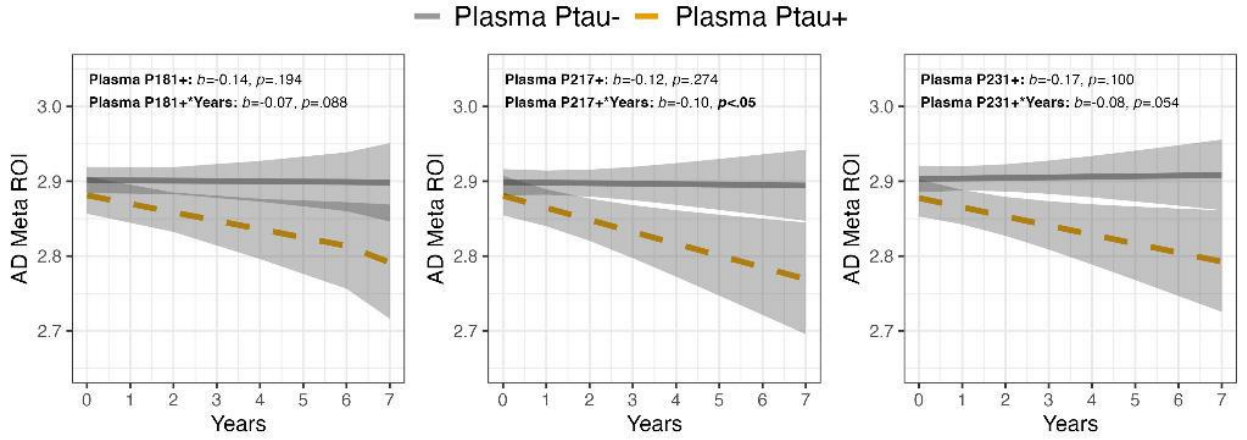
Aims: Detection of Alzheimer's disease (AD) pathophysiology among cognitively unimpaired individuals and those in the early stages of the disease continuum remains clinically challenging. Here, we aim to explore the diagnostic and prognostic value of plasma p-tau181, p-tau217 and p-tau231 by assessing baseline and longitudinal changes in cognition and AD meta-ROI in cognitively normal (CN) individuals and in those with mild cognitive impairment (MCI).
Methods: Participants from the Dementia Disease Initiation multicentre cohort (n=655) comprising CN (n=270) or MCI (n=378) cases were included. Area Under Curve (AUC) for the plasma ptau markers were determined using CSF Aβ42/40 ratio (<.077) as the standard of truth. Linear mixed models with random intercept for subject and random slopes for time were used to determined associations between the plasma ptau status (positive/negative) and future cognitive decline (n=555 subjects, 1226 observations over time, mean years = 3.41) and MRI AD Meta-ROI (n=377 subjects, 638 observations over time, mean years = 2.85).
Results: Plasma p-tau217 had the best diagnostic performance (AUC: 0.84) among the p-tau markers.



Plasma p-tau217 was the only marker associated with performance in the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test overtime in CN individuals (b=-0.09, p<0.05). In participants with MCI, plasma p-tau217 was associated with performance in CERAD at baseline and overtime (b=-0.57, p<0.001 and b=-0.13, p<0.001, respectively).



In the whole cohort, plasma p-tau217 was the only p-tau marker significantly associated with future AD meta-ROI atrophy (b=-0.10, p<.05).



Conclusions: Plasma p-tau217 can be an easily accessible and efficient way to screen and monitor patients with suspected AD pathophysiology. Moreover, p-tau217 associations with future cognitive decline and prediction of AD meta-ROI signature changes support its use as a diagnostic and prognostic marker in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0417 / #1242

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CEREBROSPINAL FLUID YKL-40 AS AN EARLY PREDICTOR OF COGNITIVE DECLINE IN AMNESTIC MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Guido Maria Giuffrè[1], Davide Quaranta[2], Maria Gabriella Vita[2], Salvatore Citro[2], Tommaso Giuseppe Morganti[2], Noemi Martellacci[1], Paolo Calabresi[2], Camillo Marra[1]
[1]Fondazione Policlinico Agostino Gemelli IRCCS, Memory Clinic, Rome, Italy, [2]Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Neurology Unit, Rome, Italy

Aims: Ongoing Alzheimer's disease (AD) research has unveiled a promising range of fluid biomarkers with diagnostic and prognostic potential. Among these, neuroinflammation biomarkers such as soluble-Triggering-receptor-expressed-on-myeloid-cells-2 (sTREM2), chitinase-3-like-1-protein (YKL-40), and glial-fibrillary-acidic-protein (GFAP) have emerged as promising candidates, which will be soon incorporated as "non-specific biomarkers relevant in AD pathogenesis" within the revised NIA-AA criteria. This study aims to investigate the role of these biomarkers in predicting cognitive decline in individuals with amnestic mild cognitive impairment (aMCI) due to AD.
Methods: Fifty-nine subjects diagnosed with aMCI due to AD underwent a comprehensive clinical evaluation, an extensive neuropsychological assessment, and CSF biomarkers quantification (Aβ42/40 ratio, p-tau181, t-tau, NfL, sTREM2, YKL-40 and GFAP). After a one-year follow-up, subjects were categorized as "fast-decliners" (n=21) or "slow-decliners" (n=38) based on the degree of MMSE score reduction. Comparisons between groups and binomial logistic regression models were performed.
Results: The two groups exhibited no significant differences in terms of age, literacy and MMSE score at baseline. When comparing CSF biomarker levels between the cohorts, only concentrations of p-tau181, t-tau, and YKL-40 were significantly higher in the "fast-decliners" group. Notably, YKL-40 emerged as the most robust predictor of MMSE decline after one year in a binomial logistic regression model.
Conclusions: Our findings confirmed the importance of tauopathy in AD progression and contribute to the growing evidence regarding the role of neuroinflammation in AD pathogenesis. YKL-40 was revealed as a predictor of cognitive decline since the early stages of AD. Further research should focus on validating these findings in larger cohorts, exploring YKL-40's potential role in refining diagnostics, prognostics, and treatment, also investigating the therapeutic potential of interventions targeting astrocytosis in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0418 / #382

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PERFORMANCE OF PLASMA NTK BIOMARKERS TO DETECT AMYLOID-B PATHOLOGY IN COGNITIVELY UNIMPAIRED INDIVIDUALS AT RISK OF ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Armand González Escalante[1,2,3], Marta Milà Alomà[3,4,5,6], Wagner Brum[7,8], Nicholas Ashton[9,10,11,12], Paula Ortiz-Romero[2,3], Carolina Minguillón[2,3,6], Mahnaz Shekari[1,2,3,6], Federica Anastasi[2,3,13], Marta Del Campo Milán[2,3,14,15], Margherita Carboni[16], Gwendlyn Kollmorgen[17], Juan Gispert[2,3,6,18,19], Henrik Zetterberg[10,20,21,22,23,24], Natalia Vilor-Tejedor[2,3,13,25], Kaj Blennow[24,26], Marc Suárez[2,3,6,27]
[1]Universitat Pompeu Fabra (UPF), Department Of Medicine And Life Sciences, Barcelona, Spain, [2]Hospital del Mar Research Insitute, (imim), Barcelona, Spain, [3]Pasqual Maragall Foundation, Barcelonabeta Brain Research Center, Barcelona, Spain, [4]University of California San Francisco, Radiology, Sabadell, Spain, [5]Northern California Institute for Research and Education (NCIRE), Department Of Veterans Affairs Medical Center, San Francisco, United States of America, [6]Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable, Instituto De Salud Carlos Iii, Madrid, Spain, [7]Universidade Federal do Rio Grande do Sul (UFRGS), Graduate Program In Biological Sciences: Biochemistry, Porto Alegre, Brazil, [8]Department of Psychiatry and Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden, [9]Stavanger University Hospital, Centre For Age-related Medicine, Stavanger, Norway, [10]King's College London, Institute Of Psychiatry, Psychology And Neuroscience, Maurice Wohl Institute Clinical Neuroscience Institute, London, United Kingdom, [11]NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia, South London And Maudsley Nhs Foundation, London, United Kingdom, [12]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg, Mölndal, Sweden, Molndal, Sweden, [13]Centre for Genomic Regulation (CRG), Barcelona Institute Of Science And Technology (bist), Barcelona, Spain, [14]Vrije Universiteit Amsterdam, Amsterdam UMC, Neurochemistry Laboratory, Department Of Clinical Chemistry, Amsterdam Neuroscience, Amsterdam, Netherlands, [15]Universidad San Pablo-CEU, CEU Universities, Departamento De Ciencias Farmacéuticas Y De La Salud, Facultad De Farmacia, Madrid, Spain, [16]Roche, Roche Diagnostics International Ltd, Rotkreuz, Switzerland, [17]Roche, Roche Diagnostics Gmbh, Penzberg, Germany, [18]Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales Y Nanomedicina (ciber-bbn), Madrid, Spain, [19]Centro Nacional de Investigaciones Cardiovasculares, (cnic), Madrid, Spain, [20]Department of Neurodegenerative Disease, Ucl Institute Of Neurology, London, United Kingdom, [21]UK Dementia Research Institute, Ucl Institute Of Neurology, London, United Kingdom, [22]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China, [23]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America, [24]Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [25]Erasmus MC University Medical Center Rotterdam, Department Of Clinical Genetics, Rotterdam, Netherlands, [26]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [27]Hospital del Mar, Servei De Neurologia, Barcelona, Spain

Aims: To determine the ability of plasma amyloid-β (Aβ)42/40, p-tau181, GFAP and NfL to detect Aβ pathology in cognitively unimpaired (CU) individuals at risk of AD.
Methods: Plasma biomarkers were measured using the plasma NTK panel (Roche Diagnostics International Ltd, Rotkreuz, Switzerland), a panel of robust prototype assays, in CU participants of the ALFA+ study. We studied their differences between AT groups (defined by CSF Aβ42/40 and p-tau181).

Next, we assessed their performance for detecting Aβ positivity (as defined by CSF Aβ42/40 or amyloid PET) by using ROC analysis. Finally, we simulated how introducing random variability to each biomarker value impacted their detection performance**.**

Results: The study included 403 CU participants (49.3 - 73.6 yo). Among them, 135 (33.5%) were CSF amyloid positive (A+). A subset (n=345) also had amyloid PET available (Table 1).

Table 1. Participants' characteristics of the ALFA+ study cohort stratified by CSF Aβ42/40 status.

Variable	N	CSF A-, N = 268	CSF A+, N = 135	p-value
Age (years), Median (IQR)	402	60.5 (57.5, 64.1)	62.9 (58.6, 66.0)	0.001[1]
Amyloid PET (CL), Median (IQR)	345	-4 (-8, 0)	10 (1, 26)	<0.001[1]
***APOE-ε4*, n (%)**	403			<0.001[2]
Non carrier		155 (58%)	32 (24%)	
Carrier		113 (42%)	103 (76%)	
BMI, Median (IQR)	403	26.5 (24.5, 30.2)	26.3 (24.1, 28.8)	0.3[1]
MMSE, n (%)	403			0.5[2]
27		18 (6.7%)	11 (8.1%)	
28		42 (16%)	24 (18%)	
29		88 (33%)	35 (26%)	
30		120 (45%)	65 (48%)	
PACC, Median (IQR)	398	0.08 (-0.40, 0.45)	0.02 (-0.52, 0.54)	0.8[1]
Sex, n (%)	403			0.6[2]
Men		100 (37%)	54 (40%)	
Women		168 (63%)	81 (60%)	
Tau group (CSF), n (%)	403			<0.001[2]
T-		255 (95%)	104 (77%)	
T+		13 (4.9%)	31 (23%)	
Education (years), Median (IQR)	403	12.0 (11.0, 17.0)	12.0 (11.0, 17.0)	0.3[1]
Plasma Aβ42/40, Median (IQR)	399	0.138 (0.132, 0.144)	0.118 (0.112, 0.127)	<0.001[1]

All plasma biomarkers, except for NfL, were significantly different in the A+T- and A+T+ groups compared to the A-T- one. However, only p-tau181 and GFAP were significantly increased in a stepwise manner from A-T- to A+T+ (Fig. 1).

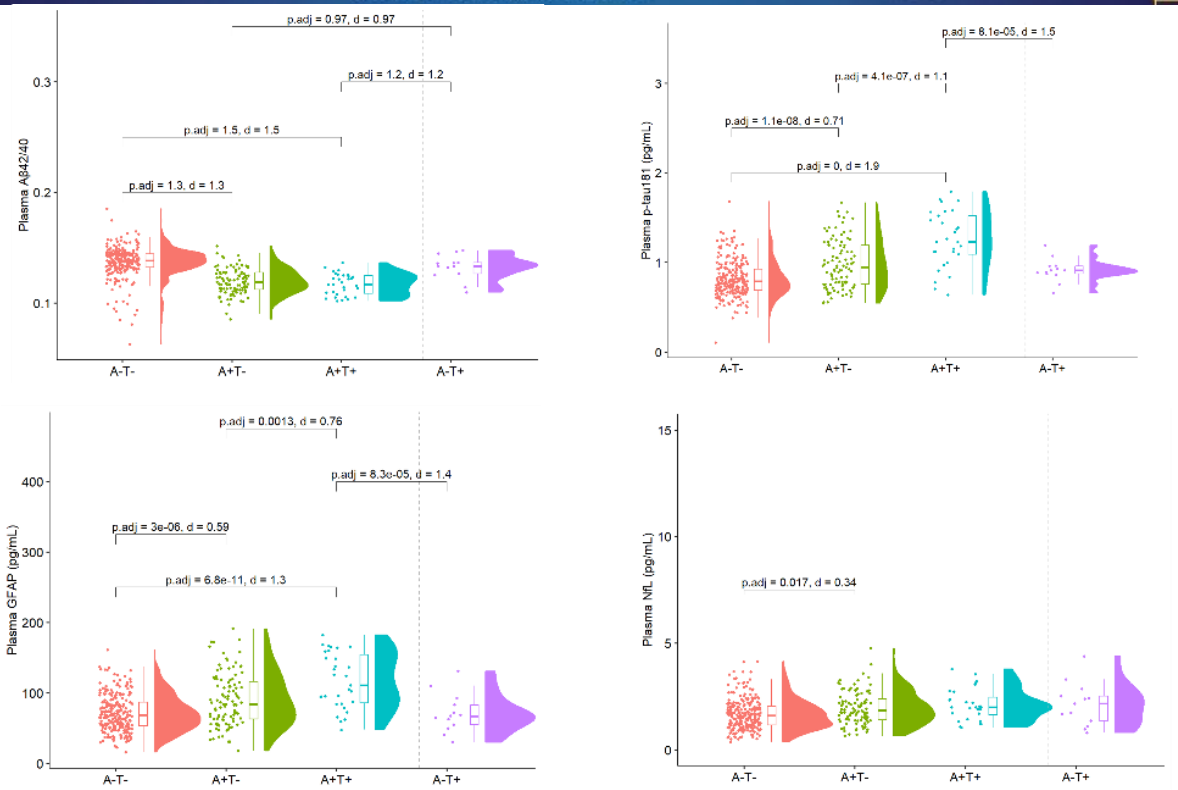


Figure 1. Raincloud plot of plasma NTK biomarkers levels by AT groups. A/T positivity was defined by CSF Aβ42/40 < 0.071 and CSF p-tau181 ≥ 24 pg/mL respectively. The p-value of Tukey HSD test and Cohen's d are reported for the significant comparisons.

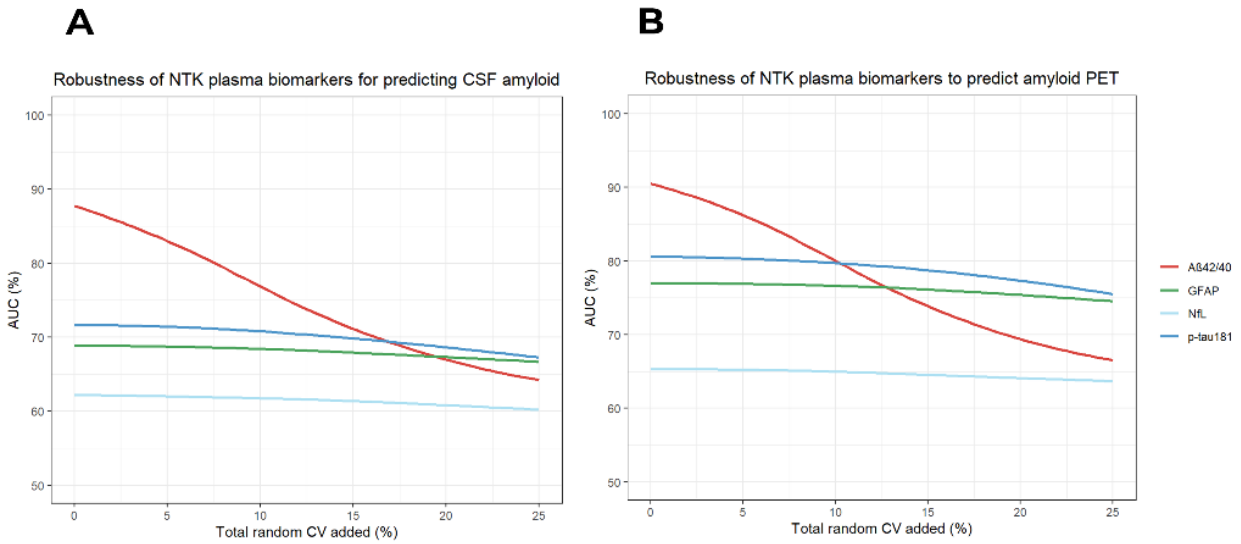
Plasma Aβ42/40 had the highest performance for Aβ positivity discrimination (CSF, AUC: 0.87; PET, AUC: 0.90), followed by p-tau181 (CSF, AUC: 0.72; PET, AUC: 0.81). Adding the plasma NTK ApoE4 measurement, rendered an AUC ranging 0.79-0.81 for p-tau181 and GFAP (Table 2). Plasma Aβ42/40 was the most sensitive biomarker to the addition of random variability, while the others remained moderately stable (Table 2 and Fig.
2).

Table 2. Summary table of the ROC analyses conducted to assess the performance of plasma NTK biomarkers for Aβ positivity discrimination. The model was assessed by the biomarker alone and then compared to a model with the addition of plasma ApoE4.

	CSF Aβ42/40 (A+ <0.071)			Amyloid PET (A+ ≥12 Centiloids)		
Model	**AUC**	**AUC (+ApoE4)**	**Improves w/ ApoE4**	**AUC**	**AUC (+ApoE4)**	**Improves w/ ApoE4**
Demog. (Age + Sex)	0.60 (0.54-0.66)	-	-	0.69 (0.61-0.76)	-	-
Aβ42/40	0.87 (0.83-0.91)*	0.88 (0.84-0.91)*	No	0.90 (0.86-0.93)*	0.90 (0.87-0.93)*	No
p-tau181	0.72 (0.66-0.77)*	0.80 (0.75-0.84)*	Yes	0.81 (0.73-0.88)*	0.81 (0.75-0.88)*	No
GFAP	0.69 (0.63-0.75)*	0.79 (0.75-0.84)*	Yes	0.77 (0.69-0.85)	0.79 (0.72-0.86)*	Yes
NfL	0.62 (0.56-0.68)	0.74 (0.69-0.79)*	Yes	0.65 (0.57-0.74)	0.68 (0.60-0.76)	Yes

* represent a corresponding AUC significantly higher (as determined by DeLong's test) than the one of the base demographics model (Age + Sex).

Figure 2. Robustness plots assessing the performance and stability of NTK plasma biomarkers for Aβ positivity discrimination. The line plot shows the AUC for each individual biomarker at each random CV variations, ranging from up to and including 0 to 25% variations of the original biomarker measurements (represented here at 0%). The results can be seen for two different amyloid standards of truth, CSF Aβ42/40 (A; cut-off: 0.071). and amyloid PET (B; cut off: 12 Centiloids). Abbreviations: AUC, area under the curve; CV, coefficient of variation.



Conclusions: Plasma Aβ42/40 decreased and p-tau181 and GFAP increased in early stages of the Alzheimer's preclinical *continuum*, namely in CU A+T- individuals. Plasma Aβ42/40 had the best performance to detect Aβ pathology but was more sensitive to measurement variability compared to p-tau181, GFAP and NfL.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0419 / #725

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

P-TAU181 AND GFAP TRACK 7T MR-BASED CHANGES IN ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Laura Göschel[1,2], Andrea Dell'Orco[1,2], Ariane Fillmer[3], Sylvain Lehmann[4], Stefan Cano[5], Jeanette Melin[6], Leslie Pendrill[6], Patty Hoede[7], Charlotte Teunissen[7], Péter Körtvélyessy[1,8], Agnes Flöel[9,10]
[1]Charité - Universitätsmedizin Berlin, Corporate Member Of Freie Universität Berlin And Humboldt-universität Zu Berlin, Department Of Neurology, Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Corporate Member Of Freie Universität Berlin And Humboldt-universität Zu Berlin, Neuroscience Clinical Research Center, Berlin, Germany, [3]Physikalisch-Technische Bundesanstalt, (ptb), Braunschweig and Berlin, Germany, [4]LBPC-PPC, Université de Montpellier, Inm Inserm, Irmb Chu De Montpellier, Montpellier, France, [5]Modus Outcomes Ltd, 4th Floor St. James House, Cheltenham, United Kingdom, [6]RISE, Research Institutes of Sweden, Division Safety And Transport, Division Measurement Science And Technology, Gothenburg, Sweden, [7]Amsterdam UMC, Neurochemistry Laboratory, Amsterdam, Netherlands, [8]German Center for Neurodegenerative Diseases (DZNE), Standort Magdeburg, Magdeburg, Germany, [9]University Medicine Greifswald, Department Of Neurology, Greifswald, Germany, [10]German Center for Neurodegenerative Diseases (DZNE), Standort Rostock/greifswald, Greifswald, Germany

Aims: Plasma biomarkers showed great potential in identifying and monitoring amyloid and tau pathology related to Alzheimer's disease (AD). Associations between longitudinal changes of plasma biomarkers and magnetic resonance (MR)-based parameters remain to be examined. We aimed to put the plasma biomarkers into better context and hypothesized that 1) they can track AD-related MR-based brain changes and that 2) they are related to pathologic distribution patterns (amyloid predominantly in frontal/parietal areas, tau predominantly in medial temporal lobes) or mechanisms (neuroinflammation, neuronal integrity).
Methods: In a cohort ranging from healthy controls (HC) to dementia due to suspected AD (total n=127, age range 55-84), we examined associations between longitudinal plasma amyloid-beta (Aβ)42/40 ratio, phosphorylated tau (p-tau181), glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL), and 7T parietal cortical thickness, hippocampus volume, resting-state default mode network and salience (Sal) connectivity, MR spectroscopy myo-inositol and N-acetylaspartylglutamic acid, and cognition. We used linear mixed models to explore cross-sectional and longitudinal associations.
Results: First, decreasing Aß42/40 was associated with increasing p-Tau181 in participants with subjective cognitive decline (SCD) but not HC. Second, of all examined plasma biomarkers, increasing p-Tau181 and GFAP showed most robust associations with 7T MR-based parameters, particularly measurements in frontal and parietal areas (decreasing parietal cortical thickness and Sal connectivity) or neuroinflammation (increasing MRS myo-inositol measured in the PCC/precuneus).
Conclusions: We contributed to the evidence that the potential of plasma Aß42/40 is limited to individuals in earliest stages of AD. Plasma p-Tau181 and GFAP seem to track disease progression in terms of continuously worsening MR-based measures and cognition. The fact that p-Tau181 and GFAP were more closely related to brain changes in regions of amyloid pathology and neuroinflammation and less tau accumulation warrants further investigation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0420 / #1542

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

A COMPREHENSIVE INVESTIGATION OF PRE-ANALYTICAL SAMPLE HANDLING FACTORS AND THEIR IMPACT ON BLOOD-BASED BIOMARKERS FOR ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Mariam Gouda[1], Daniel Antwi-Berko[1], Mardou Van Leeuwenstijn[2], Bram Bongers[1], Erik Stoops[3], Andreas Jeromin[4], Rebecca Edelmayer[5], Sjors In'T Veld[1], Charlotte Teunissen[1], Inge Verberk[1]
[1]Amsterdam UMC, Laboratory Medicine, Amsterdam, Netherlands, [2]Amsterdam UMC, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [3]ADx NeuroSciences, R&d, Gent, Belgium, [4]ALZPath, Inc, Alzpath, Inc, Carlsbad, United States of America, [5]Alzheimer's Association, Alzheimer's Association, Chicago, United States of America

Aims: Pre-analytical sample handling can significantly affect the clinical utility of blood-based Alzheimer's disease (AD) biomarkers, and thus affect their implementation. The Global Biomarker Standardization Consortium of the Alzheimer's Association has established a standardized operating procedures (SOPs) primarily based on amyloid-beta 1-40 (Aβ1-40) and 1-42 (Aβ1-42) assays. We aim to refine these SOPs by extending experimental conditions and evaluating additional blood-based biomarkers, including pTau isoforms.

Methods: We conducted 11 pre-analytical experiments on blood samples of 166 volunteers. Each experiment included a reference condition and 3-4 experimental conditions (Figure 1). Neurofilament light (NfL), glial fibrillary acidic protein (GFAP), Aβ1-42, Aβ1-40 and phosphorylated Tau (pTau) isoforms were measured on Simoa using the Neurology 4-plex E Quanterix, pTau181 Quanterix, and ALZpath pTau 217 assays. Recovery% was calculated by comparing experimental condition to their reference condition. Clinically relevant changes were defined as a median recovery change of ±10% or increased measurement variation.

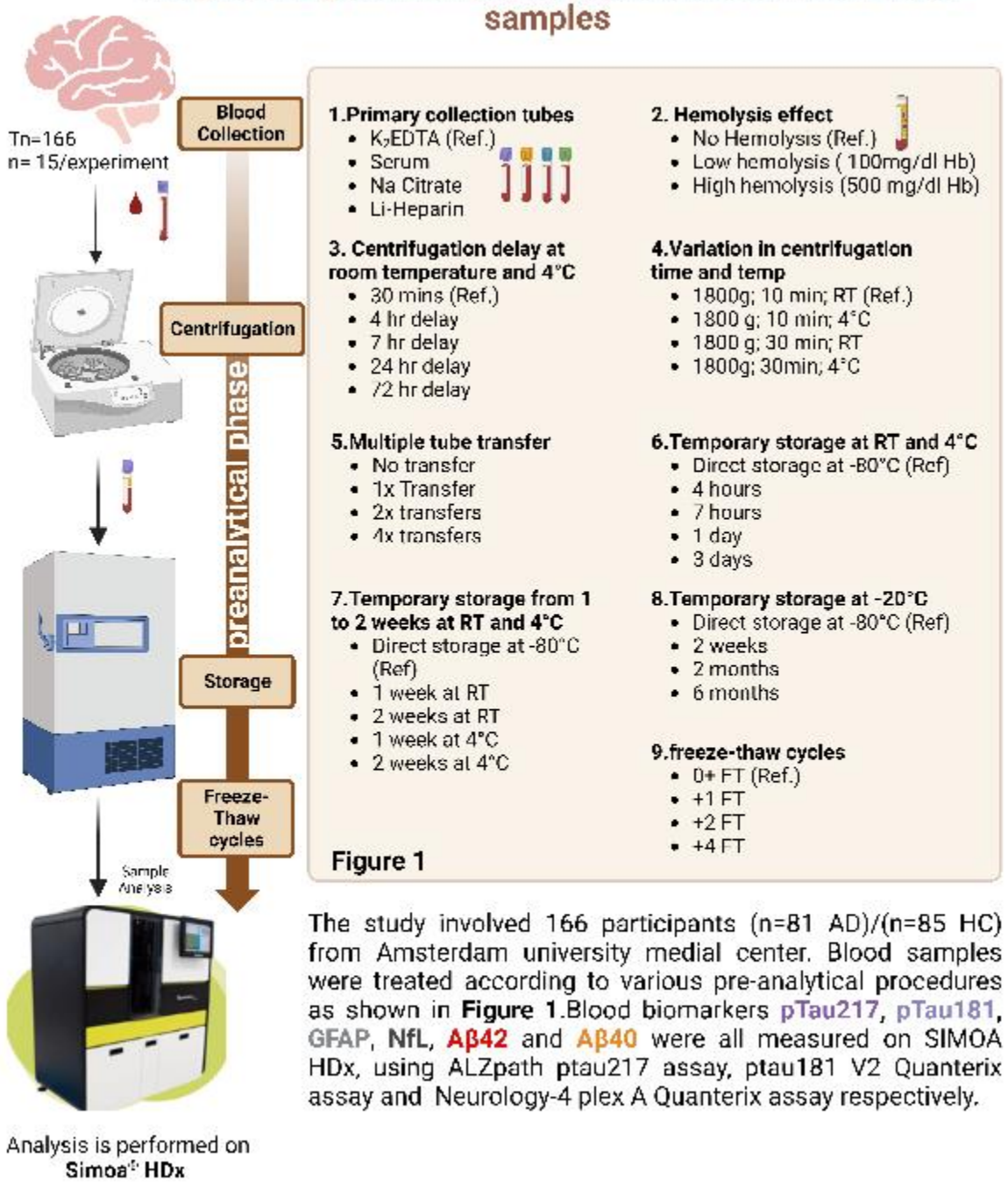


Figure 1

The study involved 166 participants (n=81 AD)/(n=85 HC) from Amsterdam university medial center. Blood samples were treated according to various pre-analytical procedures as shown in **Figure 1**.Blood biomarkers **pTau217**, **pTau181**, **GFAP**, **NfL**, **Aβ42** and **Aβ40** were all measured on SIMOA HDx, using ALZpath ptau217 assay, ptau181 V2 Quanterix assay and Neurology-4 plex A Quanterix assay respectively.

Results: Figure 2 summarizes the results. Primary collection tube types influenced the levels of all biomarkers. Aβ1-42 and Aβ1-40 were sensitive to prolonged centrifugation delays, -80°C storage delays, and high levels of hemolysis, resulting in reduced levels. The Aβ1-42/Aβ1-40 ratio partially mitigated these effects, except under extreme storage delays conditions (1-2 weeks at RT). pTau isoforms remained generally stable against experimental conditions, though pTau217 showed increased measurement variation with tube transfers. NfL and GFAP levels increased with prolonged storage delays at RT, in the fridge or at -

20°C, as well as, with sample freeze-thaw cycles

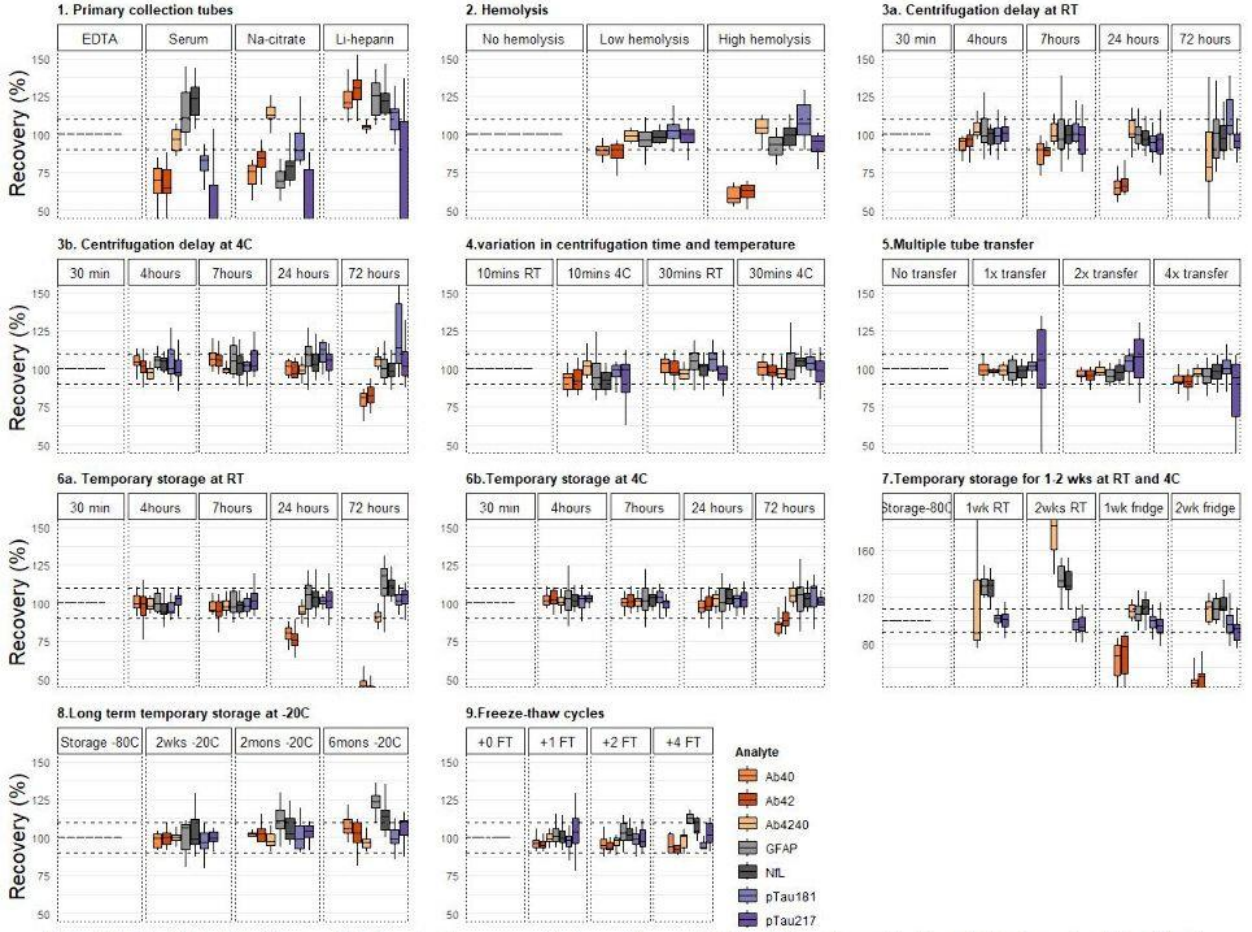


Figure 2: Results obtained from 11 pre-analytical experiments are presented. Recovery% was calculated as follows: Recovery%= (Concentration in experimental condition / Concentration in reference condition) * 100. Clinically relevant changes were defined as median recovery change of ± 10%, or visually increased measurement variability represented by the interquartile range.

Conclusions: Our findings allow refining the established SOP to counteract the impact of pre-analytical sample handling on biomarker measurement reliability. Notably, our results highlight the remarkable stability of pTau isoforms, even under extreme pre-analytical conditions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0421 / #1233

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

GENERALIZABILITY OF TAU AND AMYLOID PLASMA BIOMARKER ANALYSIS IN ALZHEIMER'S DISEASE COHORTS FROM DIVERSE GENETIC ANCESTRIES

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Anthony Griswold[1], Farid Rajabli[1], Jamie Arvizu[1], Charles Golightly[1], Patrice Whitehead[1], Kara Hamilton-Nelson[1], Larry Adams[1], Maricarmen Contreras[1], Jose Sanchez[1], Sergio Tejada[1], Pedro Mena[1], Takiyah Starks[2], Mario Cornejo-Olivas[3], Maryenela Illanes-Manrique[3], Concepcion Silva[4], Michael Cuccaro[1], Jeffery Vance[1], Briseida Feliciano-Astacio[4], Goldie Byrd[2], Gary Beecham[1], Jonathan Haines[5], Margaret Pericak-Vance[1]
[1]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [2]Wake Forest University School of Medicine, Maya Angelou Center For Health Equity, Winston-Salem, United States of America, [3]Instituto Nacional de Ciencias Neurológicas, Neurogenetics Research Center, Lima, Peru, [4]Universidad Central Del Caribe, Department Of Internal Medicine, Bayamon, Puerto Rico, [5]Case Western Reserve University, Department Of Population & Quantitative Health Sciences, Cleveland, United States of America

Aims: Plasma phosphorylated Tau (pTau181) and amyloid beta (Aβ42/Aβ40) are biomarkers for differential and preclinical diagnosis of Alzheimer disease (AD). Measurement of these biomarkers has been mostly from non-Hispanic, European individuals . Thus, we evaluated the practicality and generalizability of plasma pTau181 and Aβ42/Aβ40 in discriminating AD from cognitively intact (CI) individuals in diverse cohorts.
Methods: Plasma from was isolated, and two aliquots stored at -80°C and others at -20°C. After two, four, and six weeks, aliquots were moved from -20°C to -80°C. pTau181 and Aβ42/Aβ40 were measured with Simoa chemistry. We performed these assays on 642 African Americans (162 AD, 480 CI), 906 Puerto Ricans (385 AD, 521 CI), 149 Peruvians (49 AD, 100 CI), and 60 Cubans (26 AD, 34 CI). Differences across AD status and diagnostic performance and receiver operator characteristic curves were analyzed using logistic regression models.
Results: After six weeks at -20°C, the average change in pTau181 and Aβ42/Aβ40 across all samples was less than 10%. pTau181 was increased in AD compared to CI taking into account all individuals and in each cohort. There was no difference in the plasma Aβ42/Aβ40 ratio, however there was a trend towards decreasing concentration in AD. pTau181 was more accurate at predicting status than Aβ42/Aβ40 ratio, but classification improved when biomarkers were combined. The accuracy varied with AUC from 0.845 for African Americans to 0.683 for Peruvians.
Conclusions: These data suggest that locations lacking infrastructure of -80°C can utilize -20°C equipment and maintain biomarker fidelity, allowing for biomarker studies from low- and middle- income countries Furthermore, AD plasma biomarkers are generalizable across ancestries. Combining genomic and biomarker data will increase understanding of genetic risk and refine clinical diagnoses in individuals of diverse ancestries.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0422 / #289

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PERFORMANCE OF AN ALZHEIMER'S DISEASE PLASMA BIOMARKER PANEL IN A ROUTINE CLINICAL POPULATION WITH ESTABLISHED CEREBROSPINAL FLUID LEVELS.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Jemma Hazan[1], Emily Abel[2], Miguel Rosa Grilo[3], Deborah Alawode[2], Henrik Zetterberg[4], Robert Howard[1], Nick Fox[5], Ines Laranjinha[2]
[1]UCL, Division Of Psychiatry, Tottenham Court Road, United Kingdom, [2]UCL, Dementia Research Institute, London, United Kingdom, [3]Institute of Neurology,, Demetnia Research Centre, London, United Kingdom, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [5]Institute of Neurology,, Dementia Research Centre, London, United Kingdom

Aims: To compare Alzheimer's disease (AD) plasma immunoassays within a memory clinic population, stratified by age, and understand potential variances. To test a novel commercially available ALZpath plasma phosphorylated tau217 (p-tau217) Single Molecule array (Simoa) immunoassay.
Methods: 96 participants with cognitive complaints were categorized into two groups Alzheimer's disease (AD) and non-AD cerebrospinal fluid (CSF) profiles based on their CSF amyloid beta 42 (Aβ42) and phosphorylated tau181 (p-tau181) levels and evenly represented across the age ranges of 55-79 years. We conducted a direct comparison of seven plasma Single Molecule array (Simoa) Quanterix assays and determined their accuracy to discriminate between the two CSF profiles.
Results: There were 96 participants included in analysis (mean [SD] age, 65.3 [6.6] years; 42 females [43.8%]). Plasma p-tau217 (area under the curve [AUC] = 0.972) and the p-tau217/ Aβ42 ratio (area under the curve [AUC] = 0.972) provided high accuracy in discriminating between AD CSF and non-AD CSF and there were significant differences between participants at all ages. There were also significant differences using plasma p-tau181 between participants up to the age of 74 years, and Aβ42 and glial fibrillary acidic protein (GFAP) up to the age of 70 years.
Conclusions: Both the novel commercial Alzpath plasma p-tau217 assay and the p-tau217/ Aβ42 ratio provided the best discrimination between CSF profiles at all ages. These plasma biomarkers may have utility as a diagnostic tool in a memory clinic population. Further work is required to investigate the influence of age on plasma ptau concentrations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0423 / #1499

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

THE CASPASE-GENERATED TAU-FRAGMENT, TAU-C, IS A SENSITIVE SERUM MARKER FOR DETECTION OF PARKINSON'S DISEASE.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Signe Nielsen, Bruna Manoel, Morten Karsdal, Kim Henriksen
Nordic Bioscience A/S, Neurodegenerative Diseases, Herlev, Denmark

Aims: Objectives Parkinson's Disease (PD) is a multi-factorial degenerative disease resulting in physical dysfunction and thereby hampering normal living. Furthermore, PD increases the risk of development dementia as a complication. Currently, PD is detected in the later stages when neurons have degenerated completely, and treatment options are limited. Thus, blood-based biomarkers are essential for the early detection and as such for increasing the probability for successful treatment.
Methods: Methods Biomarkers detecting fragments of the brain-specific proteins Tau, GFAP, and Neurocan were measured in 16 PD patients, and 11 age and gender matched healthy donors by ELISAs, to determine their potential as blood-based tools for diagnosis, prognosis and monitoring of pharmacodynamic effects in PDI. Mean age was 73.7 years and 50% male for the PD patients, and 70.8 years, 63.6% male for the healthy donors.
Results: Results Levels of the caspase-3 generated Tau fragment Tau-C, which previously has shown a relation to dementia progression, were significantly elevated in PD patients ($p<0.0001$). Importantly, the levels observed in PD were very high, reaching those in subjects with Traumatic Brain Injuries, clearly indicating a pathological relevance. Importantly, when used assays detecting GFAP and Neurocan fragments, no such elevation was observed ($p=0.570$ and $p=0.278$, respectively), conferring specificity of the finding to the Tau-processing.
Conclusions: Conclusions In conclusion, Tau-C levels measured in serum samples from PD patients are highly elevated. Such blood-based biomarker may be useful for monitoring PD development and response to therapy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0424 / #2258

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DEVELOPMENT AND VALIDATION OF A NOVEL PANEL OF CSF BIOMARKERS FOR ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Yanaika Hok-A-Hin[1], Bram Bongers[1], Katharina Bolsewig[1], Lynn Boonkamp[1], Daimy Ruiters[1], Afina Lemstra[2], Wiesje Van Der Flier[2], Yolande Pijnenburg[2], Marta Del Campo Milán[1,3,4], Charlotte Teunissen[1]
[1]Amsterdam UMC, Department Of Laboratory Medicine, Amsterdam, Netherlands, [2]Amsterdam UMC, Alzheimer Center Amsterdam, Amsterdam, Netherlands, [3]Barcelonabeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain, [4]Universidad San Pablo-CEU, CEU Universities, Departamento De Ciencias Farmacéuticas Y De La Salud, Facultad De Farmacia, Madrid, Spain

Aims: Using proximity extension proteomic arrays (PEA), we previously identified a CSF protein panel reflecting different biological processes associated to Alzheimer´s disease (AD), that efficiently discriminated AD from non-AD dementias (i.e., dementia with Lewy bodies (DLB) and Frontotemporal dementia (FTD)). We aimed to translate this CSF differential diagnostic panel into immunoassays for large-scale analysis, and assess its discriminative performance in an independent cohort.
Methods: In-house or commercial immunoassays measuring five out of nine proteins identified (THOP1, NSE, DDC, ITGB2, and MMP7) were developed and analytically validated. To verify analytical performance, CSF samples (n=206) were compared between custom-PEA and Ella immunoassays. Clinical validation was performed in controls (cognitively unimpaired; n=55), patients with mild cognitive impairment having amyloid pathology (MCI-Aβ+; n=39), AD (n=47), and non-AD dementia (including 54 DLB and 50 FTD).
Results: Strong correlations between analytical platforms were observed (Figure1). THOP1 and NSE concentrations were higher in AD compared to controls and MCI-Aβ+ groups, and NSE was higher in AD compared to non-AD. However, not all differences survived a correction for multiple testing. ITGB2 concentrations were higher, and DDC concentrations were lower in AD compared to non-AD (Figure2). THOP1, ITGB2, and NSE had strong correlations with pTau and tTau (*Rho's* >0.49). The CSF panel discriminated AD from non-AD dementia with moderate accuracy (AUC=0.72, 95%CI: 0.63–0.81), which was lower compared to our previous study including the same proteins (AUC=0.84, 95%CI: 0.77–0.94).
Conclusions: We successfully developed immunoassays for novel AD biomarkers, covering multiple biological processes underlying AD pathophysiology. This panel might have added value when detecting AD subgroups with a specific pathophysiological background. While our differential diagnostic panel showed lower performance, trends are consistent with our discovery study highlighting the need for external cohorts
validation.

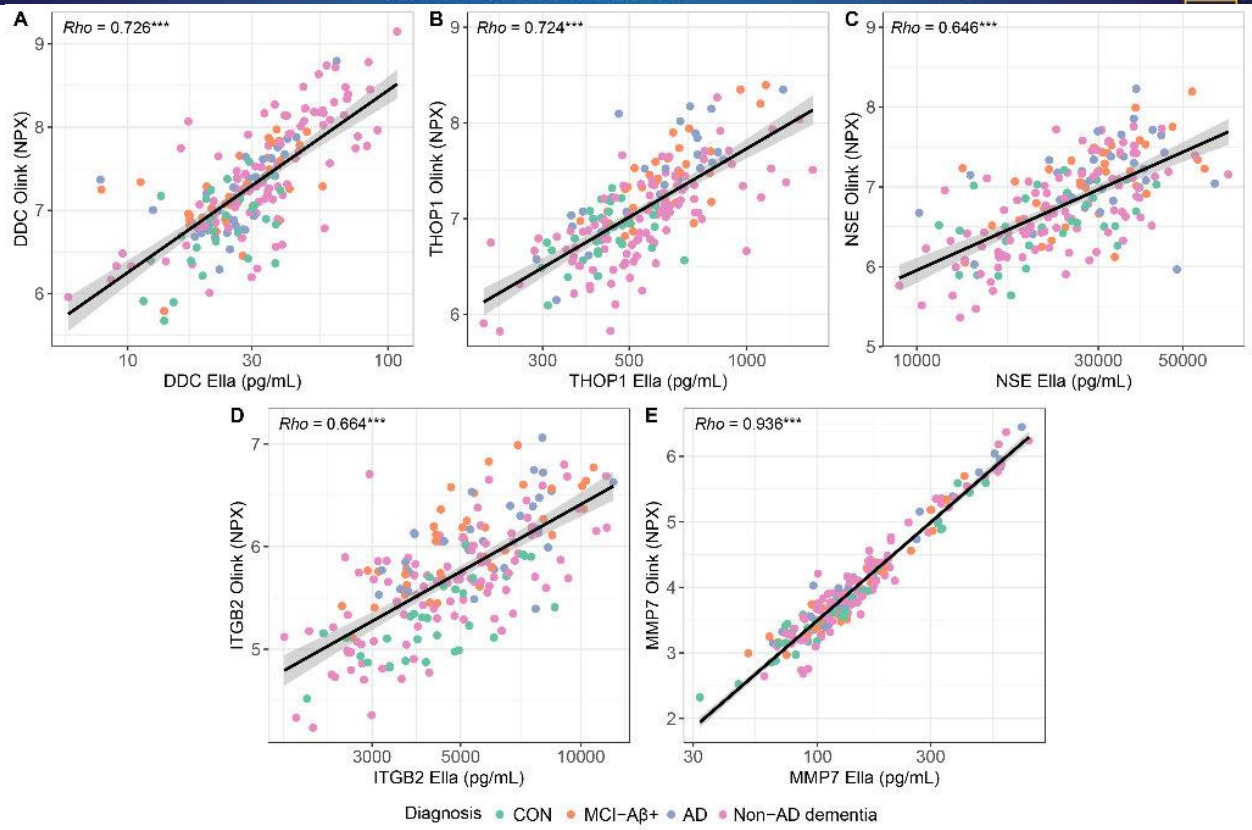


Figure 1. All Ella immunoassays significantly correlated with protein levels measured by Olink.
Protein levels were measured by custom-PEA assays (Olink) and with Ella immunoassays. Associations between platforms were determined by Spearman Rho's correlation analysis, which showed that all assays had a moderate-strong correlation between analytical platforms.

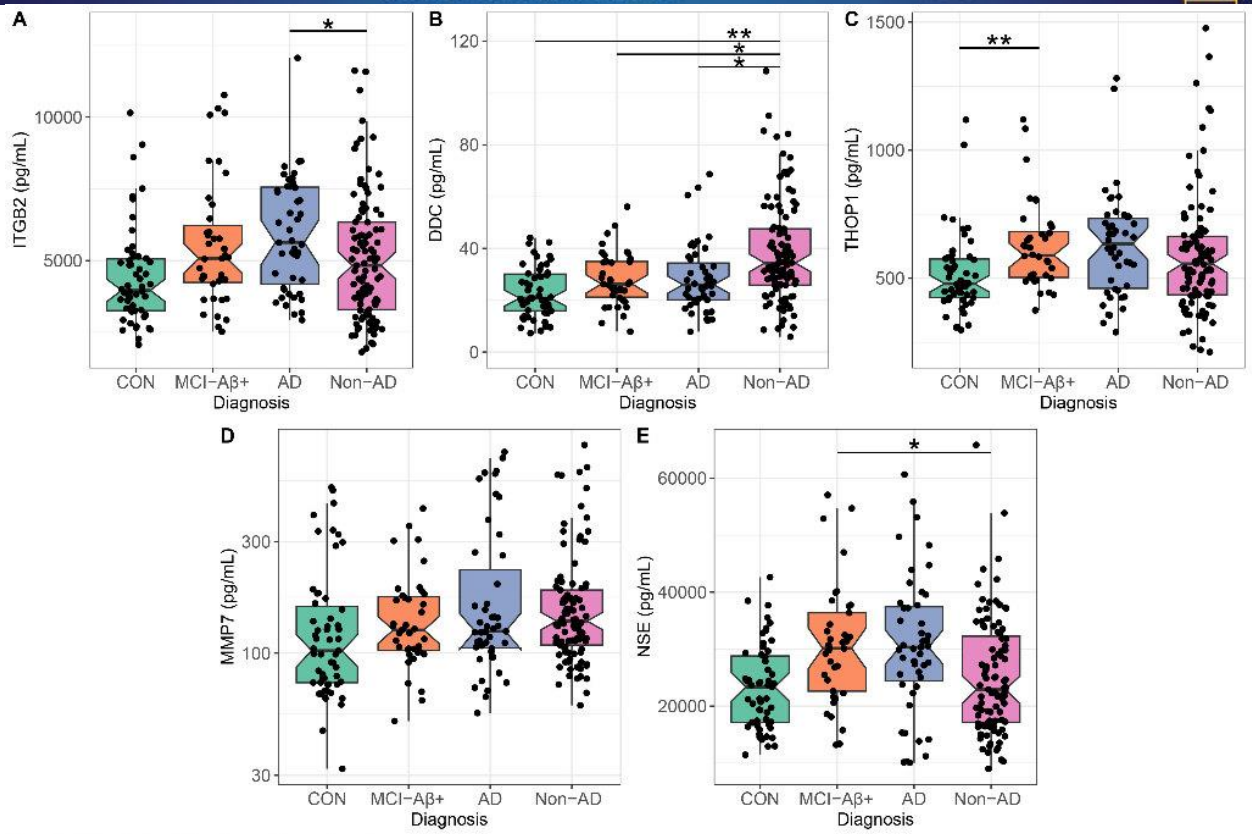


Figure 2. CSF proteins of the diagnostic panel are dysregulated
CSF protein concentrations of (A) ITGB2, (B) DDC, (C) THOP1, (D) MMP7, and (E) NSE were sequentially measured on the Ella platform.
CSF concentrations of ITGB2 and DDC are dysregulated between AD and non-AD group.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0425 / #1100

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

INDIVIDUALIZED PREDICTION OF CLINICAL PROGRESSION TO DEMENTIA IN NON-DEMENTED ELDERLY USING PLASMA BIOMARKERS.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Madison Honey[1], Ingrid Van Maurik[2,3], Argonde Van Harten[3], Mariam Gouda[1], Lior Kroeze[3], Mardou Van Leeuwenstijn[3], Arenda Mank[3], Calvin Trieu[3], Yolande Pijnenburg[3], David Wilson[4], Wiesje Van Der Flier[3], Charlotte Teunissen[1], Inge Verberk[1]
[1]Amsterdam UMC, Laboratory Medicine, Amsterdam, Netherlands, [2]Northwest Clinics Alkmaar, Northwest Academy, Alkmaar, Netherlands, [3]Amsterdam UMC, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [4]Quanterix Corporation, Product Development, Billerica, United States of America

Aims: Blood-based biomarkers can provide a low-invasive and accessible way to identify neurodegenerative disease before clinical onset of dementia. We aimed to develop individualized predictions for risk of developing any-cause dementia and Alzheimer's disease (AD) dementia, in a memory clinic population of individuals with mild cognitive impairment (MCI), using plasma phosphorylated-tau-181 (pTau181), amyloid beta1-42/1-40 (Aβ42/40), glial fibrillary acidic protein (GFAP) and/or neurofilament light (NfL).
Methods: From the Amsterdam Dementia Cohort we included 250 individuals with MCI (age 65±7 years, n=89(36%) female, MMSE 27±2), who had annual follow-up visits for re-evaluation of diagnosis (average follow-up duration:2.7±1.7 years.) Plasma biomarkers were measured using a Simoa HD-X and concentrations were Z-transformed for analysis. We evaluated the biomarkers individually, and as a panel, added to a model including age, sex and MMSE score, and assessed model discrimination (C-index) and accuracy (Brier score). We generated parsimonious models using backward selection based on the Akaike information criterion. These models were used to calculate 1-year, 3-year and 5-year probabilities for progression, which were visualised in an interactive interface.
Results: During follow-up, 99 individuals developed dementia (91 AD dementia, 8 other dementia types). High baseline GFAP and pTau181, but not NfL or Aβ42/40, were associated with an increased risk of any-cause or AD dementia when entered into the prognostic models individually (Table 1). The parsimonious model using conversion to any-cause dementia as outcome included basic demographics and GFAP. Both GFAP and pTau181 were selected in the parsimonious model using AD-dementia as outcome, and individualised risk profiles can be obtained from these models (Figure

	Hazard Ratio	*P* Value	C-index	1-year Brier score	3-year Brier score	5-year Brier score
Model 1 – Baseline demographics only						
Age	1.00 (0.97 – 1.03)	0.983	0.607	0.0314	0.201	0.220
Sex	1.64 (1.09 – 2.46)	0.017				
MMSE Score	0.90 (0.83 – 0.99)	0.024				
Model 2 - Baseline demographics + NfL						
Age	0.99 (0.96 – 1.02)	0.565	0.619	0.0313	0.198	0.220
Sex	1.72 (1.14 – 2.59)	0.010				
MMSE Score	0.90 (0.83 – 0.99)	0.025				
NfL	1.16 (0.92 – 1.46)	0.205				
Model 3 - Baseline demographics + Aβ42/40						
Age	1.00 (0.97 – 1.03)	0.991	0.615	0.0314	0.199	0.226
Sex	1.54 (1.01 – 2.34)	0.043				
MMSE Score	0.89 (0.82 – 0.98)	0.016				
Aβ42/40	0.85 (0.64 – 1.11)	0.238				
Model 4 - Baseline demographics + GFAP						
Age	0.97 (0.93 – 1.00)	0.029	0.683	0.0299	0.192	0.191
Sex	1.59 (1.06 – 2.40)	0.025				
MMSE Score	0.89 (0.81 – 0.97)	0.011				
GFAP	1.95 (1.49 – 2.54)	<0.001				
Model 5 - Baseline demographics + pTau181						
Age	0.99 (0.96 – 1.02)	0.496	0.656	0.0310	0.193	0.216
Sex	1.72 (1.14 – 2.58)	0.009				
MMSE Score	0.90 (0.82 – 0.98)	0.019				
pTau181	1.47 (1.19 – 1.81)	<0.001				
Model 6 – Baseline demographics + the panel of all four plasma biomarkers						
Age	0.97 (0.94 – 1.00)	0.074	0.698	0.0300	0.189	0.195
Sex	1.47 (0.96 – 2.26)	0.079				
MMSE Score	0.88 (0.80 – 0.96)	0.006				
NfL	0.86 (0.65 – 1.14)	0.285				
Aβ42/40	0.88 (0.67 – 1.16)	0.364				
GFAP	1.89 (1.37 – 2.59)	<0.001				
pTau181	1.21 (0.95 – 1.54)	0.131				

Table 1: Associations of model variables with risk of clinical progression to any-cause dementia and evaluation of model performances in individuals with mild cognitive impairment. The table displays hazard ratio (95% CI) for all variables in each model. Biomarker values were natural log-transformed and standardized as Z scores for comparability of effect sizes. The point at which clinical progression occurred was defined as the first visit at which dementia was diagnosed. Harrell's C-index is used to assess prognostic discrimination and ranges from 0 to 1, with a score of 0.5 indicating risk score predictions are no better than a random prediction, and a score of 1 indicating perfect model prediction. The Brier score is used to assess the accuracy of probabilistic predictions at a given time, and ranges from 0 to 1, with a score closer to 0 indicating greater accuracy. MMSE= mini-mental state examination. pTau181= phosphorylated-tau-181. Aβ42/40 = Amyloid β42/40. GFAP = glial fibrillary acidic protein. NfL = neurofilament light.

1).

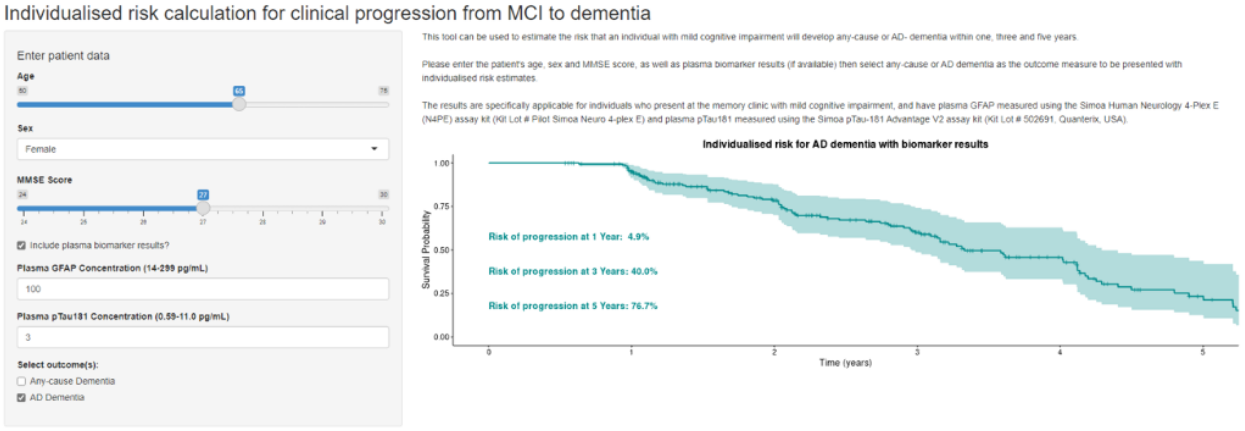


Figure 1: Screenshot of the interactive interface to estimate the risk that an individual with mild cognitive impairment will develop any-cause or AD- dementia within one, three and five years. The demographics-only prognostic model including age, sex and MMSE score is used to calculate the risk probabilities in the absence of biomarker results. The parsimonious models utilising plasma GFAP (for any-cause dementia as outcome), or both plasma GFAP and pTau181 (for AD dementia as outcome) are used to calculate the risk probabilities upon entering the biomarker results of an individual. MMSE= mini-mental state examination. pTau181= phosphorylated-tau-181. GFAP = glial fibrillary acidic protein. The interface is accessible through the link: https://gfapbiomarker.shinyapps.io/BiomarkerPredict/

Conclusions: Plasma biomarkers, particularly plasma GFAP and pTau181, can be utilized to provide prognostic risk information about progression to dementia for individuals presenting at a memory clinic.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0426 / #2120

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

FOOD INTAKE AFFECTS PROTEINS RELATED TO NEUROBIOLOGICAL PROCESSES AND ALZHEIMER'S DISEASE – A PILOT STUDY IN OBESE ADULTS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Hanna Huber[1], Anna Donkers[2], Nicholas Ashton[1], Kaj Blennow[1], Alina Schieren[2], Peter Stehle[3], Henrik Zetterberg[1], Marie-Christine Simon[2]
[1]University of Gotheburg, Neurochemistry, Mölndal, Sweden, [2]University of Bonn, Nutrition And Microbiota, Bonn, Germany, [3]University of Bonn, Nutrition Physiology, Bonn, Germany

Aims: Recent findings suggested that food intake affects plasma biomarkers related to Alzheimer's disease (AD)[1]. We investigated the impact of a single meal on markers of neurobiological processes involved in neurological diseases.
Methods: 44 cognitively healthy participants (60±7y, 24 females, BMI 30±3kg/m^2) ingested a standardized meal. The Olink Target96 Neurology panel was measured in fasting and non-fasting serum samples (60- and 180-min post-meal). Fasting vs. non-fasting protein expressions were compared using mixed models for time effect adjusted for age, sex, BMI, and multiple testing (Benjamin-Hochberg correction).
Results: We replicated our previous findings in this cohort[1]: neurofilament light, glial fibrillary acidic protein, amyloid-β 42/40, phosphorylated tau 181 and 231, and total tau changed significantly over time post-meal (all p_{adj}<.05). Further, meal ingestion significantly affected the expression of 15 out of 89 measured panel proteins. E.g., tenascin-R (p_{adj}<.00001), FLRT2 (p_{adj}=.05), and Dkk-4 (p_{adj}=.02) decreased continuously post-meal. Among others, brevican (p_{adj}<.00001) as well as of SPOCK1 (p_{adj}=.001) decreased immediately after food intake and returned to baseline at 180min. The observed effects were independent of age, BMI, and sex (p for interaction >.05).
Conclusions: The extracellular matrix proteins tenascin-R and brevican (brain-specific) are involved in brain development, repair, and synaptogenesis and might contribute to AD[2]. SPOCK1 may play a role in blood-brain-barrier regulation, axonal regeneration and the aggregation of Aβ-precursor proteins[3]. FLRT2, and Dkk-4 may be implicated in AD and cognitive decline[4,5]. To conclude, we showed that a single test meal might affect proteins related to neurobiological processes associated with brain development, synaptic function, and AD. The fact that brain-specific proteins (brevican) were affected by food intake reveals a possible direct involvement of the CNS. References: [1]PMID37243891, [2]PMID 23297096, [3]PMID 35235422, [4]PMID 29487336, [5]PMID 31191253

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0427 / #1423

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

LARGE-SCALE PLASMA PROTEOMIC PROFILING OF MILD COGNITIVE IMPAIRMENTS IDENTIFIES NOVEL BLOOD BIOMARKERS FOR EARLY SCREENING AND STAGING OF ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Yuanbing Jiang[1,2], Hyebin Uhm[1,2], Fanny Ip[1,2,3], Ronnie Lo[1,2], Xiaoyun Cao[2], Clara Tan[2], Brian Law[2], Timothy Kwok[4], Vincent Mok[5], Henrik Zetterberg[2,6,7,8,9], Amy Fu[1,2,3], Nancy Ip[1,2,3]
[1]The Hong Kong University of Science and Technology, Division Of Life Science, Hong Kong, Hong Kong PRC, [2]InnoHK, Hong Kong Center For Neurodegenerative Diseases, Hong Kong, Hong Kong PRC, [3]HKUST Shenzhen Research Institute, Guangdong Provincial Key Laboratory Of Brain Science, Disease And Drug Development; Shenzhen–hong Kong Institute Of Brain Science, Shenzhen, China, [4]The Chinese University of Hong Kong, Therese Pei Fong Chow Research Centre For Prevention Of Dementia, Division Of Geriatrics, Department Of Medicine And Therapeutics, Hong Kong, Hong Kong PRC, [5]The Chinese University of Hong Kong, Gerald Choa Neuroscience Centre, Lui Che Woo Institute Of Innovative Medicine, Therese Pei Fong Chow Research Centre For Prevention Of Dementia, Division Of Neurology, Department Of Medicine And Therapeutics, Hong Kong, Hong Kong PRC, [6]Department of Neurodegenerative Disease, Ucl Institute Of Neurology, London, United Kingdom, [7]UK Dementia Research Institute, Ucl Institute Of Neurology, London, United Kingdom, [8]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [9]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

Aims: Early detection of Alzheimer's disease (AD), particularly during the mild cognitive impairment (MCI) stage, is crucial for effective intervention and treatment. However, existing diagnostic methods, through cognitive assessments, brain imaging, or cerebrospinal fluid profiling, are subjective, expensive or invasive. We previously showed that the plasma proteome is altered in AD, suggesting the feasibility of utilizing blood biomarkers for AD detection. Therefore, to develop a blood test for early screening and staging of AD, it is important to identify blood biomarkers associated with MCI/early AD and the features of AD progression.
Methods: We conducted a comprehensive profiling of the plasma proteome of MCI by measuring 1,160 proteins in a Hong Kong Chinese cohort, to identify novel blood biomarkers for MCI/early AD. We further developed a biomarker panel based on the identified MCI/AD-associated blood biomarkers and validated its performance in an independent amyloid-PET-defined cohort.
Results: We identified 496 proteins that were dysregulated in MCI plasma, and these proteins, involved in different biological processes, exhibited distinct dysregulating patterns with disease progression. We further categorized these proteins into different groups based on their dysregulating patterns. By performing co-expression network analysis, we identified a 18-protein panel that captures the profile changes of plasma proteome in MCI and AD. This panel achieves accurate classification of MCI (AUC = 0.913-0.925) and AD (AUC = 0.970-0.993) in two independent cohorts. Moreover, this panel correlates with cognitive decline and the development of Aβ pathology in the brain, which outperforms plasma Aβ42/40, NfL, p-Tau181, and p-Tau217.
Conclusions: This study comprehensively profiled the MCI plasma proteome and demonstrates the feasibility of a blood-based biomarker assay for early detection and staging of MCI and AD, potentially facilitating early screening, monitoring, and intervention in future clinical settings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0428 / #1318

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ANALYSIS OF NEUROGRANIN RATIOS FOR AN EXPLORATION OF NEURODEGENERATION BIOMARKER

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Naoki Kaneko[1], Ryota Takahashi[1], Takashi Kato[2], Yutaka Arahata[2], Sadanori Sekiya[1], Shinichi Iwamoto[1], Koichi Tanaka[1], Akinori Nakamura[2]
[1]Shimadzu Corporation, Koichi Tanaka Mass Spectrometry Research Laboratory, Kyoto, Japan, [2]National Center for Geriatrics and Gerontology, Center For Development Of Advanced Medicine For Dementia, Obu, Japan

Aims: Neurogranin (Ng) is a cerebrospinal fluid biomarker for synaptic dysfunction at early stage of Alzheimer's disease (AD). It has been reported that some truncated forms from Ng is increased in AD brain tissue. However, the clinical significance of Ng forms in plasma has remained unclear. In this study, we applied the immunoprecipitation combined with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (IP-MALDI-MS) to investigate blood-based biomarkers for neurodegeneration.
Methods: Plasma samples were obtained from cognitively normal (CN), mild cognitive impairment (MCI), Alzheimer's dementia (AD) and non-Alzheimer's dementia (non-AD) individuals in National Center for Geriatrics and Gerontology. These subjects were classified as Aβ positive and negative based on PET with PIB tracer. Plasma Ng forms were immunoprecipitated from the samples spiked by stable isotope-labeled (SIL) Ng peptides and analyzed by MALDI-MS.
Results: We calculated intensity ratio of a Ng form-to-other Ng form (Ng ratio) in all combinations of peaks corresponding to mass of Ng forms. Five Ng ratios were significantly higher in the Aβ positive AD and Aβ negative non-AD groups than the CN group. In ROC analyses, AUC values greater than 0.80 were found in discriminating the Aβ positive AD or Aβ negative non-AD group from the CN group. Furthermore, the Ng ratios were significantly correlated with MMSE ($\rho<-0.400$).
Conclusions: Some Ng forms cleaved at or nearly the IQ domain have been found in the AD brain, which suggests the function loss of Ng in synaptic plasticity. The five plasma Ng ratios may be biomarker candidates for synaptic dysfunction involved in the change of Ng forms in the brain.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0429 / #1316

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

THE ALBUMINOME PROFILE OF BLOOD PLASMA IS ASSOCIATED WITH THE TENDENCY OF BETA-AMYLOID OLIGOMERIZATION IN ALZHEIMER'S DISEASE.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Hojin Kang[1], Hyunjung Oh[1], Hongju Kim[1], Dohyeon Kwon[1], Young Chul Youn[2], Min Jeong Wang[3], Sangyun Kim[4]
[1]PeopleBio Inc., Scientific Research, Seongnam-si, Gyeonggi-do, Korea, Republic of, [2]Chung-Ang University Hospital, Neurology, Seoul, Korea, Republic of, [3]Roa Neurology Clinic, Neurology, Seongnam-si, Gyeonggi-do, Korea, Republic of, [4]Seoul National University Bundang Hospital, Neurology, Seongnam-si, Korea, Republic of

Aims: The propensity for beta-amyloid (Aβ) oligomerization was substantially increased in the plasma of Alzheimer's disease (AD) patients when synthetic Aβ was introduced. This discovery led us to the development of a blood-based AD diagnostic tool called AlzOn. However, the molecular mechanisms underlying the phenomena have not been investigated. To elucidate the diagnostic activity, the protein interactome of Aβ and blood plasma albuminome was analyzed.
Methods: To investigate differences in albuminome compositions between individuals with AD patients and healthy controls, we isolated the plasma albuminome from patients' blood samples. Subsequently, we utillized LC-MS/MS techniques to anlyze the plasma albuminome and its correlation with the Aβ interactome.
Results: By eliminating the albuminome, we observed a loss of diagnostic specificity of AlzOn AD diagnostic kit. Remarkably, LC-MS/MS data demonstrated substantial differences between AD patients and control subjects. Additionally, our findings revealed a significant overlap between the albuminome and the Aβ interactome exclusively within AD patients.
Conclusions: This report presents evidence supporting the pivotal role of Aβ oligomerization in the plasma of AD patients, as well as the impact of the albuminome and the Aβ interactome on the diagnostic specificity of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0430 / #1385

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA PROTEOMIC PROFILING IDENTIFIES PROTEINS AND PATHWAYS INFLUENCING BETA-AMYLOID OLIGOMERIZATION IN THE BLOOD

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Hojin Kang[1], Hyunjung Oh[1], Hongju Kim[1], Dohyeon Kwon[1], Sangyun Kim[2]
[1]PeopleBio Inc., Scientific Research, Seongnam-si, Gyeonggi-do, Korea, Republic of, [2]Seoul National University Bundang Hospital, Neurology, Seongnam-si, Gyeonggi-do, Korea, Republic of

Aims: To explore the underlying mechanism of the AlzOn test, a blood-based diagnostic tool for Alzheimer's disease (AD), we conducted a plasma proteome analysis on subjects with varying levels of oligomeric Aβ after administering exogenous Aβ to identify factors influencing AlzOn test results.
Methods: Using SOMAscan technology, we quantified approximately 7,000 proteins from plasma samples collected from subjects exhibiting either a high or low AlzOn signal (n=~20 per group). Pearson's correlation coefficients were computed to determine the association between individual proteins and AlzOn results. Differences in protein levels between the two groups were assessed using t-tests. Additionally, we examined the enrichment of gene sets associated with Alzheimer's disease and annotations from the Gene Ontology database.
Results: We identified a total of 221 proteins that exhibited significant correlations with the AlzOn signal. Within the group showing a high AlzOn signal, we observed an enrichment of gene sets associated with Alzheimer's disease, synapse, and immune response. On the other hand, in the group displaying a low signal, we found an enrichment of gene sets related to purine biosynthetic processes and autophagy.
Conclusions: This study revealed a correlation between the AlzOn signal and elevated levels of inflammation, disruption of the blood-brain barrier, as well as reduced purine biosynthesis and protein clearance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0431 / #231

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CEREBROSPINAL FLUID REFERENCE PROTEINS INCREASE ACCURACY AND INTERPRETABILITY OF BIOMARKERS FOR BRAIN DISEASES

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Linda Karlsson[1], Jacob Vogel[1], Ida Arvidsson[2], Kalle Åström[2], Shorena Janelidze[1], Kaj Blennow[3], Sebastian Palmqvist[1], Erik Stomrud[1], Niklas Mattson-Carlgren[1], Oskar Hansson[1]
[1]Lund University, Department Of Clinical Sciences, Lund, Sweden, [2]Lund University, Centre For Mathematical Sciences, Lund, Sweden, [3]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: Cerebrospinal fluid (CSF) biomarkers reflect brain pathophysiology and are used extensively in translational research and in clinical practice for diagnosis of neurological diseases, e.g., Alzheimer's disease (AD). However, CSF biomarker concentrations may be influenced by non-disease related mechanisms that vary between individuals. Here we use a data-driven approach to demonstrate the existence of confounding inter-individual variability in CSF protein levels. To adjust for this variation, we identify and evaluate high-performing reference proteins that improved the diagnostic accuracy of key AD biomarkers and reduced the risk of false positive findings.
Methods: We used measurements of 2944 CSF proteins in the Swedish BioFINDER-2 cohort (n=830, 80% train and 20% test). Reference protein candidates were identified in a data-driven manner using t-distributed stochastic neighbor embedding (t-SNE) and a semi-supervised K-means clustering algorithm. The final candidate proteins were evaluated in logistic regression models, using CSF P-tau181 and CSF Aβ42 as main predictors of PET and conversion to dementia. Results were validated in the Swedish BioFINDER-1 cohort (n=904).
Results: Most proteins were associated with an individual's average protein level (Fig 1). A cluster of proteins with superior reference protein characteristics was identified and in it, single reference protein candidates were nominated. These candidates increased biomarker performance in multiple models and cohorts (Fig 2). We also show that reference proteins could explain AT(N) grouping discordance between CSF and PET (Fig 3), and that many reported CSF biomarker correlations may have been exaggerated or false positive findings due to this confounding
factor.

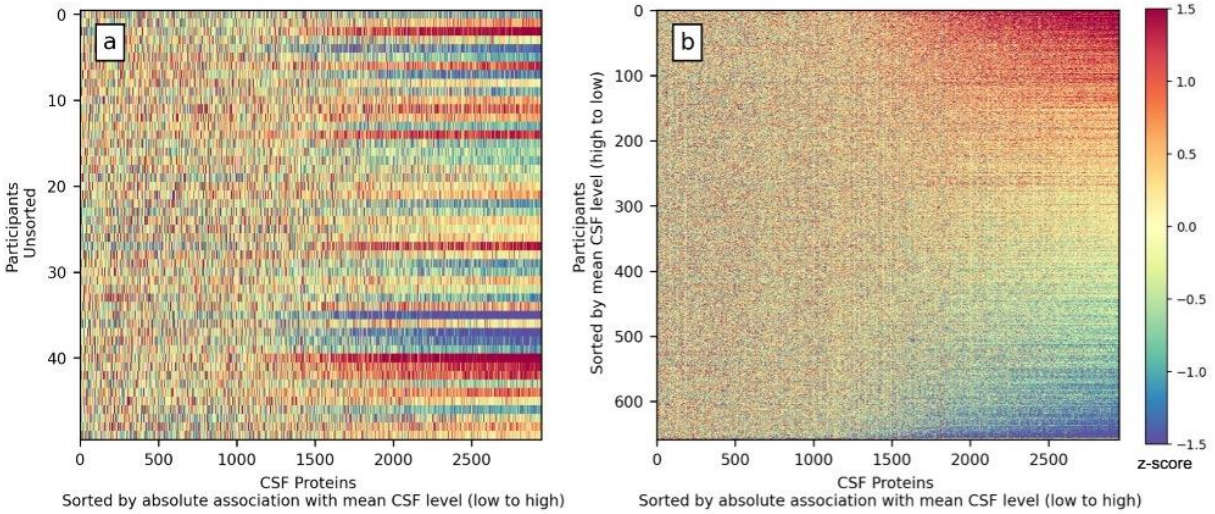


FIGURE 1: **Many CSF proteins vary in concordance with an individual protein level.** For each participant (row), the standardized concentration of 2,944 CSF proteins, sorted by increasing absolute association with the mean CSF protein level, is displayed. Systematic blue horizontal lines can be seen for individuals with consistently low values across most proteins, and correspondingly red horizontal lines for individuals with high values across most proteins (all relative to the total sample). **a)** a subset of 50 randomly selected participants. **b)** all 658 participants sorted by mean CSF level.

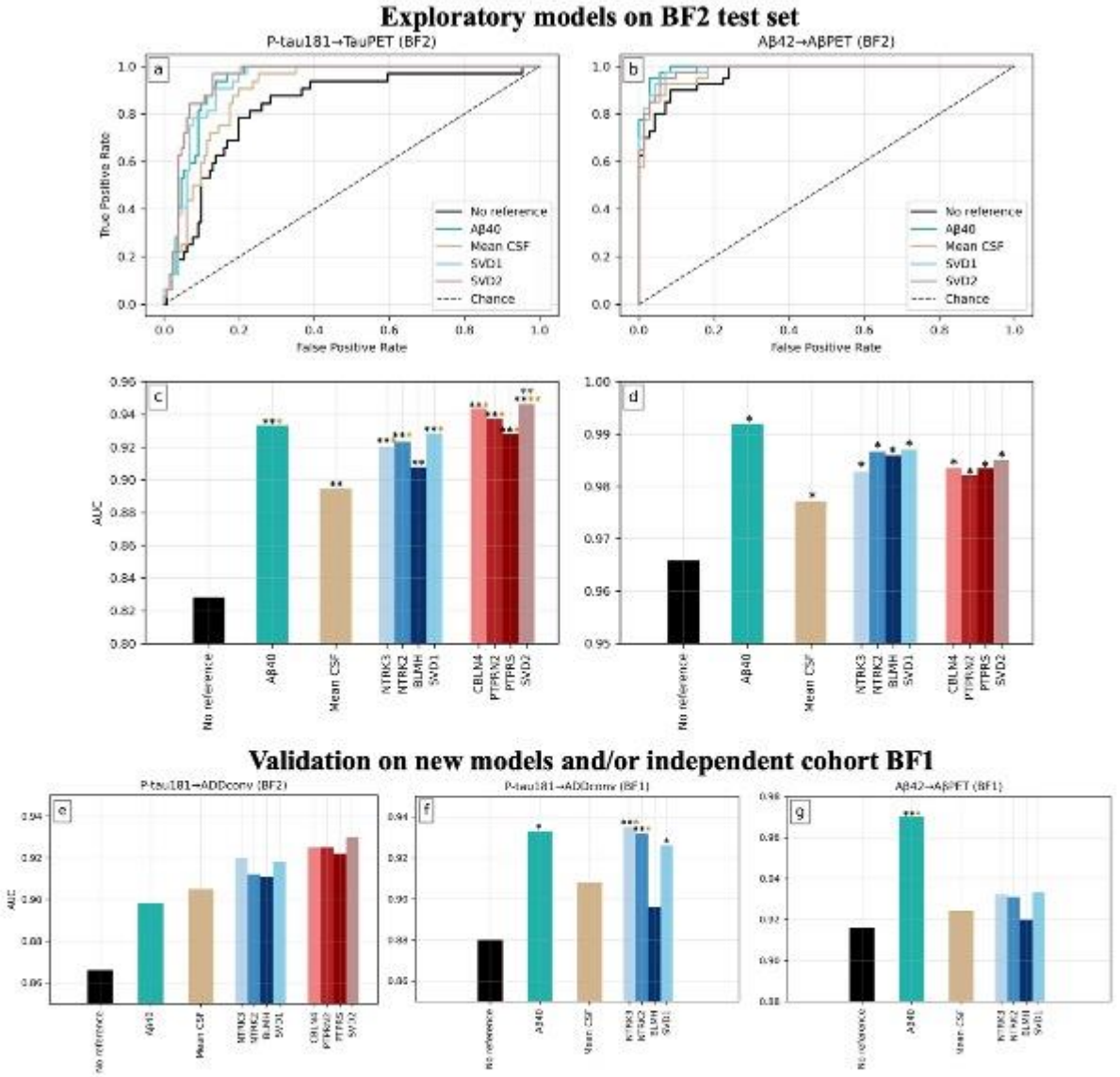
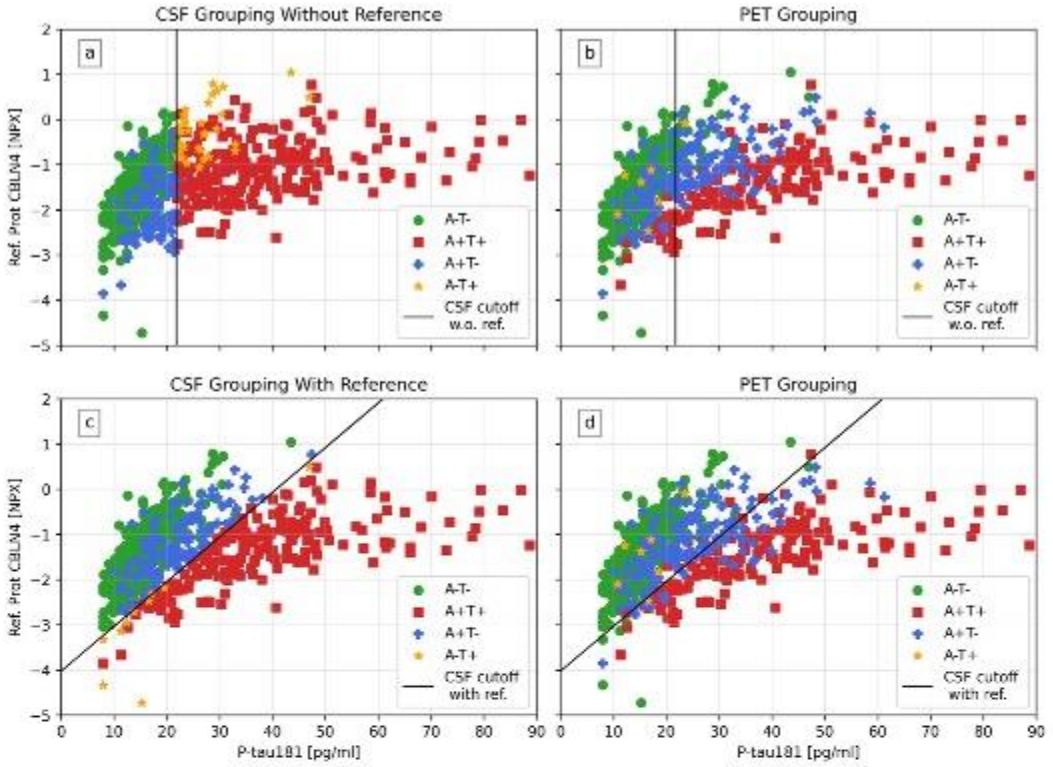


FIGURE 2: Performance evaluation of all models with and without references. ROC curves in **a)** and **b)**, and corresponding AUCs in **c)** and **d)**, for the two models **P-tau181→TauPET** and **Aβ42→AβPET**, evaluated on the BF2 test dataset. AUCs for **e)** model **P-tau181→ADDconv** on the training dataset BF2, **f)** model **P-tau181→ADDconv** on BF1 and **g)** model **Aβ42→AβPET** on BF1. No reference corresponds to the model without use of a reference protein, consistently outperformed by all tested references: Aβ40, mean CSF level, NTRK3, NTRK2, BLMH, SVD1, CBLN4, PTPRN2, PTPRS and SVD2. Quantitative details can be found in Supplementary Tab. 2. For visualization purposes, the ROC curves do not show all protein candidates but solely the corresponding SVDs.
$^{*}P < 0.05$, $^{**}P < 0.01$ compared to the bar of same color as asterisk.



e

Without Reference Tau cutoff: CSF P-tau181 > 21.8					With Reference Tau cutoff: CSF P-tau181 > 39.0 + 10.1$_{CBLN4}$				
PET / CSF	A-T-	A+T+	A+T-	A-T+	PET / CSF	A-T-	A+T+	A+T-	A-T+
A-T-	285	-	-	6	A-T-	312	-	-	6
A+T+	-	137	86	-	A+T+	-	153	44	-
A+T-	-	26	63	-	A+T-	-	10	105	-
A-T+	36	-	-	1	A-T+	9	-	-	1
Accuracy: 486/640 (76%)					Accuracy: 571/640 (89%)				

FIGURE 3: Adjusting for an individual reference protein results in a better AT(N) grouping concordance between CSF P-tau181 and tau-PET. In a)-d), the x-axis is a participant's CSF P-tau181 concentrations, and the y-axis the suggested reference protein CBLN4. In a) and c), CSF P-tau181 and CSF Aβ42/Aβ40 (cutoff 0.08) has been used to group participants. In b) and d), a tau-PET composite corresponding to Braak I-IV with ROIs > 1.36 and CSF Aβ42/Aβ40 was used to group participants. The concordance between CSF P-tau181 and tau-PET grouping increased when not requiring a vertical cutoff line (no reference, a) and b)) but allowing for it to have a slope (with reference, c) and d)). In e) corresponding concordance matrices of PET and CSF with and without using a reference for CSF P-tau181 can be seen. The concordance increased from 76% to 89% when adjusting for the reference protein. Particularly notable is that the A-T− group was reduced from n=37 to n=10 when using a reference protein, again in higher concordance with PET grouping.

Conclusions: Our novel reference protein method improves the accuracy of CSF biomarkers, and reduces the risk for false positive findings, with broad implications for both research and clinical practice.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0432 / #1791

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ASSOCIATION OF BIN1 RISK VARIANT WITH CSF BIOMARKERS IN THE LONGITUDINAL EARLY ONSET ALZHEIMER'S DISEASE STUDY

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Naazneen Khan[1], Kelly Nudelman[2], Trever Jackson[2], Suzanne Schindler[3], Elizabeth Herries[3], Rachel Henson[3], Ani Eloyan[4], Maria Carrillo[5], Bradford Dickerson[6], Gil Rabinovici[7], Liana Apostolova[1,2,8], Jeffrey Dage[1,2]
[1]Indiana University School of Medicine, Department Of Neurology, Indianapolis, United States of America, [2]Indiana University School of Medicine, Department Of Medical And Molecular Genetics, Indianapolis, United States of America, [3]Wasington University, Neurology, St. Louis, United States of America, [4]Brown university, Statistics, Providence, United States of America, [5]Medical & Scientific Relations Division, Alzheimer's Association, Chicago, United States of America, [6]Massachusetts General Hospital and Harvard Medical School, Neurology, Boston, United States of America, [7]University of California San Francisco, Neurology, San Francisco, United States of America, [8]Indiana University School of Medicine, Radiology And Imaging Sciences, Indianapolis, United States of America

Aims: Objectives: The Bridging Integrator 1 (BIN1) has been shown to be associated with late-onset Alzheimer's disease (AD) and is thought to play a role in the development or propagation of tau pathology. Explore the association of CSF biomarkers with the BIN1 risk allele rs7561528 in the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS).
Methods: Methods: In this study, biomarkers (Aß42/40, p-tau181, Neurofilament light chain (NfL), t-Tau, visinin-like protein-1 (VILIP-1), Chitinase 3-like 1 (YKL-40), Neurogranin (Ng), Synaptosomal-Associated Protein (SNAP-25) were measured in the CSF of 159 LEADS participants who were classified by diagnostic groups (cognitively normal (CN) [n=35], amyloid-positive early-onset Alzheimer's disease (EOAD)[n=96], and amyloid-negative early-onset non-Alzheimer's disease [EOnonAD; n=28]). The CSF biomarker levels in each diagnostic group were standardized and studied for their association with the BIN1 rs7561528 risk variant. Levels of significance were determined between the three diagnostic groups, CN, EOAD, and EOnonAD, using one-way ANOVA.
Results: Results: The levels of CSF biomarkers (p-tau181(Table1, Figure.1), NfL, t-Tau, VILIP-1, Ng, SNAP-25) were elevated in the BIN1 rs7561528 risk allele carrier group as compared to the non-carrier group in both CN and EOAD diagnostic groups but not in EOnonAD. The plot for p-tau181(Table 1, Figure 1) exemplifies the risk allele effect on CSF biomarkers. Table1. CSF p-tau181 biomarker level in BIN1 rs7561528 variant. Figure1. CSF p-tau181 association with BIN1 rs7561528 risk variant. The plot was constructed using standardized (z score) biomarker level and BIN1 carrier and non-carrier groups.
Conclusions: Conclusions: This study evaluates the association of CSF biomarkers with BIN1 variants within diagnostic groups. Our findings on genetic variants associated with biomarkers may help further elucidate the mechanism behind BIN1 risk variants and their contribution to the progression of Alzheimer's Disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0433 / #975

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CLINICAL PERFORMANCE EVALUATION OF PLASMA AMYLOID-BBIOMARKERS IN PREDICTING AMYLOID POSITIVITY IN COMMUNITY-BASED MILD COGNITIVE IMPAIRMENT COHORT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Noriyki Kimura[1], Teruaki Masuda[1], Tsukasa Takeuchi[2], Naoki Kaneko[2], Shinichi Iwamoto[2], Etsuro Matsubara[1]
[1]Faculty of Medicine, Oita University, Neurology, Yufu/oita, Japan, [2]Shimadzu Corporation, Koichi Tanaka Mass Spectrometry Research Laboratory, Kyoto, Japan

Aims: To determine the predictive accuracy of plasma amyloid β (Aβ) biomarkers for identifying the individuals with amyloid-positivity on amyloid positron emission tomography (PET) imaging in the community-based mild cognitive impairment (MCI) cohort.
Methods: Data from our prospective cohort study of 118 community-dwelling adults, aged 65 years and older (66 women with a mean age of 75.7 years and a median educational level of 12 years). All participants underwent ^{11}C-PiB PET and measurement of plasma Aβ biomarkers, such as amyloid-β precursor protein (APP) 669-711/ Aβ1-42 and Aβ1-40/ Aβ1-42 ratios, using immunoprecipitation coupled with mass spectrometry (IP-MS). Amyloid positivity was defined as a standardized uptake value ratio of ≥1.2. Binary logistic regression with receiver operator characteristic analysis was conducted to determine the area under the curve (AUC) values in identifying individuals with amyloid positivity.
Results: Using a cutoff value for PiB-PET SUVR of 1.2 or greater, 37 of 118 subjects (31.4%) were classified into the amyloid-positive subgroup. The AUC value of composite biomarker generated by APP669-711/ Aβ1-42 and Aβ1-40/ Aβ1-42 was 0.95.
Conclusions: Plasma Aβ biomarkers measured using IP-MS showed high performance for predicting the individuals with brain amyloid burden in community-based MCI cohort in Japan. Moreover, we conduct a prospective cohort study of 100 adults with MCI to develop diagnostic workflow for Alzheimer's disease and evaluate the diagnostic performance of plasma Aβ biomarkers, stress reactions of participants by disclosure of results, diagnostic latency, or the overall diagnostic cost.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0434 / #2325

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PROXIMITY EXTENSION ASSAY BIOMARKER DISCOVERY IN CEREBROSPINAL FLUID REVEALS NEUROFILAMENT LIGHT CHAIN AS BIOMARKER FOR CEREBRAL AMYLOID ANGIOPATHY

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

H. Bea Kuiperij, Marc Vervuurt, Anna De Kort, Iris Kersten, Karin Klijn, Floris Schreuder, Marcel Verbeek
Radboud University Medical Center, Neurology, Nijmegen, Netherlands

Aims: Cerebral amyloid angiopathy (CAA) is characterized by cerebrovascular deposition of amyloid-β (Aβ), and a cause of intracerebral hemorrhages and cognitive decline in the elderly. There is however a lack of reliable biomarkers for early diagnosis and monitoring of CAA. Such biomarkers may in addition help in the identification of Alzheimer's disease (AD) patients with a high burden of CAA, who are at risk of developing amyloid-related imaging abnormalities (ARIA) due to anti-Aβ immunotherapy. We aimed to identify novel biomarker candidates for CAA in cerebrospinal fluid (CSF) using a targeted proteomics approach.
Methods: We analyzed CSF samples of 34 CAA patients and 50 matched controls using the Olink Explore 384-Neurology panel proximity-extension assay. We used automated ELLA immunoassays to validate our results in CSF and serum of a second, partly overlapping cohort of CAA patients and controls.
Results: We identified 13 proteins with significantly different CSF levels between CAA patients and controls. The strongest difference (increase in CAA) was observed for neurofilament light chain (NFL). Other candidates included MFGE8 and uPA, which were respectively decreased and increased in CAA. ELLA analyses confirmed the increase of NFL in CSF and serum of CAA versus controls. ROC analyses of NFL levels showed good discrimination between CAA patients and controls (AUC 0.77-0.84).
Conclusions: We identified multiple CAA biomarker candidates and were able to validate NFL in CSF and serum as biomarker to differentiate between CAA patients and controls, while identification of MFGE8 and uPA confirmed our previous findings[1,2]. Our results show the validity and strength of the used approach for CAA biomarker identification, and highlights the robustness of NFL as potential biomarker for CAA. [1]*Marazuela, Acta Neuropathol Commun, 2021;9(1):154*; [2]*Vervuurt, Neuropathol Appl Neurobiol, 2022;48(5):e12804*

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0435 / #1170

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

MULTI-OMICS ANALYSIS OF NEURON-DERIVED SMALL EXTRACELLULAR VESICLES TO IDENTIFY NOVEL PERIPHERAL BIOMARKER OF COGNITIVE IMPAIRMENT IN INDIVIDUALS WITH TYPE 2 DIABETES

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ashish Kumar[1], Jacob Alexander Cleary[1], Yixin Su[1], Sangeeta Singh[1], Marjorie Howard[2], Kathleen Hayden[3], Jingyun Lee[4], Cristina Furdui[4], Mark Espeland[5], Jingzhong Ding[5], Gagan Deep[1]
[1]Wake Forest Baptist Medical Center, Cancer Biology, Winston Salem, United States of America, [2]Wake Forest Baptist Medical Center, Biostatistics And Data Science, Winston Salem, United States of America, [3]Wake Forest Baptist Medical Center, Social Sciences And Health Policy, Winston Salem, United States of America, [4]Wake Forest Baptist Medical Center, Int Med-molecular Medicine, Winston Salem, United States of America, [5]Wake Forest Baptist Medical Center, Gerontology, Winston Salem, United States of America

Aims: To isolate and characterize plasma neuron-derived small extracellular vesicles (NDE), using multi-omics approaches for the discovery of novel biomarkers of Alzheimer's disease (AD), and to better understand the possible association of AD with peripheral insulin resistance.
Methods: Plasma samples were obtained from Look AHEAD-MIND study with 28 cognitively normal (18 female and 10 male) and 28 individuals with probable dementia (11 female and 17 male) based on central adjudication by an expert panel. These individuals had established type 2 diabetes (T2D) and overweight/obesity when enrolled in a randomized controlled clinical trial of a 10-year behavioral intervention. NDE were enriched from plasma sequentially using CD171 and synaptophysin surface markers by immunoprecipitation and characterized for non-coding RNAs by small RNA-sequencing and proteomics by mass spectrometry.
Results: The small RNA-sequencing analysis identified the expression of over 100 miRNAs in NDE from both groups. The comparison of differentially expressed miRNAs revealed 42 miRNAs to be downregulated, while 23 miRNAs were upregulated in individuals with dementia. Importantly, all these miRNAs (both up- and –downregulated) were found to be over-represented in AD- and insulin signaling-related pathways. Also, the targets of these miRNAs were associated with pathways like protein phosphorylation, autophagy, cell cycle and nervous system development. Alongside, the mass spectrometry-based proteomics analysis identified 3 proteins (haptoglobin, complement component C6, and alpha-2-macroglobulin) to be significantly downregulated and 1 protein (desmocolin-1) to be upregulated in the NDE of individuals with dementia. Interestingly, NDE showed upregulated expression of miR-185-5p, and simultaneously showed a downregulation of one of its potential targets complement protein C6, both known to be associated with AD and insulin signaling.
Conclusions: The study demonstrated multi-omics approach to identify novel plasma NDE biomarkers for dementia pathogenesis in individuals with T2D.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0436 / #2772

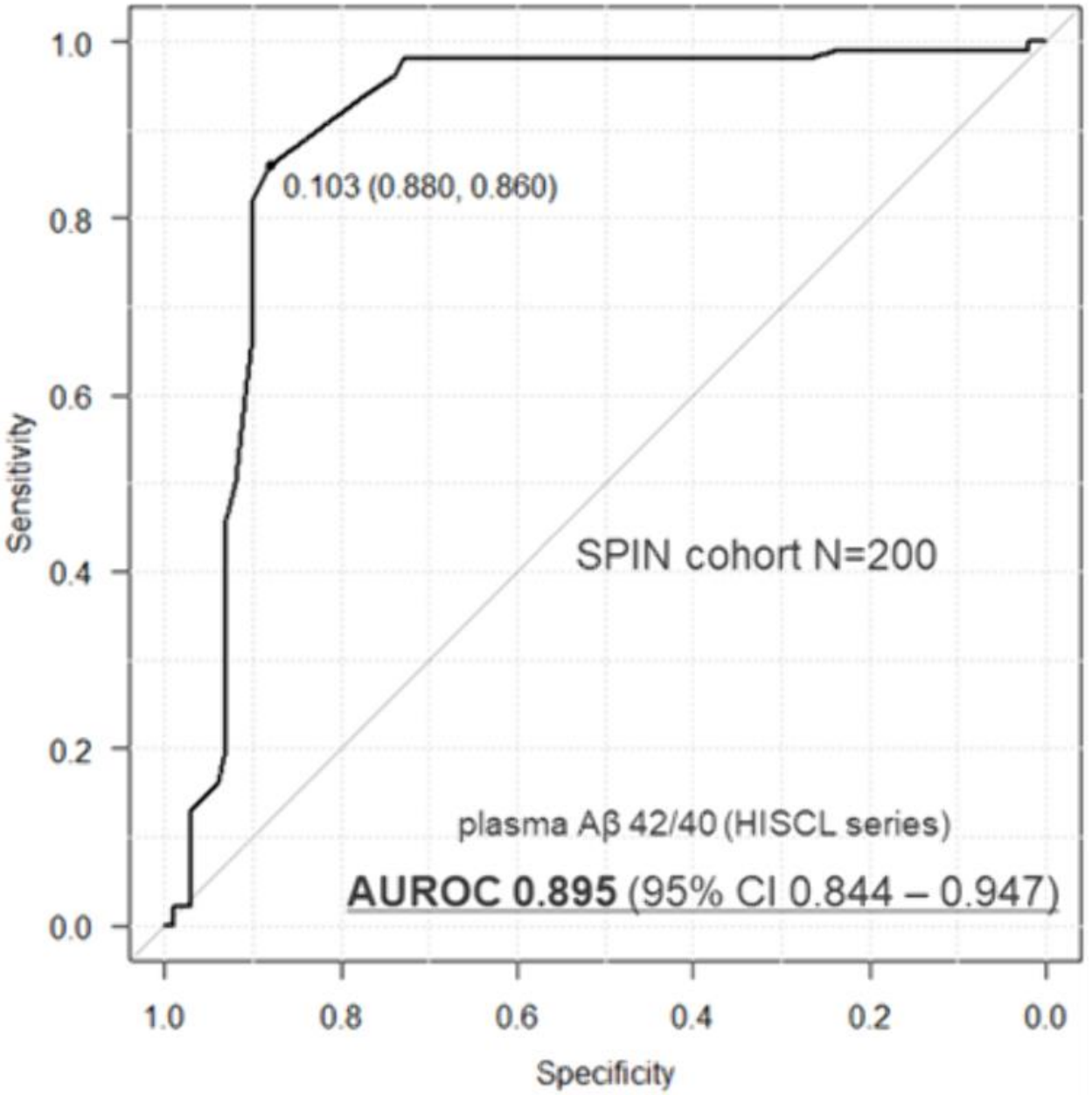
Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PERFORMANCE OF PLASMA AB42/40 RATIO TO PREDICT AB PATHOLOGY STATUS DEFINED BY CSF TESTING IN SPIN COHORT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Yuko Sasaki[1], Roman Boeer[2], Yuko Saruta[3], Javier Arranz[4], Daniel Alcolea[4]
[1]Sysmex R&D Center Europe GmbH, Strategy & Planning Division, Hamburg, Germany, [2]Sysmex Europe SE, New Business Development, Norderstedt, Germany, [3]Sysmex R&D Center Europe GmbH, Clinical & Business Development Team, Hamburg, Germany, [4]Hospital de la Santa Creu i Sant Pau – IIB Sant Pau, Department Of Neurology, Sant Pau Memory Unit, Barcelona, Spain

Aims: Predicting the Amyloid status in brain by blood-based assays is useful for screening of Alzheimer's disease. The excellent performance of plasma Aβ42/40 ratio measured by an Automated Immunoassay System HISCL™-5000 / HISCL-800 to predict Aβ pathology status defined by Amyloid PET was previously reported. In this study, we aimed to evaluate the performance of plasma Aβ42/40 ratio to predict Aβ pathology defined by CSF testing in another cohort.
Methods: This study included 200 participants: 50 cognitively unimpaired (CU), 49 mild-cognitive impairment (MCI) due to Alzheimer's disease (AD), 50 MCI due to non-AD and 51 AD from The SPIN (Sant Pau Initiative on Neurodegeneration) cohort which was enrolled at Hospital de la Santa Creu i Sant Pau from 2013 to 2022. The Aβ pathology was defined by CSF Aβ42/40 ratio measured by Lumipulse (Fujirebio-Europe). The plasma Aβ42/40 ratio was measured by HISCL-5000.
Results: Plasma Aβ42/40 ratio could predict the Aβ pathology determined by CSF Aβ42/40 ratio at AUROC: 0.895 (95% CI 0.844 – 0.947) (Fig). The threshold determined by Youden Index was an Aβ ratio of 0.103 which is similar to the previously reported threshold 0.102. The sensitivity, specificity, PPV and NPV at the threshold 0.103 were 86.0%, 88.0%, 87.8% and 86.3%, while at 0.102 were 82.0%, 90.0%, 89.1% and 83.3%, respectively. The addition of ApoE4 allele possession status didn't improve the performance significantly. (AUROC 0.903 (de Long's test p=0.519, compared to Aβ ratio only)). When analyzed only within MCI patients (due to AD and not due to AD), AUROC was 0.902 (95% CI 0.828 – 0.975).



Conclusions: Plasma Aβ42/40 ratio achieved high accuracy in predicting Aβ pathology determined by CSF testing similarly to the previous report comparing with Amyloid PET in another cohort.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0437 / #1603

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ANALYSIS OF NEUROFILAMENT LIGHT IN BRAIN AND BLOOD OF TAUP301S AND 5XFAD MICE.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Sarah Vanherle[1], Jana Hardy[1], Pablo Lucena[1], Art Janssen[1], Bieke Janssen[1], Chritica Lodder[1], Manuel Gutierrez De Rave[1], Ilie-Cosmin Stancu[1], Eline Vandeput[1], Ivo Lambrichts[1], Riet Vangheluwe[2], Rose Bruffaerts[3], Ilse Dewachter[1]
[1]Hasselt University, Biomed, Neuroscience, Diepenbeek, Belgium, [2]Universitair Ziekenhuis Oost-limburg, Neurology, Genk, Belgium, [3]Universitair ziekenhuis Antwerpen, Neurology, Edegem, Belgium

Aims: Alzheimer's Disease (AD) is characterized by Aβ pathology, followed by neurofibrillary tangles (NFTs) and neurodegeneration, referred to as the ATN framework. Neurofilament light (NfL) is increasingly found as an important biomarker for neurodegenerative disorders including AD, while its relative association and dynamics with different pathological phases of AD, reflected in the ATN continuum, remains to be studied in detail. These phases include normal healthy aging brain, amyloid pathology, and tau-pathology with tau-induced neurodegeneration.
Methods: Here, we studied the correlation of serum NfL concentrations in relation with respectively healthy aging, with amyloid pathology and tau pathology in the brain well characterized preclinical models, namely 5xFAD and TauP301S mice. We furthermore analysed pathological changes in neurofilament staining in the brain of these models. Immunohistochemical stainings of amyloid pathology, tau pathology and NfL are performed. Furthermore, measurements of NfL, in both serum and brain, at different disease stages in the different mouse models are performed.
Results: In the 5xFAD mouse model, immunohistochemical staining revealed a gradual increase of NfL in different brain regions in association with amyloid pathology. These changes correlated with the NfL concentrations in blood and brain homogenates of this mouse model. Super-resolution microscopy also showed irregularities of NfL organization in the area close to the amyloid plaques. Furthermore, in TauP301S mice, NfL signal increased in different regions of the brain after performing immunohistochemical stainings. The NfL concentrations in blood increased with age, correlating with NfL pathology in the brain.
Conclusions: No pathological staining of NfL was associated with normal aging. Our data indicate differences in Nfl biomarker dynamics and pathology, associated with different stages of the ATN continuum.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0438 / #387

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

VALUE OF BLOOD-BASED BIOMARKERS FOR DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE: THE ACTIGLIA COHORT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Carolin Kurz[1], Laura Carli[2], Selim Gürsel[2], Isabelle Schrurs[3], Alexander Jethwa[3], Sayuri Hortsch[3], Margherita Carboni[4], Dr. Bittner[4], Boris-Stephan Rauchmann[5], Matthias Brendel[6], Lena Burow[2], Jan Häckert[7], Maia Tato[2], Julia Utecht[2], Endy Weidinger[8], Sophia Stoecklein[5], Johannes Levin[8], Günter Höglinger[8], Robert Perneczky[9]
[1]LMU hospital, Department Of Psychiatry And Psychotherapy, MUNICH, Germany, [2]LMU hospital, Department Of Psychiatry And Psychotherapy, München, Germany, [3]Roche, Roche Diagnostics, Penzberg, Germany, [4]Roche, Roche Diagnostics International Ltd, Rotkreuz, Switzerland, [5]LMU Hospital, Department Of Radiology, MUNICH, Germany, [6]LMU hospital, Department Of Nuclear Medicine, München, Germany, [7]University of Augsburg, Department Of Psychiatry, Psychotherapy, And Psychosomatics, Augsburg, Germany, [8]LMU hospital, Department Of Neurology, München, Germany, [9]LMU Hospital, Department Of Psychiatry And Psychotherapy, MUNICH, Germany

Aims: The diagnostic value of Blood-based biomarkers (BBBM) in differentiating Alzheimer´s disease (AD) from other non-AD dementias like corticobasal syndrome (CBS) was investigated.
Methods: From the prospective ActiGliA study we included 27 participants with probable AD (including participants with mild cognitive impairment [n=16] and AD-related dementia [n=11]), 17 age-matched controls with subjective cognitive impairment, 9 participants with corticobasal syndrome and underlying Ab pathology (Ab[+]CBS), and 26 participants with Ab[-]negative CBS. All participants underwent a thorough diagnostic work-up, including CSF and blood sampling, neuropsychological tests, amyloid-PET, and magnetic resonance imaging. Blood biomarkers (Ab1–40, Aβ1–42, apolipoprotein E4 [ApoE4], glial fibrillary acidic protein [GFAP], neurofilament light chain [NfL], and phosphorylated-tau 181 [pTau181]) were measured using Elecsys® plasma prototype immunoassays.
Results: Results: In amyloid-positive cases, plasma concentrations of Aβ1-42/1-40 ratio were decreased while ApoE, GFAP, and pTau181 levels were elevated. In the entire cohort, blood and CSF levels of both Ab1-42/1-40 ratio and pTau181 were significantly positively correlated. ApoE4, GFAP, and particularly pTau181 levels showed a strong negative association with neuropsychological performance. A positive association between NfL levels and hippocampal atrophy was demonstrated. pTau181 levels revealed an are under the curve (AUC) of 0.885 in the discrimination between amyloid-positive and -negative cases, plasma ApoE4 levels and Ab1-42/Ab1-40 ratio showed an AUC of 0.774 resp. 0.815. Regarding differentiation of AD from healthy aging and other dementias, elevated NfL levels were associated with a diagnosis of CBS and Ab[+]CBS, while elevated pTau181 and ApoE4 levels indicated a diagnosis of AD.
Conclusions: BBBMs may be useful in differentiating amyloid PET-positive from amyloid PET-negative cases and in differentiating AD from healthy aging and non-Alzheimer dementias. These results must be validated in a larger cohort.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0439 / #2214

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ASSESSMENT OF CONCORDANCE AND DIAGNOSTIC ACCURACY OF ALZHEIMER'S DISEASE PLASMA BIOMARKERS: A COMPARISON BETWEEN THE LUMIPULSE AND SIMOA PLATFORMS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ricard Lopez-Ortega[1], Farida Dakterzada[2], Alfonso Arias[2], Iolanda Riba-Llena[2], Maria Ruiz-Julian[2], Raquel Huerto[2], Nuria Tahan[2], Gerard Piñol-Ripoll[2]
[1]Hospital Universitari Arnau de Vilanova, Clinical Laboratory, Lleida, Spain, [2]Hospital de Santa Maria - IRBLleida, Cognitive Disorders Unit. Cognition And Behaviour Study Group, Lleida, Spain

Aims: We compared plasma levels of Alzheimer's disease (AD) biomarkers measured by the Lumipulse and SiMoA platforms with their CSF levels to determine whether plasma can be a reliable CSF surrogate.
Methods: 149 patients with AD (n = 34), MCI (n = 94), and non-AD dementias (n = 21) were included. Aβ42, Aβ40, total tau, and phosphorylated tau (Ptau) were quantified in CSF using the Lumipulse platform and in plasma using the Lumipulse (Fujireibio) and SiMoA (Quanterix).
Results: We found some significant correlations between CSF and plasma measures of AD biomarkers for each platform (r_{rang}0.211-0.423). Plasma biomarkers measured by Lumipulse and SiMoA showed a good correlation between them (r = 0.794 for Aβ42; r = 0.891 for Ptau; r = 0.837 for Ptau/Aβ42; and r = 0.572 for Aβ42/40). Regarding diagnostic accuracy, the discriminatory power of plasma biomarkers measured by Lumipulse (AUC 0.735, 95% CI 0.589-0.882) and SiMoA (AUC 0.739, 95% CI 0.592-0.887) was significantly lower compared with the CSF biomarkers measured with Lumipulse (AUC 0.879, 95% CI 0.766-0.992). Finally, plasma Ptau/Aβ42 Lumipulse (AUC 0.870, 95% CI 0.806-0.934) and plasma Ptau SiMoA (AUC 0.801, 95% CI 0.712-0.890) showed the highest consistency with amyloid pathology (CSF Lumipulse Aβ42/40) at ≥ 0.084 and ≥2.127 cut-offs, respectively.
Conclusions: The Lumipulse and SiMoA platforms showed comparable clinical and analytical performances. However, their performance is lower compared with the CSF AD assays. With these data, these assays may be more useful for reducing the number of lumbar punctures in clinical settings than their use as a diagnostic tool.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0440 / #1855

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA P-TAU217 AS A COST-EFFECTIVE BIOMARKER FOR CLINICAL TRIALS ACROSS THE AD CONTINUUM

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Pamela Lukasewicz Ferreira[1], Bruna Bellaver[1], Guilherme Povala[1], Douglas Teixeira Leffa[2], Joao Pedro Ferrari-Souza[2], Firoza Lussier[3], Cristiano Schaffer Aguzzoli[4], Hussein Zalzale[4], Marina Scop-Meidros[4], Francieli Rohden[4], Carolina Soares[2], Sarah Abbas[5], Guilherme Bauer-Negrini[2], Chang Hyung Hong[6], Hyun Rho[6], Dana Tudorascu[1], Thomas Karikari[1], Beth Snitz[1], Sang Son[6], Tharick A Pascoal[1]
[1]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America, [2]University of Pittsburgh, Psychiatry, Pittsburgh, United States of America, [3]Department of Neurology and Psychiatry, University Of Pittsburgh School Of Medicine, Pittsburgh, United States of America, [4]University of Pittsburgh, Psychiatry, PITTSBURGH, United States of America, [5]3501 Forbes Avenue, Psychiatry, Pittsburgh, United States of America, [6]Ajou University School of Medicine, Psychiatry, Suwon, Korea, Republic of

Aims: Evaluate the potential utility of plasma p-tau217 as a surrogate biomarker in clinical trials across the AD spectrum.
Methods: We included 176 individuals with available plasma p-tau217 measurements at two time points across two cohorts:[MYHAT neuroimaging: 54 Cognitively Unimpaired(CU); BICWALZS: 122 Cognitively Impaired(CI) individuals]. All individuals had Aβ-PET available at baseline. Plasma p-tau217 was quantified using the ALZpath assay. Effect size was calculated as the mean change in biomarker divided by the standard deviation. We calculated the estimated sample size needed for a clinical trial testing a hypothesized 25% drug effect on longitudinal reduction in biomarkers with 80% power at a 0.05 level.
Results: The annual change in plasma p-tau217 presented a higher effect size in both groups: CU Aβ+(0.78) and CI Aβ+(0.77) compared to their respective whole population(**Figure 1**).In clinical trials targeting CU Aβ+ individuals, the sample size needed when using plasma p-tau217 as a surrogate would be 404, while trials targeting CI Aβ+ would require 458 individuals per study arm(**Figure 2A**).We compared the biomarker only and the total estimated trial cost for an Aβ+ population, using plasma p-tau217 and tau-PET for surrogacy(**Figure 2B**).Our results demonstrated that for CU Aβ+ the total cost of a clinical trial using plasma p-tau217 as a surrogate, was 4.5-fold lower than when using tau-PET. Similarly, the total cost for a clinical trial, including CI Aβ+ was 1.5-fold lower than when using plasma p-tau217 compared to using tau-PET as a
surrogate.

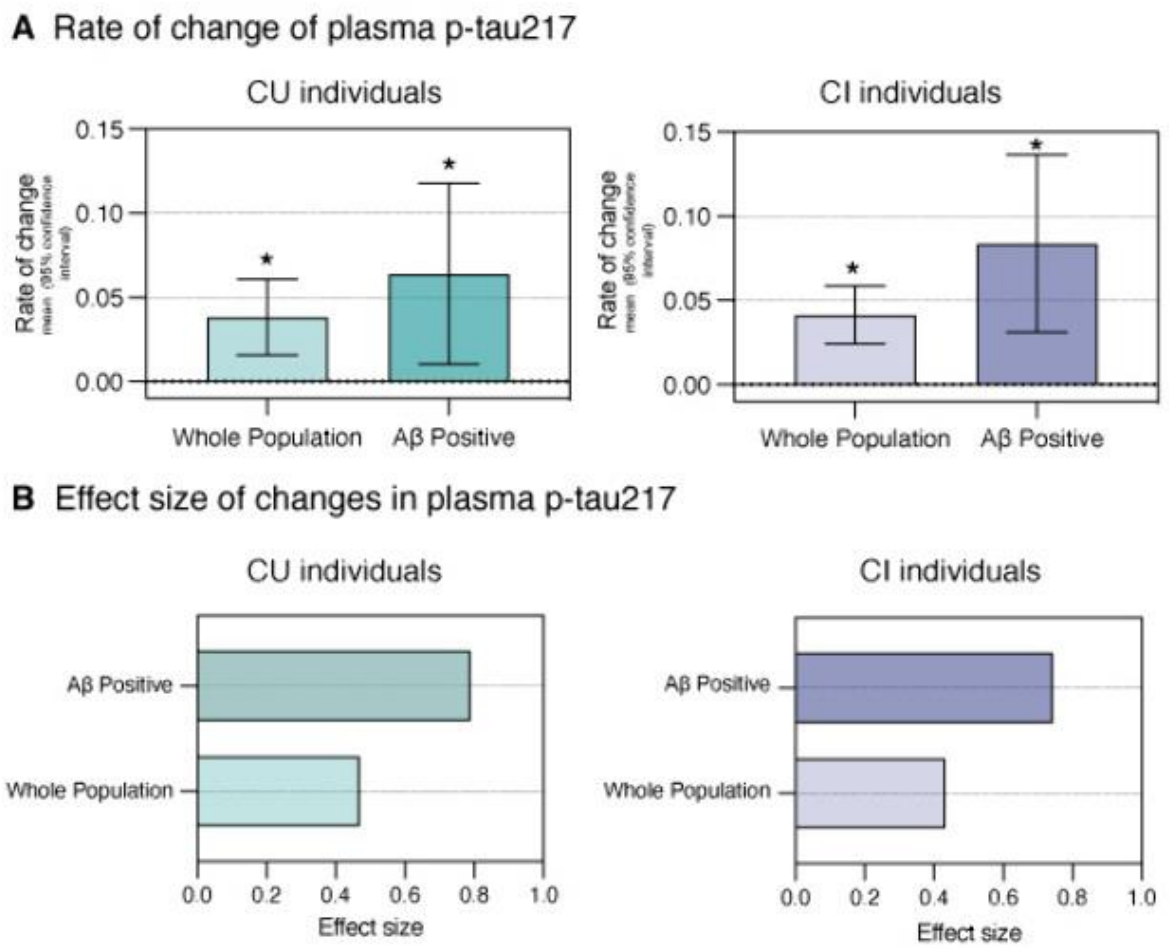


Figure 1. Annual change and effect size of plasma p-tau217 across the AD continuum. In panel **A** the bar plots show the annual change in plasma p-tau217 levels with their respective 95% confidence intervals for CU and CI individuals. Panel **B** shows that the effect size was larger in the Aβ positive group due to both a greater mean of progression and a relatively more stable change among participants (smaller standard deviation). The effect size was calculated as the ratio between the mean and standard deviation of the annual change. The higher the effect size, the smaller the measure's variability, which indicates a more precise populational estimate. * indicates that the 95% confidence interval did not cross the zero line, therefore, the longitudinal change was significantly different from zero.

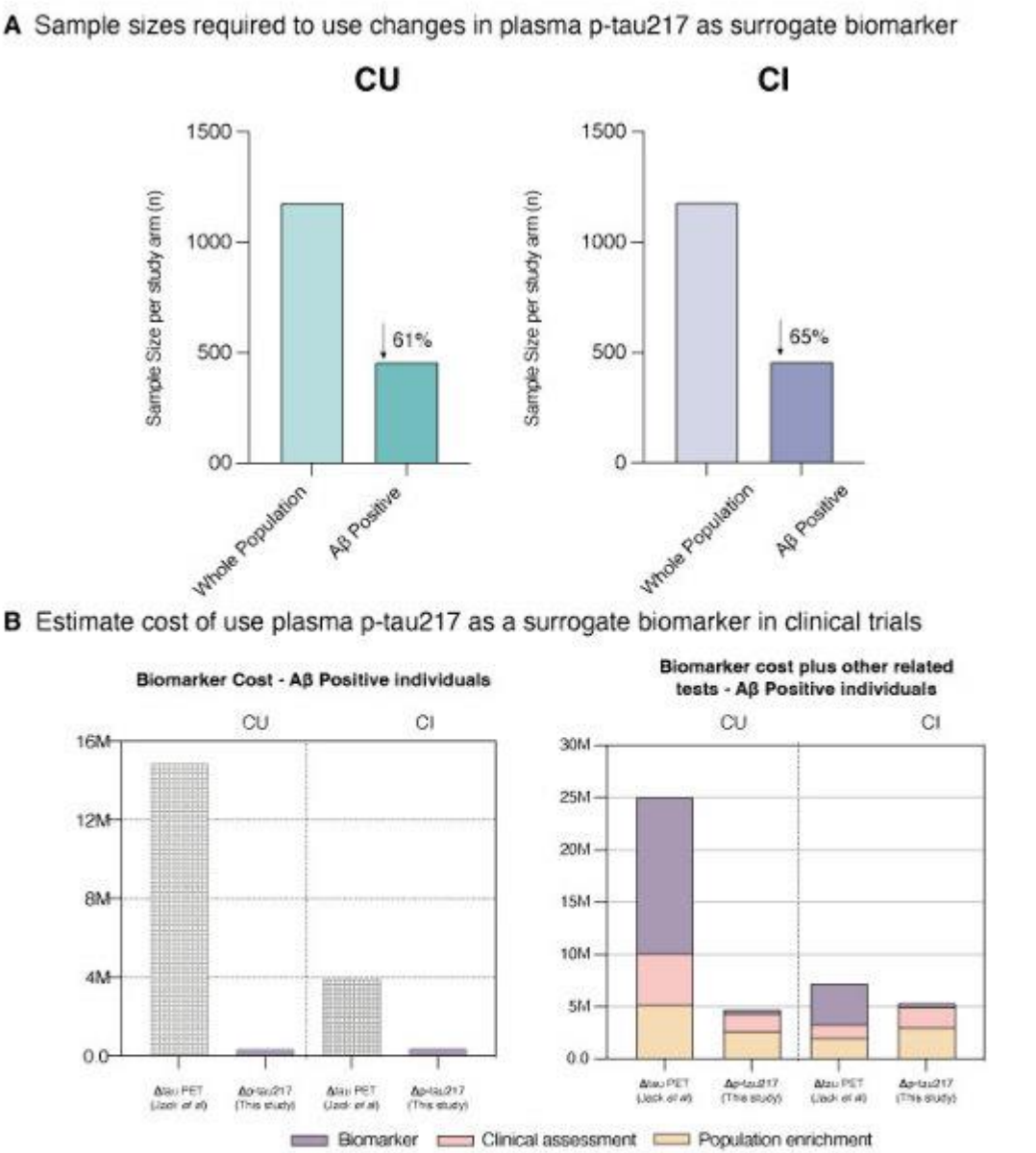


Figure 2. Cost-effectiveness of plasma p-tau217 as surrogate for preclinical and symptomatic AD clinical trials. (**A**) Sample sizes required for hypothetical clinical trials powered to use plasma biomarkers to monitor drug effects in CU and CI individuals. (**B**) The plot on the left shows the estimated cost with surrogate tau-PET (Jack et al. PMID: 29538647) and plasma p-tau217 for clinical trials powered to use changes in these biomarkers to monitor drug effects. The plot on the right shows the estimated cost of biomarkers plus the costs with some of the other necessary tests that are influenced by total sample size, such as costs of population enrichment, definition of Aβ-PET positivity, and clinical evaluation for each participant. The cost for Aβ-PET was set at $3,000; plasma p-tau217 at $200; and clinical assessments at $1,000. Δ = annual change. We estimated an attrition rate of 10% in the calculations. Δ = longitudinal change.

Conclusions: Our results suggest that plasma p-tau217 could potentially be used to monitor population interventions targeting CU and CI Aβ+ individuals. Additionally, we demonstrated that the cost of using plasma p-tau217 in clinical trials across the AD spectrum would be significantly lower than using tau-PET.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0441 / #2882

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PERFORMANCE ASSESSMENT OF NOVEL CHEMILUMINESCENCE IMMUNOASSAYS FOR THE DETECTION OF SPECIFIC BIOMARKERS FOR ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Philipp Arendt[1], Katharina Römpler[1], Britta Brix[1], Timo Lindemann[1], Viola Borchardt-Lohölter[1], Anette Schulz[1], Mandy Busse[2], Stefan Busse[3]
[1]EUROIMMUN Medizinische Labordiagnostika AG, Institute For Experimental Immunology, Lübeck, Germany, [2]University of Magdeburg, Department For Experimental Obstretics And Gynaecology, Magdeburg, Germany, [3]University of Magdeburg, Department Of Psychiatry, Magdeburg, Germany

Aims: To support diagnosis of Alzheimer's disease (AD), concentrations of $A\beta_{1-42}$, tTau and pTau(181) and the $A\beta_{1-42}/A\beta_{1-40}$ ratio are determined in cerebrospinal fluid (CSF). To increase standardization and comparability between diagnostic laboratories, certified reference material (CRM) is used to evaluate the trueness of novel assays. Due to lack of CRMs for tTau, pTau(181), and $A\beta_{1-40}$, comparability may be assessed by comparing assays from different manufacturers. This study compares the performance of novel chemiluminescence immunoassays (ChLIAs) developed by EUROIMMUN with established chemiluminescence assays.
Methods: Biomarker concentrations were determined in 110 CSF samples (patients without known diagnosis; mean age 57.2 years, range 11–94 years; 49 female, 60 male, 1 unknown) using the Beta-Amyloid (1-42), Beta-Amyloid (1-40), Total-Tau and pTau(181) ChLIAs (all EUROIMMUN) and the corresponding Lumipulse G assays (Fujirebio). The assays were performed according to the manufacturers' instructions on the fully automated random-access devices IDS-i10 (Immunodiagnostic Systems) and LUMIPULSE G 600II analyzer (Fujirebio), respectively. Agreement of results obtained with the two chemiluminescence systems was calculated.
Results: Overall agreement ranged from 89.0% to 97.3%. Agreement for the determination of normal biomarker concentrations was 93.4%–100% and 57.7%–94% for abnormal concentrations. The level of agreement was highest for $A\beta_{1-42}$ determination. Pearson's regression coefficient revealed high correlation of results (R=0.82 to R=0.99 for $A\beta_{1-42}$ determination). While concentrations determined using EUROIMMUN assays were generally higher, numerical differences had minor influence on the diagnostic evaluation.
Conclusions: Using the EUROIMMUN ChLIAs, AD-specific biomarkers can be measured with high precision and stability on fully automated random-access devices. The highest level of agreement and correlation was found for $A\beta_{1-42}$ determination as assays are aligned to the respective CRMs. This indicates the need to introduce CRMs for standardization of tTau, pTau(181), and $A\beta_{1-40}$ assays.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0442 / #1328

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

INCREASED BODY MASS INDEX AND WAIST CIRCUMFERENCE ARE ASSOCIATED WITH LOWER PLASMA LEVELS OF ALZHEIMER'S DISEASE BIOMARKERS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Arthur Macedo[1], Kok Pin Ng[2], Joseph Therriault[1], Nesrine Rahmouni[1], Stijn Servaes[1], Cécile Tissot[1], Yi-Ting Wang[1], Seyyed Ali Hosseini[1], Kely Quispialaya[1], Jaime Fernandez Arias[1], Jenna Stevenson[1], Gallen Triana-Baltzer[3], Hartmuth C Kolb[3], Tharick A Pascoal[4], Andréa L. Benedet[5], Thomas Karikari[5], Nicholas Ashton[5], Henrik Zetterberg[6], Kaj Blennow[6], Pedro Rosa-Neto[1]
[1]McGill University, Neurology And Neurosurgery, Montreal, Canada, [2]National Neuroscience Institute, Department Of Neurology, Singapore, Singapore, [3]Janssen Research & Development, Neuroscience Biomarkers, La Jolla, United States of America, [4]Department of Neurology and Psychiatry, University Of Pittsburgh School Of Medicine, Pittsburgh, United States of America, [5]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [6]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Göteborg, Sweden

Aims: The correct interpretation of Alzheimer's disease (AD) fluid biomarkers depends on the recognition of factors interfering with their levels. Here, we assess whether body mass index (BMI) and waist circumference are associated with levels of AD biomarkers measured in the blood plasma and cerebrospinal fluid (CSF).
Methods: We assessed 151 cognitively unimpaired (CU) and 107 cognitively impaired (CI) older adults with clinical examination and biomarker testing including CSF and plasma glial fibrillar acidic protein (GFAP), neurofilament light (NfL), and phosphorylated tau (pTau) 181, 217, and 231. Linear regression models adjusted for age, sex, education, APOEε4 status, amyloid-beta status, and Mini Mental State Examination scores investigated the associations of BMI and waist circumference with fluid biomarkers. Subgroup analyses were conducted regarding cognitive status.
Results: In the whole sample, higher BMI was associated with lower plasma GFAP (beta=-5.74, $p<0.001$) and pTau 181 (beta=-0.27, $p=0.01$) (Figure 1). Among CU individuals, a negative association was observed between BMI and plasma GFAP (beta=-3.91, $p=0.01$). In CI participants, higher BMI was associated with reduced plasma NfL (beta=-0.60, $p<0.01$), GFAP (beta=-8.01, $p<0.01$) and pTau 181 (beta=-0.54, $p<0.01$). Moreover, an increased waist circumference was associated with lower plasma GFAP (beta=-38.68, $p=0.01$) in the whole sample (Figure 2). In the subgroup analysis, an increased waist circumference was associated with lower plasma NfL (beta=-6.46, $p<0.01$) and GFAP (beta=-33.74, $p=0.03$) respectively in CI and CU participants. No associations were observed with CSF biomarkers.

Figure 1. Association between BMI and fluid AD biomarkers

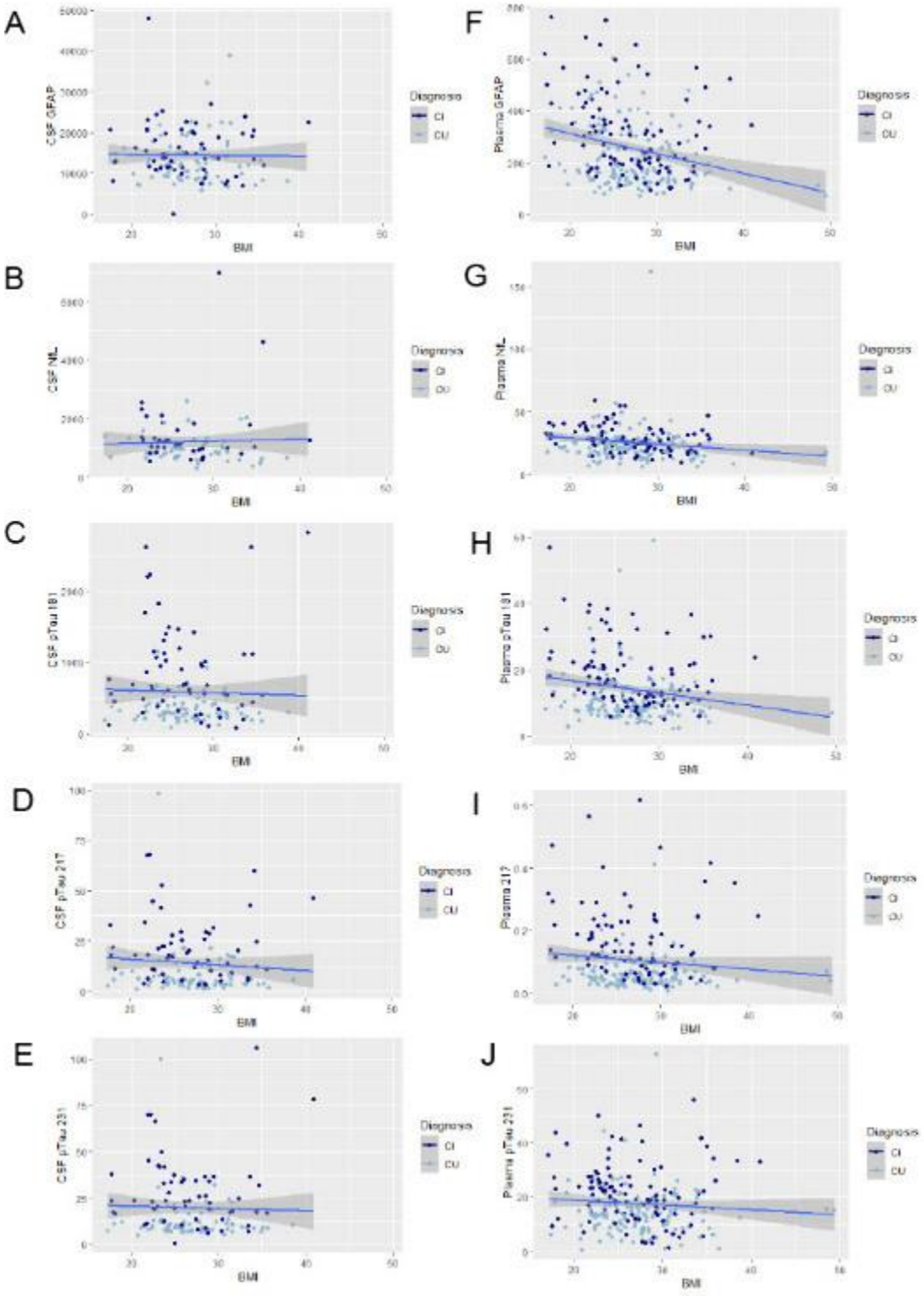
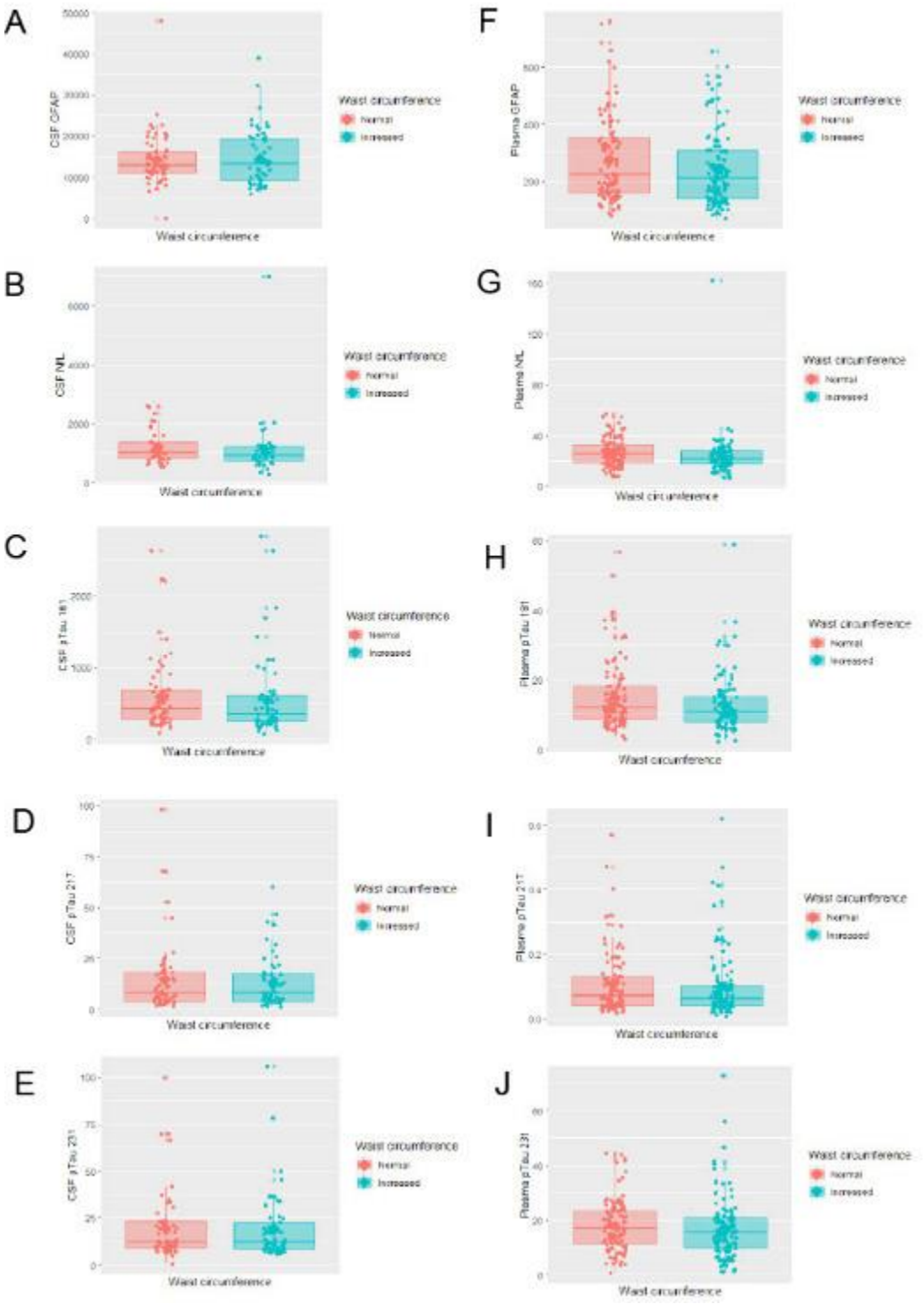


Figure 2. Levels of fluid AD biomarkers according to waist circumference



Conclusions: Our results suggest that BMI and waist circumference are factors to be considered when analyzing AD plasma biomarkers, in both preclinical and symptomatic stages. Further studies are needed to establish whether a causal relationship exists or whether those are relevant pre-analytical factors to consider.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0443 / #2216

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

BLOOD-DERIVED EXTRACELLULAR VESICLES PROTEOME AND PHOSPHOPROTEOME PROFILING IN ALZHEIMER'S DISEASE THROUGH MICROARRAY ANALYSIS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Tânia Martins[1], Steven Pelech[2,3], Maria Ferreira[1], Benedict Breitling[4], Niels Hansen[4], Hermann Esselmann[4], Jens Wiltfang[1,4,5], Odete Da Cruz E Silva[1], Ana Gabriela Henriques[1]
[1]Institute of biomedicine, University of Aveiro, Department Of Medical Sciences, Aveiro, Portugal, [2]Kinexus Bioinformatics Corporation, ., Vancouver, Canada, [3]University of British Columbia, Department Of Medicine, Vancouver, Canada, [4]Universitätsmedizin Göttingen, Klinik Für Psychiatrie Und Psychotherapie, Goettingen, Germany, [5]German Center for Neurodegenerative Diseases, Dzne, Goettingen, Germany

Aims: Extracellular vesicles (EVs) can be found in distinct body fluids, including blood, being easily accessible and carrying a variated cargo that can be disease-specific. EVs can be particularly useful as a biomarker resource for Alzheimer´s disease (AD) allowing the identification of novel protein phosphorylation candidates, since the lipid bilayer can protect their content from degradation. This study employed a targeted phosphoproteomics approach to unravel blood-derived EVs phosphospecific candidates linked to AD.
Methods: Blood-derived EVs of Controls and AD cases were isolated and analyzed using an antibody microarray from Kinexus, which contains hundreds of pan- and phosphosite-specific antibodies. Significantly altered proteins and phosphoproteins were characterized by Gene Ontology and Reactome Pathways analyses, using ClueGo and CluePedia plugins from Cytoscape v3.9.1. An heatmap was constructed to assess the groups clustering. and the protein-to-protein interaction network was retrieved from STRING database, analyzed using the Cytoscape “Network Analyzer” using the betweenness centrality option to highlight central nodes.
Results: A total of 150 significantly altered proteins or phosphoproteins in AD were identified and both Gene Ontology and Reactome pathway analysis revealed relevant disease-related pathways. A clear segregation was obtained between Controls and AD cases in the heatmap analysis; and key targets were also unveiled in the protein-to-protein interaction network.
Conclusions: In sum, the proteome and phosphoproteome profiling approach used in this work unraveled a set of putative biomarker candidates in blood-derived EVs of AD cases which may hold value in AD diagnosis. To this end research was funded by Alzheimer’s Association under Grant 2019-AARG-644347, supported by iBiMED-UIDB/04501/2020, iBiMED-UIDB/04501/2020 and TSM individual PhD grant SFRH/BD/145979/2019.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0444 / #371

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

A PROSPECTIVE MULTICENTER STUDY TO EVALUATE IMPLEMENTATION OF CONFIRMATORY BLOOD-BASED BIOMARKERS FOR ALZHEIMER'S DISEASE IN REAL-WORLD CLINICAL PRACTICE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Soeren Mattke[1], Jo Vandercappellen[2], Daryl Jones[3], Harald Hampel[2], Richard Batrla[3], Leah Zullig[4]
[1]University Of Southern California, Cesr, Los Angeles, United States of America, [2]Eisai, Inc., Global Medical Affairs, Nutley, United States of America, [3]Eisai Inc, Us Medical Affairs, Nutley, United States of America, [4]Duke University School of Medicine, Department Of Population Health Sciences, Durham, United States of America

Aims: Blood-based biomarkers (BBBMs) may enable scalable confirmation of amyloid pathology in the Alzheimer's disease (AD) care pathway, and some have shown test performance similar to cerebrospinal fluid (CSF) testing and positron emission tomography (PET). However, establishing effectiveness does not guarantee translation into the AD care pathway. The objective of this study is to demonstrate the clinical utility of a confirmatory BBBM in real-world settings by evaluating the feasibility of implementing amyloid confirmatory BBBM in clinical practice.
Methods: Based on the Consolidated Framework for Implementation Research (CFIR), we will conduct a US-based multicenter hybrid type II study. We will enroll a diverse population of individuals ≥55 years with mild cognitive impairment and mild AD but no prior dementia diagnosis. The diagnostic pathway (tests for reversible causes of cognitive impairment, cognitive and magnetic resonance imaging assessments, PET or CSF testing for amyloid pathology) will be compared between the standard-of-care arm and the confirmatory BBBM arm. Consistent with the CFIR, we will conduct qualitative semi-structured interviews at baseline and at the end of the study. When possible, we will use validated questionnaires to assess implementation science outcomes.
Results: The study will generate real-world data on clinical effectiveness of BBBMs (proportion of patients and time to biomarker-confirmed diagnosis [AD/non-AD] and proportion of eligible patients initiated on AD therapy within 6 months), implementation of BBBMs (feasibility, acceptability, appropriateness, sustainability, reach, adoption) and healthcare resource utilization.
Conclusions: This study will provide a blueprint for implementing BBBMs into healthcare systems by identifying facilitators and barriers, and will provide recommendations for implementation of BBBMs into routine practice. The study outcomes may lead to programs for accelerated uptake of BBBMs, simplifying the AD diagnostic pathway.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0445 / #1663

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

RELATION OF DIFFERENT CEREBROSPINAL FLUID BIOSIGNATURES TO CLINICAL PHENOTYPES IN A MEMORY CLINIC COHORT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Vilma Alanko[1,2], Sara Mravinacová[3], Anette Hall[1,4], Göran Hagman[1,5], Miia Kivipelto[1,5,6,7,8], Anna Månberg[3], Anna Matton[1,2,7,8]
[1]Karolinska Institutet, Division Of Clinical Geriatrics, Centre For Alzheimers Research, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden, [2]Karolinska Institutet, Division Of Neurogeriatrics, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden, [3]KTH Royal Institute of Technology, SciLifeLab, Division Of Affinity Proteomics, Department Of Protein Science, Solna, Sweden, [4]University of Eastern Finland, Department Of Neurology, Institute Of Clinical Medicine, Kuopio, Finland, [5]Karolinska University Hospital, Theme Inflammation And Aging, Solna, Sweden, [6]Imperial College London, Ageing Epidemiology Research Unit (age), School Of Public Health, Faculty Of Medicine, London, United Kingdom, [7]Imperial College London, Ageing Epidemiology Research Unit, London, United Kingdom, [8]Fingers Brain Health Institute, Stockholms Sjukhem, Stockholm, Sweden

Aims: Due to the heterogeneous nature of Alzheimer's disease (AD), stratification of patients into biological subtypes employing multiple biomarker data may prove to be crucial for finding the most suitable prevention and treatment options. Despite advancements in subtype identification, a better understanding of how clinical characteristics are distributed between subgroups across the dementia spectrum is needed.
Methods: Cerebrospinal fluid (CSF) samples from 288 patients examined at the Karolinska University Hospital memory clinic in Solna, Sweden, were analyzed. The cohort containing subjective cognitive impairment (SCI), mild cognitive impairment (MCI), AD, and other dementias is deeply phenotyped with thorough neuropsychological tests, brain imaging, physical examinations, routine blood tests, and AD biomarker data from CSF and plasma. Using an antibody-based suspension bead array, a panel of 73 proteins was measured. Principal component analysis (PCA) was used to characterize the markers that contribute to variability. Furthermore, unsupervised clustering algorithm was used to identify subtypes of patients.
Results: The assessed panel revealed differences in protein levels between and within each diagnostic group. Neither PC1 nor PC2 was related to clinical diagnosis. PC1 was still associated with Aβ42, p-tau and t-tau, but not PC2. PC3 was associated with diagnostic groups, AD biomarkers in blood and CSF and results from cognitive tests. In ongoing analyses we further explore the data using unsupervised clustering algorithms. Identified protein signatures may reflect dementia related (patho)physiological states.
Conclusions: To conclude, AD, which falls under the umbrella term dementia, could in fact also be considered an umbrella itself with subgroups. In the current study, we demonstrate that measuring only tens of proteins in the CSF is adequate to stratify patients into subgroups with distinct pathological markers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0446 / #785

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

VALIDITY STUDY OF PLASMA AND CEREBROSPINAL FLUID P-TAU217 ACROSS CLINICAL AND BIOMARKER GROUPS FROM A MEMORY CLINIC COHORT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Augusto José Mendes[1], Federica Ribaldi[1], Aurelien Lathuiliere[1], Nicholas Ashton[2], Henrik Zetterberg[3], Max Scheffler[4], Frédéric Assal[5], Valentina Garibotto[6], Kaj Blennow[3], Oskar Hansson[7], Giovanni Frisoni[8]
[1]University of Geneva, Laboratory Of Neuroimaging Of Aging (lanvie), Geneva, Switzerland, [2]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [3]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [4]University of Geneve, Radiology And Medical Informatics, Geneve, Switzerland, [5]Geneva Memory Center, Department Of Rehabilitation And Geriatrics,, Geneva, Switzerland, [6]Laboratory of Neuroimaging and Innovative Molecular Tracers (NIMTlab), Geneva University Neurocentre, Faculty of Medicine, University of Geneva, Division Of Nuclear Medicine And Molecular Imaging, Geneva, Switzerland, [7]Lund University, Department Of Clinical Sciences, Lund, Sweden, [8]University of Geneva (UNIGE and Geneva University Hospital (HUG), Department Of Rehabilitation And Geriatrics, Geneva, Switzerland

Aims: Phosphorylated tau (p-tau) 217 has recently received attention because it is more precise than other p-tau variants for identifying Alzheimer's disease (AD) pathology. Thus, we aimed to assess the diagnostic accuracy of p-tau217 in the blood and CSF, in comparison with p-tau181 and p-tau231 isoforms in a memory clinic cohort.
Methods: The study included 114 participants (CU=33; MCI=67; dementia=14) with measured plasma p-tau217. In 36 of them, p-tau217 was also quantified in the CSF. The association of p-tau isoforms was computed against a-PET Centiloid, tau-PET global-SUVR, hippocampal atrophy, and cognition. The diagnostic validity was evaluated by (i) effect sizes (δ) between diagnostic and A(+/-)T(+/-) groups; and (ii) receiver operating characteristic (ROC) analyses versus a- and tau-PET.
Results: The correlations between both plasma and CSF p-tau217 and a- and tau-PET (r from 0.64 to 0.83) were stronger than those of p-tau181 (r from 0.44 to 0.79) and p-tau231 (r from 0.46 to 0.76). Plasma p-tau217 showed significantly higher diagnostic accuracy in comparison with p-tau181 and p-tau231: (i) between diagnostic and biomarkers groups (δ ranges: p-tau217=0.55-0.96; p-tau181=0.51-0.67; p-tau231=0.53-0.71); and (ii) ROC curves to identify a- and tau-PET positivity (averageAUC: p-tau217=0.96; p-tau181=0.76; p-tau231=0.79). In contrast to this, CSF p-tau217 (averageAUC=0.95) did not show significantly superior accuracy to detect A and T positivity than p-tau181 (averageAUC=0.88) and p-tau231 (averageAUC=0.89).
Conclusions: Plasma p-tau217 demonstrated better performance in identifying AD pathology and clinical phenotypes in comparison with other p-tau isoforms in a memory clinic cohort. Furthermore, p-tau217 had comparable diagnostic performances in plasma and CSF. Our findings underline the potential of plasma p-tau217 in the diagnosis and screening for AD, which could decrease the need for more invasive biomarkers in the future.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0447 / #811

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

GLOBAL ANALYSIS OF THE HEPARIN-ENRICHED PLASMA PROTEOME CAPTURES MATRISOME ASSOCIATED PROTEINS IN ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Qi Guo[1], Lingyan Ping[1], Eric Dammer[1], Edward Fox[1], Duc Duong[1], Luming Yin[1], Anantharaman Shantaraman[1], Erik Johnson[2], James Lah[2], Blaine Roberts[1], Allan Levey[2], Nicholas Seyfried[1]
[1]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [2]Emory University School of Medicine, Neurology, Atlanta, United States of America

Aims: Matrisome-associated heparin binding proteins are strongly correlated to β-amyloid (Aβ) and Tau pathology in Alzheimer's disease (AD) brain and cerebrospinal fluid (CSF). However, it remains challenging to detect these proteins in plasma using standard mass spectrometry-based proteomic approaches. Here we developed a heparin affinity approach for the capture and enrichment of heparin-binding protiens in plasma from healthy control and individuals with AD.
Methods: Plasma samples were collected from well-characterized participants in the Emory Goizueta Alzheimer's Disease research center and consensus clinical diagnoses were established. The diagnoses of control and AD were further supported by CSF Aβ levels and total Tau and phosphorylated Tau (pTau) levels detected by immunoassays. Plasma proteins were captured by heparin affinity chromatography and proteomic quantification was conducted in a discovery (n=36; 18 control, 18 AD) and replication dataset (n=85; 36 control, 49 AD) using tandem-mass tag mass spectrometry (TMT-MS). Differential expression and regression analyses were performed to assess the relationship of plasma proteins to CSF AD biomarkers and pTau in plasma.
Results: Collectively, 2865 heparin-enriched proteins were identified across 121 plasma samples. This included a significant increase in AD plasma of members of the matrisome-associated module in brain, SMOC1 and SPON1. Heparin-enriched proteins also exhibited strong correlations CSF Aβ, total tau, and pTau as well as plasma pTau. Utilizing a consensus AD brain protein co-expression network, we assessed relationship between the plasma and brain proteomes and observed that specific plasma proteins exhibited consistent direction of change in both brain and plasma, whereas others displayed divergent changes.
Conclusions: These findings provide support for coupled heparin-enrichment with TMT-MS based proteomics for identifying a wide spectrum of plasma biomarkers that mirror pathological changes in the AD brain.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0448 / #1811

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA PTAU217 CONCORDANCE WITH AMYLOID PET IN PRECLINICAL ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Rachael Wilson[1], Karly Cody[1], Erin Jonaitis[1], Rebecca Langhough[1,2], Lianlian Du[1,3], Tobey Betthauser[1,2,4], Bradley Christian[1], Ozioma Okonkwo[2,4,5,6], Barbara Bendlin[1,2,5,7], Corinne Engelman[1], Carey Gleason[1,3,7], Kirk Hogan[4,8], Nathaniel Chin[2,4], Cynthia Carlsson[1,2,4,5], Sanjay Asthana[1,4], Henrik Zetterberg[1,9,10,11,12], Sterling Johnson[1,3,7]
[1]University of Wisconsin, Department Of Medicine - Geriatrics, Madison, United States of America, [2]University of Wisconsin-Madison, Wisconsin Alzheimer's Institute, Madison, United States of America, [3]University of Wisconsin-Madison, Wisconsin Alzheimer's Institute, School Of Medicine And Public Health, Madison, United States of America, [4]University of Wisconsin-Madison, Wisconsin Alzheimer's Disease Research Center, Madison, United States of America, [5]William S. Middleton VA Hospital, Geriatric Research Education And Clinical Center, Madison, United States of America, [6]University of Wisconsin - Madison, Geriatrics/department Of Medicine, Madison, United States of America, [7]University of Wisconsin-Madison, Wisconsin Alzheimer's Disease Research Center, School Of Medicine And Public Health, Madison, United States of America, [8]University of Wisconsin-Madison, Anesthesiology, Madison, United States of America, [9]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [10]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [11]UCL London, Uk Dementia Research Institute, London, United Kingdom, [12]Clear Water Bay, Hong Kong Center For Neurodegenerative Diseases, Hong Kong, China

Aims: Tau phosphorylated at threonine 217 (pTau217) is a promising plasma biomarker for monitoring Alzheimer's disease (AD) pathology. Commercial release of the ALZpath pTau217 Single molecule array (Simoa) immunoassay has expanded the availability of this biomarker, enabling studies across multiple laboratories and cohorts. The objective of this work was to understand the analytical performance of this assay in our local laboratory and to examine concordance with gold standard amyloid PET imaging in our mostly preclinical AD cohort.
Methods: The ALZpath pTau217 assay was validated on our Quanterix HD-X analyzer using pooled EDTA plasma. A pilot study was then performed with cross-sectional samples from 295 participants of Wisconsin Registry for Alzheimer's Prevention and the Wisconsin Alzheimer's Disease Research Cente. Some samples (N=90) were previously analyzed at the University of Gothenburg (UGOT, reported in PMID: 37502842). Amyloid positivity was determined by [^{11}C]-PiB PET and was based on a global PiB DVR threshold of 1.19 (21.6 centiloids).
Results: The ALZpath pTau217 assay demonstrated acceptable precision (<10 %CV), linearity, and recovery (102-111%) for endogenous protein. In the pilot study, the Pearson correlation coefficient (r) between samples analyzed locally and at UGOT was 0.95 ($p < 0.001$). Plasma pTau217 concentrations were significantly correlated with global PiB DVR ($r = 0.78$, $p < 0.001$), and the ROC AUC predicting PiB positivity was 0.92 (95% CI: 0.88-0.96). The optimal Youden-based threshold corresponding to PiB positivity was 0.60 pg/mL for pTau217.
Conclusions: These data suggest that the ALZpath pTau217 assay is fit-for-use to detect AD pathology in our late-middle aged preclinical cohort. The accessibility of blood-based biomarkers combined with a commercially available assay will enhance our ability to obtain longitudinal data across the preclinical phase, especially in difficult to reach communities.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0449 / #1625

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PREDICTION OF COGNITIVE DECLINE BY PLASMA AND NEUROIMAGING BIOMARKERS IN NON-DEMENTED MEMORY CLINIC PATIENTS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Augusto José Mendes[1], Federica Ribaldi[2], Aurelien Lathuiliere[1], Nicholas Ashton[3], Henrik Zetterberg[4], Marc Abramowicz[5], Max Scheffler[6], Frédéric Assal[7], Valentina Garibotto[8], Kaj Blennow[4], Giovanni Frisoni[9]
[1]University of Geneva, Laboratory Of Neuroimaging Of Aging (lanvie), Geneva, Switzerland, [2]University of Geneve, Laboratory Of Neuroimaging Of Aging (lanvie), Geneve, Switzerland, [3]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [5]Geneva University Hospitals, Genetic Medicine, Diagnostics Dept,, Geneva, Switzerland, [6]University of Geneve, Radiology And Medical Informatics, Geneve, Switzerland, [7]Geneva Memory Center, Department Of Rehabilitation And Geriatrics,, Geneva, Switzerland, [8]Laboratory of Neuroimaging and Innovative Molecular Tracers (NIMTlab), Geneva University Neurocentre, Faculty of Medicine, University of Geneva, Division Of Nuclear Medicine And Molecular Imaging, Geneva, Switzerland, [9]University of Geneva (UNIGE and Geneva University Hospital (HUG), Department Of Rehabilitation And Geriatrics, Geneva, Switzerland

Aims: Plasma biomarkers hold great potential in the management of Alzheimer's disease patients due to their high accessibility, affordability, and low invasiveness. Recently, baseline plasma levels were shown to predict cognitive decline in cognitively unimpaired (CU) subjects and patients with mild cognitive impairment (MCI). If neuroimaging biomarkers are also strong predictors of cognitive deterioration, it is still unclear how well they perform when compared to plasma biomarkers.
Methods: A total of 140 CU and 78 MCI subjects from the memory clinic of Geneva University Hospitals were included. Plasma and neuroimaging biomarkers were assessed at baseline, whereas global cognition was evaluated for up to 5.7 years. Linear mixed-effects (LME) models were built to test the prognostic value of plasma and neuroimaging biomarkers. Moreover, based on these analyses, sample size calculations for future AD clinical trials were also performed.
Results: Cognitive decline in MCI was significantly predicted by baseline NfL (β=-0.55, p<0.001), and GFAP (β=-0.36, p=0.016). All neuroimaging biomarkers significantly predicted cognitive decline in MCI, namely hippocampal volume (β=0.44, p = 0.01), Centiloid (β=-0.38, p=0.04), and tau-SUVR (β=-0.66, p<0.001). The multivariate LME model revealed that only NfL (β=-0.81, p=0.009) and tau-SUVR (β=-0.69, p=0.02) significantly predicted cognitive decline in MCI, whereas no significant effect was detected in CU subjects. Lastly, it was demonstrated that identifying at-risk subjects by adding NfL in inclusion criteria, it would be possible to reduce the sample sizes of future AD clinical trials by up to one-fourth, in subjects with amyloid-PET positivity.
Conclusions: Plasma NfL, and GFAP are equally good predictors of cognitive deterioration as neuroimaging biomarkers in MCI patients. Future clinical trials could employ plasma biomarkers in screening, as this would allow for smaller sample sizes and lower research expenses.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0450 / #578

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EVALUATION OF SAMPLE STABILITY FOR THE ELECSYS CSF II IMMUNOASSAYS AT 25°C, 2 TO 8°C AND -15 TO -25°C

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ekaterina Manuilova[1], Isabelle Schrurs[2], Sandra Rutz[3], Silja Mcilwrick[4], Patrick Sommer[5], Oliver Goldhardt[5], Timo Grimmer[5]
[1]Roche Diagnostics GmbH, Phcs Biostatistics And Data Management, Penzberg, Germany, [2]Roche Diagnostics Int. AG, Co Phc Studies Sub-chapter Study Management, Rotkreuz, Switzerland, [3]Roche Diagnostics GmbH, Heterogeneous Assay Development And System Reagents Components (dsrci), Penzberg, Germany, [4]Roche Diagnostics GmbH, Co Oncology Pl Sc, Penzberg, Germany, [5]Technical University Munich, Center For Cognitive Disorders, Munich, Germany

Aims: In fluid biomarker testing, sample storage conditions are one of the pre-analytical variables potentially impacting assay performance. To better understand the impact of sample storage conditions on AD CSF biomarker levels, fresh cerebrospinal fluid (CSF) samples from subjects being evaluated for Alzheimer's disease were stored at different temperature and time ranges (8 days at 25°C, 15 days at 2 to 8°C and 12 weeks at -15 to -25°C). Abeta42, pTau and tTau were measured after storage and compared to baseline levels.
Methods: Three experiments evaluating sample stability at 25°C, 2 to 8°C and -15 to -25°C were performed. Per subject, four to five aliquots were collected following the routine-use procedure recommended in the respective method sheet for the Elecsys® CSF assays. Storage at -80°C was not investigated.
Results: pTau and tTau remained stable in all experiments. Abeta42 was stable for up to 8 days at 25°C and up to 15 days at 2 to 8°C. Freezing and storage over 8 weeks at -15 to -25°C had a small but significant effect on Abeta42 concentrations shown in an Abeta42 value reduction; the storage effect was slightly greater after 12 weeks.
Conclusions: For all three biomarkers, the observed concentration bias was below 10% over the entire tested period. Abeta42 was less stable than pTau and tTau at 25°C for storage periods over 8 days, and overall at -15 to -25°C, probably due to the physical characteristics of the analyte. As a conservative approach, it is recommended to store fresh CSF samples for ≤ 5 days at room temperature and for ≤ 14 days at 2 to 8°C. The frozen samples can be stored for ≤ 8 weeks at -15 to -25°C.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0451 / #1256

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PERFORMANCE OF LUMIPULSE G PTAU 217 PLASMA ASSAY COMBINED WITH PRE-ANALYTICAL TAU-IMMUNOPRECIPITATION

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Barbara Morgado[1], Hans Klafki[1], Hermann Esselmann[1], Els Huyck[2], Peter Jagiello[2], Nathalie Le Bastard[2], Manu Vandijck[2], Rosina Degrieck[2], Ingolf Lachmann[3], Dirk Osterloh[3], Katharina Waniek[3], Jens Wiltfang[1,4,5]
[1]Universitätsmedizin Göttingen, Klinik Für Psychiatrie Und Psychotherapie, Goettingen, Germany, [2]Fujirebio Europe NV, Fujirebio Europe Nv, Gent, Belgium, [3]Roboscreen GmbH, Roboscreen Gmbh, Leipzig, Germany, [4]German Center for Neurodegenerative Diseases (DZNE), German Center For Neurodegenerative Diseases (dzne), Goettingen, Germany, [5]Institute of Biomedicine (iBiMED), Neurosciences And Signaling Group, Aveiro, Portugal

Aims: Phosphorylated pTau 217 in plasma has emerged as a promising biomarker for the early detection of Alzheimer's disease (AD). We previously developed a pre-analytical sample workup based on semi-automated immunoprecipitation on FeliX platform followed by biomarker quantification using immunoassays (IP-IA). This study aims to compare the clinical performance of the novel pTau217 prototype immunoassay on the fully automated LUMIPULSE platform with and without the respective pre-analytical sample workup by Tau-immunoprecipitation in a preselected cohort.
Methods: A pre-selected cohort was studied comprising of 84 subjects dichotomized according to AT(N) classification. The IP-IA approach consists of semi-automated magnetic bead Aβ-IP followed by total Tau-IP and subsequent measurements of plasma Aβ1-42/1-40 ratio and pTau217 levels on Lumipulse.
Results: The levels of pTau217 after pre-analytical immunoprecipitation of Aβ and Tau correlated with the corresponding concentrations from direct measurements in plasma ($r=0.93$, $p<0.0001$). The Tau-IP prior to Lumipulse measurement resulted in a numerical increase in the area under the ROC curve (AUC) for identifying individuals A+ from 0.955 to 0.973 ($p=0.149$) for plasma pTau217. Although pTau217 performed generally better than Aβ1-42/1-40 ratio, the latter became superior when used to identify the early stages of AD defined as A+T-. We additionally assessed a novel term (AT-term) combining Aβ and pTau biomarkers, here defined as Aβ1-40/1-42*pTau217, which showed a further improvement in performance relative to the individual biomarkers.
Conclusions: Our preliminary findings in this preselected cohort indicate that reducing matrix effects potentially interfering in immunoassay performance by implementing pre-analytical Aβ and Tau immunoprecipitation can improve the performance of plasma biomarker assays for detecting brain amyloid pathology in a research context. Our observations also support the importance of the Aβ1-42/1-40 ratio as a biomarker for predicting early stages of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0452 / #265

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

BLOOD CD34+ CELL LEVEL IS A BIOMARKER OF PRECLINICAL ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Daniel Nation[1], Arunima Kapoor[2], Amy Nguyen[1], Aimée Gaubert[1], Kathleen Rodgers[3], David Robert Bradford[3], Elizabeth Head[4], Trevor Lohman[1]
[1]University of Southern California, Leonard Davis School Of Gerontology, Los Angeles, United States of America, [2]University of California Irvine, Psychological Science, Irvine, United States of America, [3]University of Arizona, Center For Innovations In Brain Science, Department Of Pharmacology, Tucson, United States of America, [4]University of California Irvine, Pathology & Laboratory Medicine, Irvine, United States of America

Aims: Prior studies examining blood CD34+ cell levels in Alzheimer's dementia have been mixed, with increased, decreased and no differences being reported relative to controls. The present study aimed to evaluate blood CD34+ cell levels in older adults with and without preclinical Alzheimer's disease biomarker abnormality.
Methods: One-hundred participants age 55-to-89 years were recruited from the community to undergo clinical examination and venipuncture. Participants were screened for history of stroke, dementia or other major illness. Blood CD34+ cell levels were determined by flow cytometry. Plasma Aβ42, Aβ40, ptau181, total tau, GFAP and NfL levels were obtained by SIMOA (Quanterix) assay. Longitudinal follow-up was obtained on a subset. T-tests and regression analyses evaluated the relationship between CD34+ cell levels and plasma biomarkers.
Results: Blood CD34+ cell levels were not associated with age or sex, p's>.60. CD34+ cell levels were significantly elevated in individuals who met the cutoff for amyloid positivity compared to those who did not based of either plasma Aβ42/40 ratio, $t(91) = -6.8$, $p<0.001$, or p-tau181, $t(90) = -3.9$, $p<0.001$. CD34+ cell levels were linearly associated with Aβ42/40 ratio ($B = -2.1$, $p <. 001$) and p-tau181 levels ($B = 1730.7$, $p<0.001$). There was no association between CD34+ cell counts and either GFAP or NfL. Longitudinal analysis indicated greater increases in CD34+ cell levels in amyloid positive versus negative individuals.
Conclusions: Older adults with preclinical Alzheimer's disease biomarker abnormality on plasma Aβ42/40 ratio and/or ptau181 levels exhibit substantially elevated blood CD34+ cell levels. Amyloid positive older adults exhibit increasing blood CD34+ cell levels over time. Further study of CD34+ cell counts as a preclinical biomarker of Alzheimer's disease is warranted.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0453 / #1578

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

A ROBUST BLOOD-BASED MULTI-PATHWAY BIOMARKER ASSAY FOR EARLY SCREENING AND CLASSIFICATION OF ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Li Ouyang[1,2], Yuanbing Jiang[1,2], Hyebin Uhm[1,2], Fanny Ip[1,2,3], Elaine Cheng[1,2], Ronnie Lo[1,2], Xiaoyun Cao[2], Clara Tan[2], Brian Law[2], Timothy Kwok[4], Vincent Mok[5], Marc Suárez[6,7,8,9], Henrik Zetterberg[2,10,11,12,13], Amy Fu[1,2,3], Nancy Ip[1,2,3]
[1]The Hong Kong University of Science and Technology, Division Of Life Science, Hong Kong, Hong Kong PRC, [2]InnoHK, Hong Kong Center For Neurodegenerative Diseases, Hong Kong, Hong Kong PRC, [3]HKUST Shenzhen Research Institute, Guangdong Provincial Key Laboratory Of Brain Science, Disease And Drug Development; Shenzhen–hong Kong Institute Of Brain Science, Shenzhen, China, [4]The Chinese University of Hong Kong, Therese Pei Fong Chow Research Centre For Prevention Of Dementia, Division Of Geriatrics, Department Of Medicine And Therapeutics, Hong Kong, Hong Kong PRC, [5]The Chinese University of Hong Kong, Gerald Choa Neuroscience Centre, Lui Che Woo Institute Of Innovative Medicine, Therese Pei Fong Chow Research Centre For Prevention Of Dementia, Division Of Neurology, Department Of Medicine And Therapeutics, Hong Kong, Hong Kong PRC, [6]Pasqual Maragall Foundatio, Barcelonabeta Brain Research Center, Barcelona, Spain, [7]Hospital del Mar Research Insitute (IMIM), Fluid Biomarkers And Translational Neurology, Barcelona, Spain, [8]Hospital del Mar, Servei De Neurologia, Barcelona, Spain, [9]Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable, Instituto De Salud Carlos Iii, Madrid, Spain, [10]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [11]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [12]UCL London, Uk Dementia Research Institute, London, United Kingdom, [13]Department of Neurodegenerative Disease, Ucl Institute Of Neurology, London, United Kingdom

Aims: Alzheimer's disease (AD) is a devastating neurodegenerative disease with delayed diagnosis until the manifestation of symptoms. Although the emergence of blood-based biomarkers offers hope for easy detection of AD, existing AD-associated blood biomarkers, known as the "blood ATN biomarkers", mainly capture the pathological hallmarks of AD, overlooking other AD-associated biological processes such as inflammation and vascular dysfunctions. Therefore, developing a blood-based biomarker assay that captures dysregulation beyond the ATN biomarkers may help advance early detection and staging of AD, enabling a comprehensive examination of the disease status.
Methods: We leveraged ultrasensitive proteomic technology to develop a blood-based, multiplex biomarker assay for AD. This assay simultaneously measures the levels of 21 blood proteins associated with different biological pathways, including neurodegeneration, inflammation, innate immunity, vascular functions, and metabolic activities. Moreover, we developed an AD risk scoring system by integrating the level changes of these 21 proteins in a machine learning-based model. The performance of this 21-protein biomarker assay in AD classification and indication of AD-related endophenotypes was evaluated in three independent cohorts.
Results: We showed that this 21-protein biomarker assay accurately classifies AD (AUC = 0.9407–0.9867) and mild cognitive impairment (MCI) (AUC = 0.8434–0.8945). It also indicates amyloid pathology in Chinese and European populations. Moreover, this assay simultaneously evaluates changes in five biological processes, providing comprehensive assessment of disease status and revealing heterogeneity of AD among individuals. Notably, dysregulations of biological processes upon AD progression are different between Chinese and European populations, particularly in biological pathways related to inflammation and vascular functions.

Conclusions: Our findings demonstrate the utility of a blood-based multi-pathway biomarker assay for early screening and staging of AD in clinical settings and provide insights for patient stratification and the development of precision medicine.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0454 / #1931

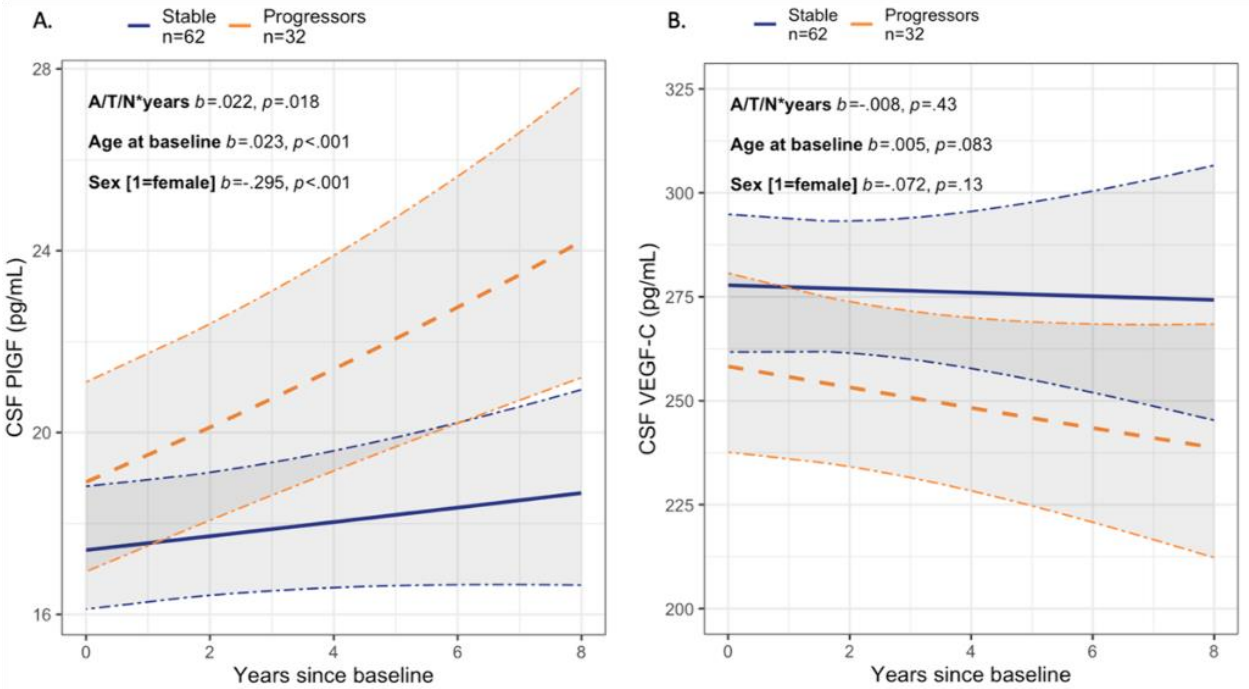
Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PROGRESSION OF ALZHEIMER'S DISEASE IS ASSOCIATED WITH INCREASING PLACENTAL GROWTH FACTOR IN CEREBROSPINAL FLUID

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Lene Pålhaugen[1,2], Julia Gundersen[1,3], Bjørn-Eivind Kirsebom[2,4,5], Berglind Gísladóttir[1], Jonas Jarholm[1,2], Per Selnes[1,2], Tormod Fladby[1,2]
[1]Akerhus University Hospital, Department Of Neurology, Lørenskog, Norway, [2]University of Oslo, Institute Of Clinical Medicine, Oslo, Norway, [3]University of Oslo, Institute Of Basic Medical Sciences, Oslo, Norway, [4]UiT The Arctic University of Norway, Department Of Psychology, Faculty Of Health Sciences, Tromsø, Norway, [5]University Hospital of North Norway, Department Of Neurology, Tromsø, Norway

Aims: Angiogenic mediators like placental growth factor (PlGF) and vascular endothelial growth factor-C (VEFG-C) are suggested as promising markers of cerebral small vessel disease. We aimed to compare these vascular markers in cerebrospinal fluid (CSF) between subjects with stable versus progressive A/T/N classification to explore a possible role of angiopathy in Alzheimer´s disease (AD) progression.
Methods: We analysed subjects (n=94) from the Norwegian multi-centre Dementia Disease Initiation (DDI) study. Participants were classified at baseline with either normal cognition (NC), subjective cognitive decline (SCD) or mild cognitive impairment (MCI). A/T/N staging based on CSF biomarkers was assessed in all participants at baseline, with biennial follow-up. Based on follow-up data, subjects were classified as stable A-/T-/N- (n=62) or progressing from A-/T-/N- to A+/T-/N- (n=23) or A+/T+ or N+ (n=9). Quantification of VEGF-C and PlGF in CSF was obtained at each follow-up. Linear mixed-effects models were used to estimate the longitudinal difference in biomarkers between stable A-/T-/N- and progressors, adjusted for age and sex.
Results: Degree of cognitive impairment at baseline differed between stable A-/T-/N- (25.8% NC, 74.2% SCD, none with MCI) and progressors (34.7% NC, 26.1% SCD and 39.1% MCI). We also observed a sex difference between stable A-/T-/N- (53.2% female) and progressors (39.1% female). Interestingly, PlGF showed a linear increase over time in progressors as compared to subjects with stable A-/T-/N- (*fig. 1*). Conversely, VEGF-C did not differ significantly between the groups.



Conclusions: Our longitudinal analysis shows that progression from A-/T-/N- to A+/T-/N- or A+/T+ or N+ is associated with increasing levels of PlGF, whereas VEGF-C levels remain stable. These findings suggest that PlGF-mediated angiopathy may play a role in AD pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0455 / #1947

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

TWO-STEPS DIAGNOSTIC ALGORITHM BASED ON PLASMA MARKERS TO PREDICT ALZHEIMER CSF PATHOLOGY IN CLINICAL ROUTINE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Andrea Pilotto[1], Alice Galli[2], Chiara Trasciati[2], Marta Parigi[2], Virginia Quaresima[2], Chiara Tolassi[2], Salvatore Caratozzolo[2], Alberto Benussi[2], Clara Tirloni[2], Silvia Giliani[3], Nicholas Ashton[4], Henrik Zetterberg[5], Alessandro Padovani[1]
[1]University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy, [2]University of Brescia, Neurology Unit, Department Of Clinical And Experimental Sciences, Brescia, Italy, [3]university of brescia, Nocivelli Institute, Brescia, Italy, [4]Wallenberg Centre for Molecular Medicine, University Of Gothenburg, Gothenburg, Sweden, [5]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: Plasma biomarkers whoed high performance at group level but their as markers of Alzheimer's disease (AD) is debated as single-ubject level. Aim of the study was to evaluate the performance at single subject level of plasma biomarkers to diagnose CSF AD-related pattern
Methods: each patient underwent standard clinical and cognitive assessment and CSF analyses for biomarker-based AD diagnosis. Plasma p-tau181, p-tau231, NfL, GFAP, T-tau abeta 1-42, Abeta 1-40 Tau, P-tau and Abeta amyloid, NfL, using SIMOA analyses. The ability of different biomarkers to distinguish AD from other neurodegenerative diseases was evaluated using ROC analyses and binary logistic regression analyses
Results: 125 AD and 55 other neurodegenerative disorders (NDD) with CSF analyses and 115 matched controls entered included in the analyses. The combined cut-off based on P-tau181 and NfL assessment was able to correctly classified 85% of AD and 78% controls at individual level. A two.-step plasma process Amyloid42 and P-tau truly identified 83% of AD and 65% NDD at individual level
Conclusions: this study confirmed the relevance of p-tau and NfL to distinguish AD from controls, whereas amyloid markers were important to distinguish in a fair way AD from NDD at individual level. Further larger studies including other markers and different subtypes of disease are needed to implement plasma biomarkers in clinical routine.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0456 / #1994

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA AND CSF P-TAU AND AMYLOID MARKERS DETECTED BY LUMIPULSE AND SIMOA TECHNIQUE FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE IN CLINICAL PRACTICE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Andrea Pilotto, Virginia Quaresima, Diego Bertoli, Chiara Tolassi, Marta Parigi, Alice Galli, Clara Tirloni, Andrea Rizzardi, Alberto Benussi, Salvatore Caratozzolo, Maura Cosseddu, Rosanna Turrone, Nicholas Ashton, Kaj Blennow, Henrik Zetterberg, Silvia Giliani, Duilio Brugnoni, Alessandro Padovani
University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy

Aims: Cerebrospinal fluid (CSF) biomarkers have proved to be highly informative, sensitive, and specific in detecting the preclinical as well as symptomatic stages of clinical Alzheimer's diseases (AD). The aim of this study is to access the robustness of LUMIPULSE G600II (Fujirebio®) compared to SR-X Ultra-Sensitive Biomarker Detection System (Simoa®, Quanterix), in detecting CSF and plasma biomarkers AD and no-AD subjects.
Methods: AD diagnosis was based on CSF biomarkers evaluation. Plasma p-tau181, amyloid β protein (A*β)* 42, A*β*-40, were performed on both platforms. AD neurodegenerative conditions and fluid biomarkers correlation were evaluated by ROC analyses and Spearman's rank correlation. Forty-nine A+T+N+ AD and 34 other neurodegenerative disorders (NDD) A-T-N+/- were included in the analyses. A group of cognitively normal subjects (CN) (n = 50) were also tested on plasma.
Results: The analytical values showed higher stability for plasma p-tau181 compared with AB42 and AB40 in Lumipulse testing . Plasma p-tau181 analysed on LUMIPULSE and SIMOA showed high correlation eachother and fair correlation with CSF values The ratio of p-tau181/AB42 and AB42/AB40 resulted to be robust in both system, presenting AUCs of 0.89 and 0.74 for Lumipulse and SIMOA for CSF AD-pattern, respectively.
Conclusions: Plasma markers showed high correlation between both Lumipulse and SIMOA techniques with a comparable discriminative value for the detection of CSF Alzheimer-related pattern in clinical setting.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0457 / #889

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CHARACTERISTICS OF DISCORDANCE BETWEEN AMYLOID POSITRON EMISSION TOMOGRAPHY AND PLASMA AMYLOID-B 42/40 POSITIVITY

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Jung-Min Pyun[1], Young Ho Park[2], Young Chul Youn[3], Min Ju Kang[4], Kyuhwan Shim[5], Jae-Won Jang[6], Jihwan You[1], Yongjin Yi[7], Kwangsik Nho[8], Sangyun Kim[9]
[1]Soonchunhyang University Seoul Hospital, Neurology, Seoul, Korea, Republic of, [2]Seoul National University Bundang Hospital, Neurology, Seongnam, Korea, Republic of, [3]Chung-Ang University Hospital, Neurology, Seoul, Korea, Republic of, [4]Central Veterans Hospital, Neurology, Seou, Korea, Republic of, [5]Gachon University, Department Of Bionano Technology, Seongnam-si, Korea, Republic of, [6]Kangwon National University Hospital, Department Of Neurology, Chunchoen-si, Korea, Republic of, [7]Dankook University Hospital, Department Of Internal Medicine, Cheonan, Korea, Republic of, [8]Indiana University School of Medicine, Radiology And Imaging Sciences, Indianapolis, United States of America, [9]Seoul National University Bundang Hospital, Neurology, Seongnam-si, Korea, Republic of

Aims: Although plasma biomarkers for amyloid-β showed high predictability of amyloid positron emission tomography (PET) positivity, the characteristics of discordance between PET and plasma amyloid positivity is poorly understood.
Methods: We compared tau burden measured by PET, brain volume assessed by magnetic resonance imaging, cross-sectional cognitive function, longitudinal cognitive decline and polygenic risk score (PRS) between PET/plasma groups (PET-/plasma-, PET-/plasma+, PET+/plasma-, PET+/plasma+) using Alzheimer's Disease Neuroimaging Initiative database. Additionally, we investigated inter-assays variability between immunoprecipitation followed by mass spectrometry method and Elecsys immunoassay.
Results: The PET-/plasma+ showed intermediate changes between PET-/plasma- and PET+/plasma+ in terms of tau burden, hippocampal and precuneus volume, cross-sectional and longitudinal cognition, and PRS. PET+/plasma- represented heterogeneous characteristics with variability depending on plasma assays.
Conclusions: Characteristics of PET-/plasma+ support plasma biomarkers as early biomarker of amyloidopathy prior to amyloid PET. Various plasma biomarker assays might be applied distinctively to detect different target subjects or disease stages.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0458 / #2753

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

NOVEL IMMUNOASSAYS FOR GFAP DETECTION BASED ON WELL-CHARACTERIZED N- AND C-TERMINAL SPECIFIC MABS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Laure De Waele[1], Leentje Demeyer[1], Melanie Vanhooren[1], Kazushige Moriyama[2], Hideo Sato[2], Daniel Antwi-Berko[3], Wiesje Van Der Flier[4], Inge Verberk[3], Charlotte Teunissen[3], Erik Stoops[1]
[1]ADx Neurosciences N.V., R&d, Ghent, Belgium, [2]Fujirebio INC, Research And Development Division, Tokyo, Japan, [3]Amsterdam UMC, Department Of Laboratory Medicine, Amsterdam, Netherlands, [4]Amsterdam UMC, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands

Aims: Glial fibrillary acidic protein (GFAP) is a cytoskeletal protein expressed in astrocytes. Reactive astrogliosis, hallmarked by increased GFAP expression, is part of the pathogenesis of Alzheimer's disease (AD). A set of N- and C-terminal monoclonal antibodies (mAbs) allowed us to build GFAP fragment-specific immunoassays that can help to understand the potential value of GFAP N- and C-terminal fragments in biomarker testing in AD and beyond. Here we report the preliminary clinical performance of a previously developed in-house N-terminal GFAP ELISA, and the development of a novel immunoassay allowing preliminary detection of C-terminal GFAP fragments.
Methods: Plasma samples from 50 AD patients (defined by CSF biomarker profile) and 50 healthy donors (HD) were tested in duplicate with our N-terminal research prototype ELISA. To develop the C-terminal GFAP immunoassay, mAb combinations including at least one mAb targeting the C-terminal tail were explored in ELISA. Detection of GFAP in brain lysate was evaluated.
Results: Using the N-terminal ELISA, GFAP concentrations in the AD group (median 623, IQR 420-889 pg/mL) were found to be significantly higher than in the HD group (median 385, IQR 275-478 pg/mL) (Mann-Whitney, $p<0.0001$) which is in line with published data. An ELISA set-up using C-terminal mAbs detected GFAP in AD and HD brain lysates (n=3).
Conclusions: Our N-terminal ELISA shows clinical value in this exploratory cohort and is therefore suitable for further clinical evaluation of GFAP levels in plasma from patients with different pathologies. Our C-terminal immunoassay demonstrated successful detection of GFAP in brain lysates and is under further development. Finally, analyzing clinical samples in both the N- and C-terminal assay would help to gain novel insights into the role of N- and C-terminal GFAP fragments as biomarker.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0459 / #890

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

INTEGRATION OF AMYLOID-B OLIGOMERIZATION TENDENCY AS A PLASMA BIOMARKER IN ALZHEIMER'S DISEASE DIAGNOSIS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Jung-Min Pyun[1], Young Chul Youn[2], Young Ho Park[3], Sangyun Kim[4]
[1]Soonchunhyang University Seoul Hospital, Neurology, Seoul, Korea, Republic of, [2]Chung-Ang University Hospital, Neurology, Seoul, Korea, Republic of, [3]Seoul National University Bundang Hospital, Neurology, Seongnam, Korea, Republic of, [4]Seoul National University Bundang Hospital, Neurology, Seongnam-si, Korea, Republic of

Aims: There has been significant development in blood-based biomarkers targeting amyloidopathy of Alzheimer's disease (AD). However, guidelines for integrating such biomarkers into AD diagnosis are still inadequate. Multimer Detection System-Oligomeric Amyloid-β (MDS-OAβ) as a plasma biomarker detecting oligomerization tendency is available in clinical practice.
Methods: We suggest how to interpret results of plasma biomarker for amyloidopathy using MDS-OAβ with neuropsychological test, brain MRI, and amyloid PET for AD diagnosis. Combination of each test result differentiates various stages of AD, other neurodegenerative diseases, or cognitive impairment due to causes other than neurodegeneration.
Results:

MDS-OAβ	Neuropsychological test	Brain MRI	The most probable diagnosis	Remarks
Positive	Cognitive impairment	AD-compatible atrophy	AD	Rarely, other ND LATE etc.) + am
		Normal	Early stage of AD	Rarely, cognitive (depression, vita electrolyte imbal condition etc.) +
	Normal	AD-compatible atrophy	Preclinical AD	Other preclinical VD, LATE etc.) +
		Normal	Preclinical amyloidopathy	
Negative	Cognitive impairment	AD-compatible atrophy	Other NDDs (DLB, FTD, NPH, PDD, VD, LATE etc.)	
		Normal	Cognitive impairment due to other causes (depression, vitamin B12/folate deficiency, electrolyte imbalance, poor general medical condition etc.)	
	Normal	Abnormal	Other preclinical NDDs (DLB, FTD, NPH, PDD, VD, LATE etc.)	
		Normal	Normal	

Conclusions: A systematic interpretation strategy could support accurate diagnosis and staging of AD. Moreover, comprehensive use of biomarkers which target

amyloidopathy such as amyloid PET on brain amyloid plaque and MDS-OAβ on amyloid-β oligomerization tendency can complement to gain advanced insights of amyloid-β dynamics in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0460 / #2960

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA BIOMARKERS AND COGNITIVE PERFORMANCE AMONG HISPANICS/LATINOS: STUDY OF LATINOS-INVESTIGATION OF NEUROCOGNITIVE AGING (SOL-INCA) RESULTS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Freddie Marquez[1], Wassim Tarraf[2], Sayaka Kuwayama[1], Ariana Stickel[3], Kevin Gonzalez[1], Deisha Valencia[1], Robert Kaplan[4], Carmen Isasi[4], Richard Lipton[5], Linda Gallo[3], Gregory Talavera[3], Martha Daviglus[6], Fernando Testai[7], Jianwen Cai[8], Charles Decarli[9], Bharat Thyagarajan[10], Douglas Galasko[1,11], Hector Gonzalez[1]
[1]University of California, San Diego, Department Of Neurosciences, La Jolla, United States of America, [2]Wayne State University, Health Sciences, Detroit, United States of America, [3]San Diego State University, Psychology, San Diego, United States of America, [4]Albert Einstein College of Medicine, Department Of Epidemiology & Population Health, Bronx, United States of America, [5]Albert Einstein College of Medicine, Department Of Neurology, Bronx, United States of America, [6]University of Illinois at Chicago, Institute For Minority Health Research, Chicago, United States of America, [7]University of Illinois at Chicago, Department Of Neurology And Rehabilitation, Chicago, United States of America, [8]University of North Carolina, Department Of Biostatistics, Chapel Hill, United States of America, [9]UC Davis, Neurology, Sacramento, United States of America, [10]University of Minnesota, Department Of Laboratory Medicine And Pathology, Minneapolis, United States of America, [11]University of California, San Diego, Department Of Neurology, San Diego, United States of America

Aims: Plasma biomarkers related to amyloid, tau, neurodegeneration (ATN) and glial activation hold promise for both research and clinical applications. We sought to examine their relationship with cognitive performance in a diverse population of community-dwelling Hispanic/Latino adults.
Methods: Plasma samples from middle-aged and older adults (50 to 86 years) in the *Study of Latinos-Investigation of Neurocognitive Aging* (SOL-INCA; 2016–2018) were analyzed to quantify amyloid-beta ($A\beta_{42/40}$), phosphorylated tau-181 (p-tau), neurofilament light chain (NfL; neurodegeneration), and glial fibrillary acidic protein (GFAP) using the Simoa digital immunoassay platform. We used regression models to examine associations between plasma biomarkers and cognitive performance on the Brief-Spanish English Verbal Learning Test (verbal episodic learning and memory), Word Fluency (verbal fluency), Digit Symbol Subtest (processing speed/executive functioning), and a cognitive composite (global cognition). Adjusted models included demographic (age, sex, education, Hispanic/Latino background, field center), medical (body mass index, Framingham risk score, chronic kidney disease), and genetic factors (APOE genotype). Sampling weights and survey techniques were used to account for the complex design.
Results: The target subpopulation (unweighted n=6,071) was 54% female with mean age of 63.39 ± 8.16 years. In adjusted models, plasma NfL was associated with all cognitive measures (global cognition: β=-0.06; 95% CI=[-0.10;-0.02]; p<0.01). Plasma p-tau and GFAP were significantly associated with learning, memory, and global cognition (global cognition: β=-0.04; 95% CI=[-0.06;-0.01]; p<0.01, and global cognition: β=-0.04; 95% CI=[-0.07;-0.00]; p<0.05, respectively).
Conclusions: Our findings suggest p-tau, neurodegeneration, and glial activation, but not amyloid-beta, are negatively linked to cognitive performance in community dwelling diverse middle-aged and older Hispanic/Latino adults. Further research is needed to specify the mechanisms by which plasma ATN and glial activation biomarkers are associated with cognition.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0461 / #1659

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ALZHEIMER'S DISEASE PLASMA BIOMARKERS IN AFRICAN AND AFRICAN AMERICAN POPULATIONS: CROSS-SECTIONAL ANALYSIS OF THE INDIANAPOLIS-IBADAN DEMENTIA PROJECT COHORT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Kristen A. Russ[1], Kathleen Lane[2], Sujuan Gao[3], Fred Unverzagt[4], Hugh Hendrie[4], Tatiana Foroud[1], Jeffrey Dage[5]
[1]Indiana University School of Medicine, Medical And Molecular Genetics, Indianapolis, United States of America, [2]Indiana University School of Medicine, Biostatistics And Health Data Science, Indianapolis, United States of America, [3]Indiana University School of Medicine, Department Of Biostatistics, Indianapolis, United States of America, [4]Indiana University School of Medicine, Psychiatry, Indianapolis, United States of America, [5]Indiana University School of Medicine, Stark Neurosciences Research Institute, Indianapolis, United States of America

Aims: Study the use of plasma biomarkers in The Indianapolis-Ibadan Dementia Project (IIDP) to assess the effect of population differences between geographies on biomarker associations.
Methods: IIDP is a longitudinal study that evaluated subjects in Indianapolis, Indiana and Ibadan, Nigeria. Plasma collected from study participants in the 2001 evaluation wave (N= 1028 African Americans; N=1091 Yoruba) was analyzed for Alzheimer's Disease and neurodegenerative biomarkers using the Quanterix Simoa HD-X Neurology 4-Plex and pTau181 v2.1 Advantage kits. The concentrations of neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), beta amyloid 42/40 ratio (Abeta 42/40), and phosphorylated Tau 181 (pTau181) were determined for each subject with available plasma samples. Biomarker data were log transformed and standardized prior to analysis. Multivariate and other association analysis was performed in JMP Pro v16 software.
Results: The demographics of study subjects can be seen in Table 1. Biomarkers were standardized and assessed by site for correlation in subjects with and without dementia. NfL, GFAP, and pTau181 associations were the same when comparing subjects with dementia between sites; however, higher NfL, GFAP, and pTau181 correlations were observed in cognitively normal (CN) subjects in Indiana compared to Ibadan (Figure 1). Additional analysis is still ongoing and will be included in the presentation.

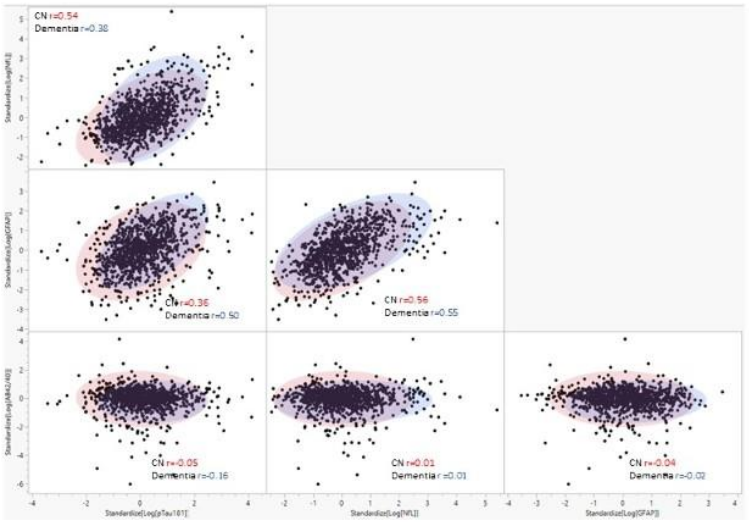
Table 1) Sample Demographics by Site

	Indiana, USA (N=1028)	Ibadan, Nigeria (N=1091)	Site differences P-value
Gender (n)	M: 334; F:686	M: 360; F:730	0.8902
Age at baseline visit Mean (SD)	75.6 (5.88)	73.4 (5.69)	<0.0001
Age at plasma collection Mean (SD)	78.5 (5.64)	77.8 (5.64)	0.0051
Age at diagnosis Mean (SD)	83.4 (5.70)	82.3 (5.79)	<0.001

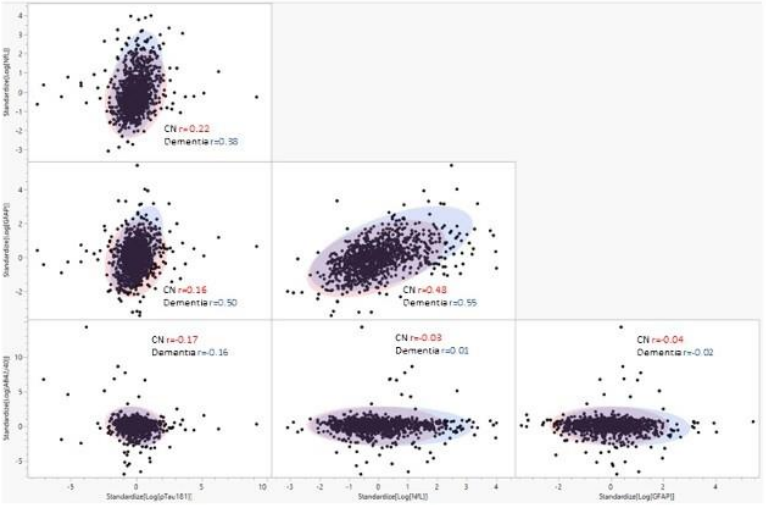
Table 1: Demographic info of samples with plasma collected as part of the 2001 cohort of IIDP. Mean age at plasma collection was calculated based on the collection date in associated with the sample. Mean age at diagnosis is the age at diagnosis of dementia or AD or the age at which they were non-demented at the last study visit. Group comparisons were tested for significance using t-test for continuous variables or Chi-square test for categorical variables.

Figure 1) Biomarker multivariate analysis by demented and non-demented (CN) groups

A) Site: Indiana, USA



B) Site: Ibadan, Nigeria



Conclusions: While biomarker associations for NFL, GFAP and pTau181 are consistent across sites for subjects with dementia, there are observed differences in biomarker associations for CN subjects between Indianapolis, Indiana, and Ibadan Nigeria. Previously published analyses (Deeg et al., 2008) regarding differences in potential comorbidities for these populations may be driving these differences. More analyses must be completed to determine the cause of these differences.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0462 / #2755

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

SERUM NEUROFILAMENT AS A TREATMENT-RESPONSE BIOMARKER IN THE EMERGE AND ENGAGE PHASE 3 TRIALS OF ADUCANUMAB IN ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Carrie Rubel[1], Kyle Fraser[1], Laura Nisenbaum[2], Tianle Chen[1], Kyle Ferber[1], Tao Sun[1], John O'Gorman[1], Gersham Dent[1], Kate Dawson[1], Danielle Graham[1]
[1]Biogen Inc., Medical Affairs, Cambridge, United States of America, [2]Alzheimer's Drug Discovery Foundation, Drug Development, New York, United States of America

Aims: Neurofilament light chain (NfL) is a disease biomarker supporting clinical efficacy in several neurodegenerative diseases. We investigated the utility of serum NfL as a treatment-response biomarker in Alzheimer's disease (AD) using data from Phase 3 clinical trials of aducanumab, EMERGE (NCT02484547) and ENGAGE (NCT02477800).
Methods: Serum NfL levels were analyzed in 8303 samples from 4773 participants from EMERGE and ENGAGE, including screening samples from unenrolled amyloid-negative participants. Correlations between baseline serum NfL and *APOE* ε4 carrier status, age, baseline amyloid-PET, structural MRI, clinical progression, and plasma p-tau^{181} levels were evaluated. Change from baseline (CFB) in NfL at Weeks 56 and 78 were assessed and correlated with CFB in biomarker and clinical endpoints.
Results: Baseline serum NfL levels were modestly elevated in amyloid PET-positive vs. negative participants and increased with age, with no significant differences between *APOE* ε4 carriers and non-carriers. Baseline NfL correlated with baseline plasma p-tau^{181}, structural MRI, baseline and CFB in clinical endpoints. CFB in NfL correlated with CFB in plasma p-tau^{181}. Longitudinal changes in NfL were small and highly variable with no clear treatment effect from aducanumab on NfL; a small number of outliers significantly impacted the analysis despite strong assay analytical performance. A consistent biological cause for observed extreme values was unclear; however, cardiovascular disease, type 2 diabetes, and chronic kidney disease have been associated with higher NfL.
Conclusions: While NfL is a highly informative treatment-response biomarker in other therapeutic areas, in AD the small-magnitude, slow rate of change, and high biological variability limit its ability to reflect clinical efficacy. Future work will examine the utility of NfL as a biomarker for AD therapies targeting different aspects of disease pathophysiology and in predicting/monitoring amyloid-related imaging abnormalities.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0463 / #1959

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EFFECTS OF APOE RISK ALLELE AND SEX ON THREE CORE CEREBROSPINAL FLUID BIOMARKERS ACROSS ANCESTRIES

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ruiqi Yan[1], Xiaoyi Xu[1], Qijun Yang[1], Catherine Apio[1], Jigyasha Timsina[1], Lihua Wang[1], Taesung Park[2], Carlos Cruchaga[1], Yun Ju Sung[1]
[1]Washington University School of Medicine in Saint Louis, Psychiatry, Saint Louis, MO, USA, United States of America, [2]Seoul National University, Statistics, Seoul, Korea, Democratic People's Republic of

Aims: Women are at a higher risk of developing AD and present faster progression. APOE-e4 risk allele is the strongest genetic risk factor for late-onset AD. The three core CSF biomarkers are amyloid β 42 (Aβ42) for cortical amyloid deposition, total tau for neurodegeneration intensity, and phosphorylated tau 181 (p-tau) for neurofibrillary pathological changes. The study aims to investigate the effect of sex and APOE4 on these three CSF biomarkers across ancestries.
Methods: We obtained three core CSF biomarkers from 20 cohorts. Based on genetic principal components anchored with the 1000 Genomes Project data, participants were grouped into Europeans (N=5,699), Africans (N=149), and Asians (N=65). For each biomarker, we considered the main effect (sex and APOE4) model, the interaction model (additionally including the interaction between sex and APOE4), and the sex-stratified model. The heterogeneity test was used to determine fixed or random effect model for European meta-analysis. African and Asian samples were jointly analyzed.
Results: Tau and pTau were significantly associated with sex and APOE4 in Europeans and Africans. Asians had consistent effects. Aβ42 had significant APOE4 effects consistently in three ancestries. Females had higher APOE4 effects for Tau than males across all three ancestries. Tau had significant interaction between sex and APOE4 in Europeans ($\beta=0.11$; $P < 0.01$). We found some heterogeneity within European cohorts. Results from Africans and Asians were consistent.
Conclusions: This study found that the effect of the APOE risk allele on CSF tau biomarker is sex-specific and higher in females than males. This effect is consistent across ancestries. With the increase in sample size and number of studies, the precision and power of the meta-analyses were improved. Validations in Asians may require additional follow-up.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0464 / #1035

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

MINIMALLY INVASIVE DETECTION OF AD BIOMARKERS FOR DIFFERENTIATION OF AD IN COGNITIVELY IMPAIRED PATIENTS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Marion San Nicolo[1], Oliver Peters[2], Hilary Wunderlich[1], Lutz Froelich[3], Jens Wiltfang[4], Timo Grimmer[5], Arno Schaepe[1], Richard Metzler[1], Sabine Mertzig[1], Klaus Hallermayer[1], Harald Waltenberger[1], Peter Kaspar[1], Thomas Heydler[1], Mareike Haack[1]
[1]Noselab, Na, Munich, Germany, [2]Department of Psychiatry, Charité-universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, [3]Heidelberg University, Department Of Geriatric Psychiatry, Central Institute Of Mental Health,medical Faculty Mannheim, Mannheim, Germany, [4]Universitätsmedizin Göttingen, Klinik Für Psychiatrie Und Psychotherapie, Goettingen, Germany, [5]Technical University Munich, Center For Cognitive Disorders, Munich, Germany

Aims: Evaluation of our proprietary diagnostic platform for minimally invasive, detailed quantification of the key Alzheimer's disease (AD) biomarkers in size and relative amount: pTau181 (pTau), total Tau (tTau), Amyloid-β1-40 (Aβ40), Amyloid-β1-42 (Aβ42) and total Amyloid β (Aβ).
Methods: Multicenter, prospective cohort study including patients with cognitive impairment. The presence (A+) or absence (A-) of amyloid pathology was determined by the Aβ42/Aβ40 ratio in CSF as reference test and compared to nasal secretion-based classification of AD biomarkers. Nasal secretion was collected from the vicinity of the olfactory cleft using a proprietary collection device (nosecollect®) and the relative protein amount as well as protein specific quaternary substructures (monomeric and oligomeric species) were quantified for the AD biomarkers using an automated protein separation and immunodetection system.
Results: Sampling procedure using nosecollect® is well tolerated, painless and yields a high sample volume. Different monomeric, oligomeric, and higher n-meric protein species of AD biomarkers were quantified. Patients with CSF-confirmed amyloid pathology (A+) show a significantly different protein-specific biomarker signature in nasal secretion as compared to patients without amyloid pathology (A-). Our protein-specific biomarker signature allows for a highly significant discrimination (p-value <0.001) of A+ vs. A- with an AUC of >0.90.
Conclusions: Simultaneous detection of multiple AD relevant biomarkers along the olfactory route constitutes a safe, minimally invasive, easy to obtain diagnostic procedure. Among patients with cognitive impairment, A+ patients and A- patients can be discriminated with high accuracy. Thus, our diagnostic platform has the potential for screening, diagnostics, patient stratification, intraindividual disease and treatment monitoring in AD as well as other neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0465 / #2148

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

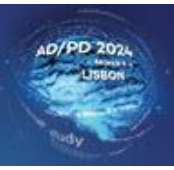
PROTEIN FIBRIL AGGREGATION ON RED BLOOD CELLS: A POTENTIAL BIOMARKER TO DISTINGUISH NEURODEGENERATIVE DISEASES FROM HEALTHY AGING

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Thomas Schneider[1], Luisa Stöckli[1], Ansgar Felbecker[1], Peter Nirmalraj[2]
[1]Cantonal Hospital of St. Gallen, Neurology, St. Gallen, Switzerland, [2]Swiss Federal Laboratories for Materials Science and Technology, Transport At Nanoscale Interfaces Laboratory, Dübendorf, Switzerland

Aims: To investigate the prevalence and significance of fibril aggregation on red blood cells (RBCs) in both cognitively healthy adults and patients with cognitive complaints, and to assess its potential as a biomarker for neurodegenerative diseases, especially Alzheimer's disease (AD).
Methods: Study Population: Data from 50 cognitively healthy adults (aged 18-88 years), 8 patients with no evidence of a neurodegenerative disease, 11 patients with MCI or dementia who were amyloid negative and 18 patients with MCI or dementia who were amyloid positive were analyzed. **RBC Analysis:** Atomic Force Microscopy (AFM) was employed to study the nanoscale morphology of fibril aggregates on RBCs in blood smear samples. Approximately 1000 RBCs on 30-50 scanned areas were analyzed for each participant. **Statistical Analyses:** Descriptive statistics, grouo comparisons, and ROC analyses were conducted to differentiate between diagnosis groups based on the prevalence of fibrils on RBCs.
Results: Only a minority of healthy participants but all patients displayed fibril aggregates on RBCs. Patients with AD pathology, confirmed by a positive cerebrospinal fluid (CSF) Aβ 1-42/1-40 ratio, showed the highest levels of fibrils on RBCs. Healthy subjects had a mean fibril coverage of RBCs of 2.96 ± 6.1%, which was significantly lower than all patient groups. The 'MCI/D A+' group showed the highest fibril prevalence at 68.0 ± 14.1%. Different cutoffs of fibril prevalence accurately differentiated the healthy group from the patient groups with an accuracy ranging from 0.95 - 1.0 and AUC from 0.98 - 1.
Conclusions: Fibril aggregation on RBCs may serve as a potential biomarker for neurodegenerative diseases, though its specificity for AD remains uncertain. Combining AFM with chemical spectroscopy could enhance diagnostic precision, but further research is essential.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0466 / #2388

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

VALIDATION OF A NOVEL, LYSOSOME-FOCUSED, MULTIPARAMETRIC BIOMARKER PLATFORM FOR ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Adam Shellard, Owen Connolly, Hernando M. Vergara, Florence Young, Souvik Modi
Esya Labs, R&d, London, United Kingdom

Aims: Biomarker development in Alzheimer's Disease (AD) has relied on techniques such as neuroimaging and proteomics to investigate tauopathy and amyloidosis. However, multiple studies show that lysosomal dysfunction is associated with AD by regulating both the formation and degradation of Aβ. To leverage this paradigm shift in our understanding of AD pathology, Esya's aim is to use a multiparametric approach that combines lysosomal two ion-mapping technology, an RNA panel and plasma biomarkers for early detection of AD.
Methods: Esya's multiparametric platform incoporates 1) 2-ion probes that ratiometrically measure concentrations of ions such as H^+ and Ca^{2+} with single lysosome resolution 2) ApoE genotyping 3) a panel comprising 12 RNA targets identified through RNA-Seq and 4) plasma biomarkers. The diagnostic utility of our platform was assessed through application to blood plasma analytes, and fibroblasts from a clinically diagnosed cohort comprising controls and patients diagnosed with AD, frontotemporal dementia, Parkinson's, and Huntington's disease. A model probability score of predicting AD was calculated using a logistic binary regression.
Results: The diagnostic power of Esya's platform is improved by addition of a custom RNA panel, ApoE genotyping and blood plasma analytes to our pre-existing 2-ion model. Logistic regression demonstrates that the assay is accurate in differentiating AD from controls. This was further validated using an independent sample set comprising AD and non-AD samples. The platform's accuracy of differentiating between AD and non-AD samples is >90%.
Conclusions: The multiparametric approach described here that incorporates four independent features accurately differentiates AD from non-AD dementias. This technology can be further optimised and applied to other neurological disorders and will allow Esya to develop a more accurate platform for diagnostics, drug discovery for organellar dysfunction and personalized medicine in neurology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0467 / #1406

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

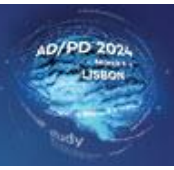
BLOOD-BASED BIOMARKERS AND COGNITIVE PROFILING AS EARLY INDICATORS OF ALZHEIMER'S DISEASE PATHOLOGY IN INDIVIDUALS WITH MEMORY COMPLAINTS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Anuschka Silva-Spínola[1], Diogo Damas[2], Diana Duro[2], Marisa Lima[2], Maria João Leitão[3], Miguel Tábuas-Pereira[2], João Durães[2], Isabel Santana[2], Inês Baldeiras[1]
[1]University of Coimbra, Faculty Of Medicine, Coimbra, Portugal, [2]Coimbra University Hospital, Neurology, Coimbra, Portugal, [3]Center for Innovative Biomedicine and Biotechnology, Neurochemistry Lab, Coimbra, Portugal

Aims: In this work, we explored the associations between blood Alzheimer's disease (AD) biomarkers and comprehensive neuropsychological data in a cohort of individuals with memory complaints, characterized by their cerebrospinal fluid (CSF)-AD biomarkers profile.
Methods: We studied a prospective group of 73 non-demented individuals (67 years of median age, 67% female) with memory complaints followed at Coimbra University Hospital, with available CSF-AD biomarkers. Our measures consisted of baseline neuropsychological scores (encompassing orientation, episodic and working memory, language, abstract reasoning, executive and visuospatial function, learning, and verbal fluency) and plasma/serum AD biomarkers (Aβ42, Aβ40, t-tau, p-tau181, NfL and GFAP), determined by Single Molecule Array (SiMoA). As a measure of AD pathology, individuals were classified by their amyloid status (A) using the CSF Aβ42/Aβ40 ratio.
Results: When comparing A+ (n=30) and A- individuals (n=43), we observed significant differences in normative z-scores for confrontation naming and cube copy tests (p=0.019; p=0.043). A+ individuals had significantly higher levels of serum GFAP and plasma p-Tau181, as well as lower levels of plasma Aβ42, Aβ40 and Aβ42/40 ratio. They showed significant ($p<0.01$) moderate negative associations between serum GFAP levels and the previously mentioned tests (ρ=-0.53; ρ=-0.45), as well as with token (ρ=-0.47) and trail making section B (ρ=-0.52) tests. In contrast, these associations were very weak in A- individuals. Furthermore, our multinomial logistic regression model identified plasma p-Tau181 (β=1.72, p=0.007), serum GFAP (β=0.02, p=0.01) and confrontation naming (β=1.18, p=0.05), as independent significant predictors of amyloid status.
Conclusions: Our cohort displays a distinct pattern of deficits encompassing attention, working memory, and visuospatial function, which, in combination with blood GFAP and p-Tau181, emerged as early indicators of AD pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0468 / #867

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

LARGE-SCALE PLASMA PROTEOMIC PROFILING OF AMYLOID BETA POSITIVITY IDENTIFIES A ROBUST SET OF BIOMARKERS FOR EARLY DETECTION OF CLINICAL ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Gyujin Heo, Muhammad Ali, Jigyasha Timsina, Menghan Liu, Lihua Wang, Carlos Cruchaga, Yun Ju Sung
Washington University School of Medicine, Department Of Psychiatry, St. Louis, United States of America

Aims: Several non-invasive plasma biomarkers for Alzheimer's disease (AD) show promise for routine clinical uses for early detection of amyloid beta (Aβ) positivity and for guiding AD treatment decisions. This study aimed to examine plasma proteins for their relevance in predicting Aβ positivity and clinical AD and monitoring disease progression.
Methods: We obtained approximately 7,000 proteins (SomaScan) from 2,916 plasma samples and performed differential abundance analysis. We examined Aβ positivity (638 Aβ+ vs. 908 Aβ-) and clinical AD status (685 AD vs. 685 cognitively normal) in separate data. We then developed a prediction model for clinical AD diagnosis. Protein-protein interaction network analysis using STRING and enrichment analysis with gene ontology were performed to understand the biological significance of the identified proteins.
Results: We identified 109 differentially abundant proteins with Aβ positivity and 148 with clinical AD status at FDR < 0.05. 20 proteins (including NEFL, SPC25, ACHE, CPLX1, and CPLX2) were associated with both outcomes in the same direction. The predictive model based on these 20 proteins achieved area under the curve (AUC) values of 0.714 in clinical AD status dataset and 0.759 in Aβ positivity dataset. With the use of 20 proteins, prediction model provided an AUC of 0.882 in cerebrospinal fluid data. Protein network analysis revealed interactions among multiple proteins (ACHE, CRP, PLA2G7, and STX1A) and key AD proteins (APP, APOE, and MAPT). Pathway analysis emphasized biological processes related to synaptic function (synaptic vesicle membrane organization, FDR=2.54E-03; regulation of neurotransmitter transport, FDR=2.18E-02).
Conclusions: We identified 20 plasma proteins as potential biomarkers for clinical AD diagnosis, highlighting the role of synaptic dysfunction in AD pathogenesis. The validation of our findings in additional samples and their relevance for tau pathology is underway.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0469 / #2048

Poster Topic: *Theme A: β-Amyloid Diseases / A04.f. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

EXPLORING AGE-RELATED ALTERATIONS IN LOCUS COERULEUS ANATOMICAL AND FUNCTIONAL CONNECTIVITY WITH DEEP LEARNING

POSTERS: A04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Blanca Zufiria Gerboles[1], Dániel Veréb[1], Jiawei Sun[1], Giovanni Volpe[2], Joana Pereira[1]
[1]Karolinska Institutet, Department Of Clinical Neuroscience, Stockholm, Sweden, [2]University of Gothenburg, Department Of Physics, Soft Matter Lab, Gothenburg, Sweden

Aims: The locus coeruleus (LC) is a structure in the brainstem responsible for producing and releasing noradrenaline in the brain. Although the LC sends widespread axonal projections to many brain regions, how these connections change across aging remains unclear. To address this question, we studied the anatomical and functional connections of the LC on diffusion-weighted and functional magnetic resonance imaging in 640 cognitively normal individuals between 18 and 88 years old.
Methods: We generated individual anatomical and functional connectivity vectors with probabilistic tractography and seed based analysis, respectively, using the regions of the Brainnectome atlas. To investigate the effects of aging on the LC connections we used a well-established deep learning architecture (multilayer perceptron).
Results: Two models were successfully trained to predict age using the anatomical (r2=0.331±0.113) and functional (r2=0.211±0.096) connectivity independently. Additionally, we developed a joint model combining anatomical and functional connectivity that outperformed the previous models in the prediction of age (r2=0.382±0.085). By employing a feature importance approach, we identified the most predictive connections and we calculated their Spearman's rank correlation (rs) with age. Anatomical connections significantly decreased with age and were located in the frontal lobe (rs = - 0.46,p- value=2.98e-34), bilateral thalami (left rs = -028,p-value=2.32e-13;right rs = -0.27,p-value=5.82e-12), left caudate (rs = -0.3,p-value=9.92e-15), left amygdala (rs = -0.3,p-value=6.77e-15) and right hippocampus (rs = -0.24, p-value=2.81e-10). Functional connections significantly increased with age in the temporal lobe (rs = 0.18,p-value=1.94e-06) and significantly decreased in frontal (rs = -0.16,p-value=3.05e-05), limbic (rs = -0.14, p-value= 0.0003) regions and right thalamus (rs = -0.18,p-value=2.27e-06).
Conclusions: Our study provides new insights into the anatomical and functional neural mechanisms underlying aging in LC and demonstrates the potential of deep learning to investigate brain connectivity patterns.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0470 / #1488

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CHANGES IN THE CA2+ ACTIVITY OF PIEZO1 RECEPTORS IN RED BLOOD CELLS AS A NOVEL FUNCTIONAL HALLMARK FOR ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Valeriia Sitnikova[1], Dilyara Nurkhametova[1], Nicoletta Braidotti[2,3], Catalin Ciubotaru[2], Sari Kärkkäinen[4], Silja Kuivamäki[1], Paula Korhonen[1], Raisa Giniatullina[1], Ilkka Fagerlund[1], Juho Kalapudas[5], Elina Penttilä[6], Heikki Löppönen[6], Anne Koivisto[7,8,9], Tarja Kokkola[4], Dan Cojoc[2], Rashid Giniatullin[1], Tarja Malm[1]
[1]A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Faculty Of Health Sciences, Kuopio, Finland, [2]National Research Council of Italy, Materials Floundry, Trieste, Italy, [3]University of Trieste, Department Of Physics, Trieste, Italy, [4]University of Eastern Finland, Institute Of Clinical Medicine/neurology, Kuopio, Finland, [5]Kuopio University Hospital, Department Of Neurology, Kuopio, Finland, [6]University of Eastern Finland and Kuopio University Hospital, Department Of Otorhinolaryngology, Kuopio, Finland, [7]Kuopio University Hospital, Department Of Neurology, Neuro Centre, Kuopio, Finland, [8]University of Eastern Finland, Brain Research Unit, Department Of Neurology, School Of Medicine, Kuopio, Finland, [9]University of Helsinki, Department Of Neurology And Geriatrics, Helsinki University Hospital And Neurosciences, Faculty Of Medicine, Helsinki, Finland

Aims: Emerging evidence suggests that impaired microcirculation contributes to Alzheimer's disease (AD) pathology exaggerating neurodegeneration due to a limited supply of nutrients and oxygen to affected brain areas. This may require the adaptation of red blood cells (RBC) to squeeze through narrowed capillaries in the microcirculatory bed. Here, we hypothesized that, in AD patients, RBCs are undergoing modifications in the expression and function of calcium-permeable mechanosensitive Piezo1 channels which control the flexibility of these cells.
Methods: To assess the function of Piezo channels, we either measured using a flow cytometry assay, Yoda1-induced Piezo1-mediated calcium responses in RBCs of healthy individuals, patients with mild cognitive impairment, and AD patients or tested the physical properties of the RBCs with a novel micropipette aspiration technique.
Results: RBCs obtained from patients with MCI and AD patients showed significantly higher calcium responses to the Piezo agonist Yoda1, compared to RBCs from age-matched healthy individuals suggesting enhanced function of Piezo1 channels in AD pathology. RBC membrane incubated with Aβ showed significantly higher activated pressure during aspiration and a decrease in the ability to withstand changes in the length during deformation implying that the blood level of this AD-associated peptide can control the function of Piezo1 channels in RBC.
Conclusions: Together, our data suggest a significantly altered function of Piezo1 channels in peripheral circulation which might be an adaptive reaction to the impaired microcirculation, and therefore, Yoda1 elicited activation of Piezo1 in RBCs may be used as a functional biomarker for early AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0471 / #1938

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

YOUNG-ONSET ALZHEIMER'S DISEASE (AD) DIFFERS IN INFLAMMATORY PROFILE FROM LATE-ONSET AD: A PROTEOMICS APPROACH

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Simrika Thapa[1], Chloe Anastassiadis[2], Anna Vasilevskaya[2], Mohsen Hadian[1], Patrick Salwierz[2], Faiza Robbani[2], Foad Taghdiri[2], Pia Kivisäkk[3], Bradley Hyman[3], Steven Arnold[3], Martin Ingelsson[1], Andres Lozano[1], David Tang-Wai[1], Maria Tartaglia[1]
[1]University Health Network, Krembil Brain Institute, Toronto, Canada, [2]Tanz Centre for Research in Neurodegenerative Diseases, University Of Toronto, Toronto, Canada, [3]Massachusetts General Hospital, Department Of Neurology, Boston, United States of America

Aims: Neuroinflammation is involved in Alzheimer's disease (AD) pathophysiology, including young-onset AD (YOAD) and late-onset AD (LOAD) subtypes. Limited post-mortem studies show a hyper-reactive immune response in YOAD compared to LOAD. Our aim was to investigate whether distinct neuroinflammatory profiles exist in YOAD and LOAD and their relationship to neurodegeneration markers.
Methods: We measured 737 inflammatory proteins in cerebrospinal fluid (CSF) from 90 AD [57 YOAD: mean age 60.84, %female 70; 33 LOAD: mean age 76.55, %female 55], and 26 healthy controls (HC: mean age 63.92, %female 46) using Olink's proximity extension assay. ANCOVAs, adjusted for age and sex, were used to compare inflammatory protein levels among the groups (FDR-corrected). To assess the link between inflammatory markers and neurodegeneration, we ran multiple linear regression analyses with an interaction of inflammatory markers by disease group as independent variable, and neurofilament light chain (NfL) as dependent variable.
Results: Comparing biomarkers of AD (Aβ42, p181-tau, total-tau), neuroaxonal injury (NfL), and astrogliosis (GFAP) across groups, only Aβ42 level differed significantly between YOAD and LOAD (mean=361.92 vs 456.21pg/mL, $q<0.05$). YOAD exhibited a significant elevation in twenty-six inflammatory proteins involved in extracellular matrix regulation, neuroprotection, signal transduction, synapse maintenance, and immune regulation compared to HC CSF ($q<0.05$). In LOAD, only two proteins (SCRN1 and MMP10) were significantly elevated compared to HC ($q<0.05$). Interestingly, among 72 proteins that showed a significant interaction of protein levels by AD-subtype on NfL, for 40 proteins LOAD displayed a positive linear relationship with NfL, while YOAD showed a negative linear relationship.
Conclusions: YOAD and LOAD patients display distinct inflammatory profiles with diverging relationships between markers of inflammation and neurodegeneration. Future analysis will investigate the effect of markers in clinical phenotype.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0472 / #1054

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

FASTING CONDITION DOES NOT IMPACT ON BLOOD BIOMARKERS PERFORMANCE TO IDENTIFY ALZHEIMER'S ASSOCIATED PATHOLOGY.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Javier Torres-Torronteras[1,2], Paula Ortiz-Romero[1,2], Armand González Escalante[1,2,3], Carolina Minguillón[1,2,4], Federica Anastasi[1,2,5], Esther Jiménez-Moyano[1,2], Marc Suárez[1,2,4,6], Marta Del Campo Milán[1,2,7]
[1]Barcelonabeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain, [2]Hospital del Mar Research Insitute (IMIM), Fluid Biomarkers And Translational Neurology, Barcelona, Spain, [3]Universitat Pompeu Fabra, Dcexs, Barcelona, Spain, [4]Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable, Instituto De Salud Carlos Iii, Madrid, Spain, [5]Centre for Genomic Regulation, (crg), Barcelona, Spain, [6]Hospital del Mar, Servei De Neurologia, Barcelona, Spain, [7]Universidad San Pablo-CEU, CEU Universities, Departamento De Ciencias Farmacéuticas Y De La Salud, Facultad De Farmacia, Madrid, Spain

Aims: Blood biomarker analyses have become a valuable method to identify Alzheimer's disease (AD) related pathology. Identification of the pre-analytical factors that may alter blood biomarker concentration is critical for their implementation in clinical practice. This study aimed to evaluate the impact of fasting condition on the concentration of common plasma biomarkers used to detect AD pathology and neurodegeneration.
Methods: Plasma samples were obtained from 16 participants of the ALFA cohort under fasting (F) and non-fasting (NF) conditions. We measured plasma concentrations of Aβ40, Aβ42, NfL, GFAP and pTau181 in a Simoa HD-X analyser using the N4PE and the pTau181 v2.1 advantage kits (Quanterix). Aβ positivity was established using a previously defined CSF Aβ42/40 ratio cut-off.
Results: Plasma concentrations of Aβ40 and Aβ42 were lower in samples obtained under F conditions than NF ones independently of their amyloid status, but such effect was not observed in plasma Aβ42/40 ratio. No differences in the plasma concentration of GFAP, NfL or pTau181 were detected between F and NF conditions. The performance of the different markers to discriminate amyloid positivity was similar across fasting conditions. Concordance analysis (Bland-Altman test) between fasting status showed biases of less than 10% in all markers except for GFAP (16%).
Conclusions: These results indicate that the quantification of the canonical blood biomarkers for AD are not affected by the fasting condition except for the Aβ quantification, which can be overcome when considering the Aβ42/40 ratio. Importantly, pTau181, the marker that could best predict amyloid pathology, was not influenced by fasting conditions. Further studies in larger data sets will be needed to assess the impact of fasting conditions and on novel blood biomarkers developed for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0473 / #2590

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DEVELOPMENT AND OPTIMIZATION OF A HOMEBREW ASSAY FOR THE QUANTIFICATION OF DYRK1A LEVELS IN BODY FLUIDS FROM HUMAN AND RODENTS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Idil Yuksekel[1], Daniella Victorino[1], Jean Delabar[1], Nicolas Villain[1,2], Kaj Blennow[1,3,4], Marie-Claude Potier[1]
[1]Sorbonne Université, INSERM U1127, CNRS 7225, Paris Brain Institute - Icm, Paris, France, [2]Hôpital Pitié-Salpêtrière, Département De Neurologie, Paris, France, [3]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg, Mölndal, Sweden, Molndal, Sweden, [4]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden

Aims: Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A (*DYRK1A*) plays a role in Alzheimer's disease (AD) pathology. DYRK1A level increases with age in humans, whereas we have previously shown that individuals with AD, dementia, Down Syndrome or tauopathies have decreased plasma DYRK1A levels compared to controls. So far, we have been using Meso Scale Discovery (MSD) technology for assessing DYRK1A levels in different matrices. We now aim to implement our DYRK1A immunoassay in ultrasensitive single-molecule array (SIMOA HD-X platform), especially considering recent advances in the AD field regarding assessment of low concentrations of biomarkers in brain-derived exosomes isolated from blood.
Methods: In this study, antibody pairs and calibrators were evaluated, efficiency of the prepared beads and detectors were measured. Using the SIMOA technology; 2 step vs 3 step assay, detector antibody concentrations, buffers, diluents, sample volume effect and several dilution factors were tested.
Results: Currently, our DYRK1A homebrew assay is a 2-step digital immunoassay for the quantification of DYRK1A levels in plasma isolated from humans and rodents. Using the B diluent in our assay yielded higher percentage of recovery after spiking with 4 and 40pg/ml of DYRK1A (compared to Homebrew and A-E Sample Diluents, Quanterix).
Conclusions: At this point, our findings show a lack of dilution linearity and a low % of spike recovery in mice samples, which suggest a potential matrix effect. We expect to address this issue by optimizing assay conditions, such as adjusting the concentration of the agents and testing additional dilution factors. Once met the required acceptance criteria specified in our validation plan, our homebrew assay will be used for the quantification of DYRK1A levels in plasma longitudinally collected from newly generated mouse models of AD in our research team.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0474 / #1009

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

BLOOD-BASED MEASUREMENT OF CIRCULATING PREFIBRILLAR AMYLOID BIOMARKER DIFFERNTIATES PET VERIFIED BRAIN AMYLOID POSITIVITY STATUS IN AN AD COHORT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Carine Lim[1], Mario Morken[2], Calvin Ko[1], Jia Qi Fu[1], Jing Xuan Wong[1], Olivia Oh[1], Nicole Tsang[3], Huilin Shao[4], Peter Maimonis[1]
[1]Sunbird Bio, Product Development, Cambridge, United States of America, [2]Sunbird Bio, Business Development, Cambridge, United States of America, [3]Sunbird Bio, Project Management, Cambridge, United States of America, [4]National University of Singapore, Department Of Biomedical Engineering, Singapore, Singapore

Aims: To assess blood-based levels of a circulating prefibrillar amyloid population to differentiate brain amyloid positivity in subjects across the Alzheimer's disease (AD) spectrum and to evaluate the APEX platform as a tool to facilitate AD disease diagnosis and monitoring.
Methods: Leveraging our discovery that prefibrillar beta-amyloid(Aβ) protein preferentially associates with extra-cellular vesicles (EVs), we have developed a dedicated detection platform, Amplified Plasmonic EXosome (APEX) that is size-matched for the enhanced detection of EV-associated prefibrillar Aβ directly from blood plasma, without a need for pre-enrichment, preserving the native association of the protein. Not achievable with conventional technologies, APEX uses Transmission Surface Plasmon Resonance to enhance the signal of an immunoassay and enables the direct detection of low circulating levels of intact EV-associated prefibrillar Aβ. We prospectively collected blood plasma from 18 subjects across the AD spectrum who were amyloid-PET positive by PET imaging of amyloid deposition in the brain and 15 age-matched healthy subjects who were amyloid-PET negative. Using the APEX technology, we measured the EV-associated Aβ levels in all samples and correlated them to brain Aβ PET status.
Results: Direct APEX measurements of an EV-associated prefibrillar Aβ biomarker showed high correlation (AUC >0.85) with amyloid brain deposition as determined by PET imaging. The biomarker measurements also showed a PPV of 80% and an NPV of >80%. One limitation of this study was a small sample size. Future work will include evaluation of an expanded clinical cohort.
Conclusions: We have developed APEX platform that is capable of detecting low levels of circulating EV-associated prefibrillar Aβ biomarker in blood. With this, we have demonstrated that measurements of blood-based prefibrillar Aβ biomarker can accurately differentiate brain amyloid positivity determined by PET imaging in a second cohort.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0475 / #521

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CSF BIOMARKERS AND COGNITIVE TRAJECTORIES IN PATIENTS WITH ALZHEIMER'S DISEASE AND A HISTORY OF TRAUMATIC BRAIN INJURY

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Suzan Van Amerongen[1,2], Shreyasee Das[3,4], Julie Goossens[4], Dirk Jacobs[4], Bram Bongers[3], Yolande Pijnenburg[1,5], Eugeen Vanmechelen[4], Everard Vijverberg[1,2], Charlotte Teunissen[2,3], Inge Verberk[2,3]
[1]Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [2]Amsterdam Neuroscience, Neurodegeneration, Amsterdam, Netherlands, [3]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Laboratory Medicine, Neurochemistry Laboratory, Amsterdam, Netherlands, [4]AdX, Neurosciences, Gent, Belgium, [5]Neurodegeneration, Amsterdam Neuroscience, Amsterdam, Netherlands

Aims: Traumatic brain injury (TBI) is associated with increased risk of dementia, suggested of the Alzheimer's disease (AD) type. It remains unknown if AD pathophysiology is influenced by TBI history. Here, we investigate whether history of TBI modifies the biological characteristics or cognitive trajectories in AD.
Methods: We included 1:1 matched AD patients with TBI history (ADTBI+, n=110), or without (ADTBI-, n=110), with mild cognitive impairment (MCI) or dementia. Baseline CSF was measured for amyloid beta-42 (Aβ42), total-tau (Tau), phosphorylated tau-181 (PTau181), neurofilament light (NfL), synaptosomal associated protein-25 (SNAP25), neurogranin (Ng), neuronal pentraxin-2 (NPTX2) and glutamate receptor-4 (GluR4). Group differences in biomarkers were calculated. Longitudinal cognition was assessed with neuropsychological test batteries. Baseline cognitive performance and cognitive changes over time were assessed with linear mixed models for MMSE and four cognitive domains, measuring the effect of TBI history and the interaction with biomarker concentrations. Exploratory, ADTBI+ was stratified by number of years since latest TBI; ≤5 years (TBI≤5yrs) or >5 years (TBI>5yrs) and analyses were repeated.
Results: No differences in baseline CSF biomarker levels or cognitive performance were detected between ADTBI+ and ADTBI- patients (Table 1). There were also no differences in cognitive trajectories (Table 2). Combinations of TBI history and high levels of Ptau181 (B=-0.117, p=0.021) or Ng (B=-0.154, p=0.002) were associated with greater attention decline over time (Figure 1, Table 2). TBI≤5yrs had lower NPTX2 concentrations compared to TBI>5yrs (p=0.027), but not compared to ADTBI- patients (Figure

Table 1. Baseline characteristics of cohort

	ADTBI- (n=110)	ADTBI+ (n=110)	*p-value*
Demographics			
Age, mean ± SD	65.4 ± 5.9	65.7 ± 6.8	*N/A*
Sex, female N (%)	52 (47.3)	52 (47.3)	*N/A*
Education level, mean ± SD	4.8 ± 1.4	4.9 ± 1.3	*N/A*
ApoE4 Carrier, N (%)	69 (64.5)	69 (63.3)	*N/A*
Disease stage 'Dementia', N (%)	92 (84)	89 (81)	*N/A*
TBI Specifics			
≥ 2 TBI, N (%)	*N/A*	21 (19)	*N/A*
TBI with loss of consciousness, N (%)	*N/A*	54 (60)	*N/A*
Years since last TBI, mean ± SD	*N/A*	26.8 ± 21.9	*N/A*
Last TBI ≤5 years, N (%)	*N/A*	33 (33)	*N/A*
Cognition			
MMSE, mean ± SD	21.3 ± 4.6	21.4 ± 5.0	*0.763*
Memory Composite, mean ± SD	0.02 ± 0.84	0.10 ± 0.82	*0.486*
Attention Composite, mean ± SD	0.18 ± 0.67	0.06 ± 0.76	*0.214*
Executive Functioning Composite, mean ± SD	0.10 ± 0.77	0.07 ± 0.75	*0.806*
Language Composite, mean ± SD	0.11 ± 0.81	0.18 ± 0.67	*0.508*
CSF biomarker concentrations (pg/mL)			
Aβ42, mean ± SD	618.2 ± 175.1	617.0 ± 128.3	*0.956*
Tau, mean ± SD	719.4 ± 388.9	784.6 ± 420.1	*0.234*
PTau181, mean ± SD	91.9 ± 40.4	97.1 ± 39.1	*0.334*
NfL, mean ± SD	675.3 ± 403.2	758.7 ± 415.8	*0.090*
SNAP25, mean ± SD	47.2 ± 17.6	51.3 ± 23.1	*0.137*
Ng, mean ± SD	584.4 ± 390.5	568.9 ± 344.5	*0.757*
NPTX2, mean ± SD	361.9 ± 149.4	396.5 ± 190.6	*0.272*
GluR4, mean ± SD	1172.4 ± 634.9	1305.6 ± 928.9	*0.268*

Note. Data is presented as frequencies (N) with percentages (%) or means ± SD. Group differences for baseline cognition and biomarker concentrations were assessed using independent samples T-tests or Mann-Whitney U where appropriate.

2).

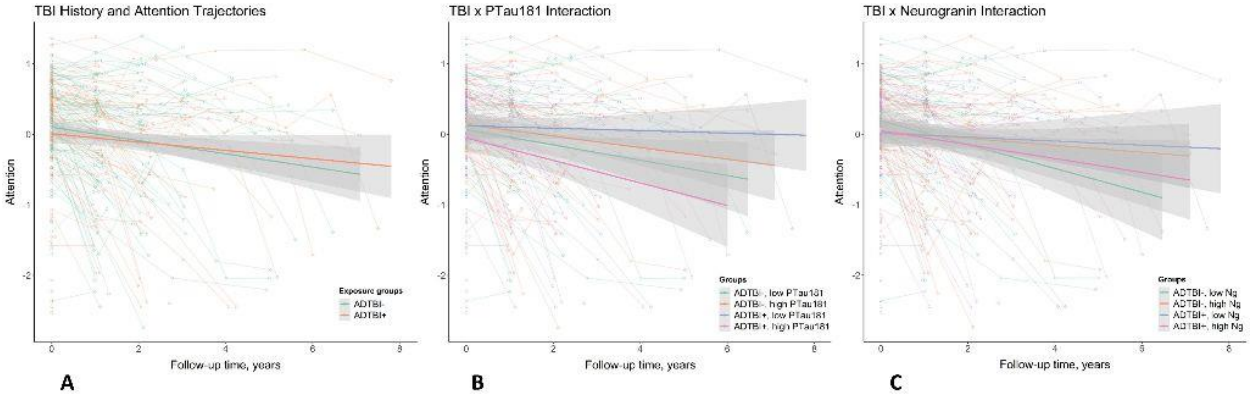
Table 2. Changes in cognitive test scores

	MMSE B (SE)	Memory B (SE)	Attention B (SE)	Executive Functioning B (SE)	Language B (SE)
TBI x Time	0.027 (0.039)	0.000 (0.046)	-0.060 (0.050)	-0.005 (0.041)	-0.034 (0.049)
TBI x Aβ42 x Time	-0.018 (0.043)	0.000 (0.056)	-0.082 (0.064)	-0.038 (0.048)	-0.025 (0.062)
TBI x Tau x Time	0.026 (0.040)	0.028 (0.046)	-0.088 (0.049)	-0.007 (0.038)	-0.009 (0.050)
TBI x PTau181 x Time	0.011 (0.041)	0.025 (0.046)	**-0.117 (0.049)***	-0.017 (0.040)	-0.016 (0.050)
TBI x NfL x Time	0.031 (0.039)	0.051 (0.051)	-0.003 (0.060)	0.032 (0.045)	-0.016 (0.051)
TBI x SNAP25 x Time	0.040 (0.043)	0.010 (0.051)	-0.097 (0.057)	-0.002 (0.044)	0.007 (0.055)
TBI x Ng x Time	0.000 (0.040)	-0.010 (0.050)	**-0.154 (0.050)****	-0.028 (0.044)	0.016 (0.053)
TBI x NPTX2 x Time	0.028 (0.038)	0.018 (0.043)	-0.092 (0.050)	-0.050 (0.043)	-0.022 (0.051)
TBI x GluR4 x Time	0.049 (0.045)	0.040 (0.064)	-0.095 (0.071)	-0.020 (0.062)	0.034 (0.073)

Note. Changes in MMSE and cognitive composite scores between AD patients with TBI history compared to AD patients without TBI history (Model: TBI x Time), as well as the interaction between TBI history and biomarker concentration (Model: TBI x biomarker x Time). Models included years of education as covariate. Data is presented with standardized beta (B) and standard errors (SE). * **p<0.05**, ** **p<0.01**

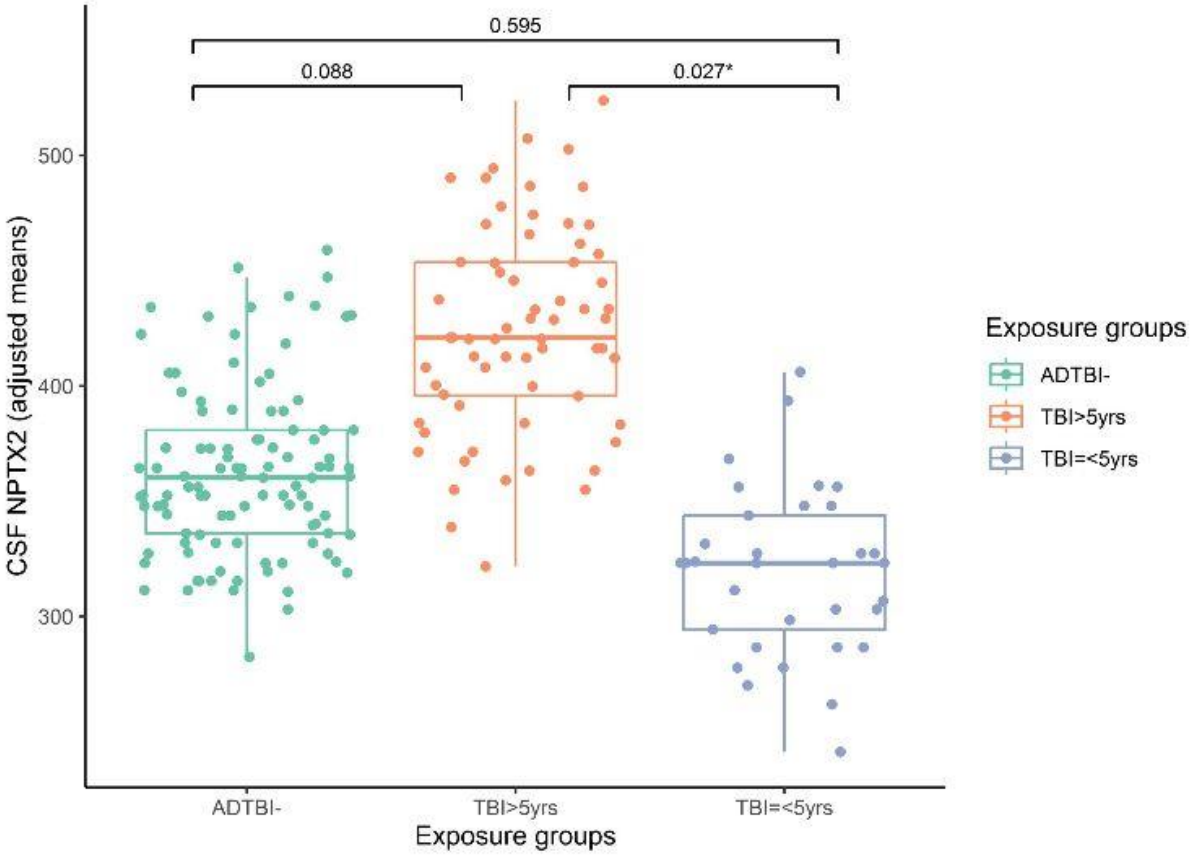
Conclusions: The link between TBI history and stronger attention decline in AD appeared to be dependent on more severe p-tau pathology and synaptic dysfunction. A recent TBI in AD patients was associated with different biological characteristics but not cognitive characteristics than a remote TBI.

Figure 1. Trajectories of Attention



Note. Attention decline over time visualized with spaghetti plots. Four groups were created by median splits of biomarkers concentrations. No differences in decline were seen between ADTBI- and ADTBI+ groups (Figure 1A), but the interaction between TBI and PTau181 (Figure 1B) or Neurogranin (Figure 1C) was significant..

Figure 2. Group differences in NPTX2 concentrations



Note. Differences in baseline NPTX2 concentrations in CSF among ADTBI-, TBI>5yrs, TBI≤5yrs groups. Group differences were assessed using analysis of covariance (ANCOVA), including covariates age, sex, and disease stage, and presented with adjusted means.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0476 / #1076

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ALTERATIONS OF HUMAN CSF AND SERUM-BASED MITOPHAGY BIOMARKERS: PATIENTS FROM CZECH BRAIN AGING STUDY (CBAS)

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Katerina Veverova, Alzbeta Katonova, Jan Laczó, Hana Horáková, Martina Laczó, Francesco Angelucci, Jakub Hort, Martin Vyhnálek
Second Faculty of Medicine, Charles University, Department Of Neurology, Prague, Czech Republic

Aims: Mitophagy impairment has been identified as an important pathophysiological hallmark of Alzheimer's disease (AD) in animal models, cell models, and brain biopsies of AD. However, whether these changes are reflected in the biofluids of individuals with AD and non-AD pathologies and whether these changes are associated with AD-related phenotypes remains unknown.
Methods: We evaluated levels of mitophagy markers (ULK1, PINK1, BNIP3L, TFEB) in cerebrospinal fluid and serum samples from 300 biomarker-defined individuals with AD, with frontotemporal lobar degeneration (FTLD) and cognitively unimpaired individuals (CU) from the Czech Brain Aging Study. Levels of mitophagy markers were correlated with biomarker, cognitive, and brain atrophy profiles.
Results: We identified increased levels of CSF PINK1 in AD dementia compared to MCI-AD (p<.001) and CU individuals (p<.001). Also, the levels of serum BNIP3L were higher in AD dementia compared to other groups (p=0.020). In contrast, serum TFEB levels were decreased compared to MCI-AD (p=0.033) and CU (p=0.040). In FTLD, there was a significant increase in CSF ULK1 and serum TFEB levels compared to AD (p**<.**05). Additionally, the CSF PINK1 levels correlated with AD biomarkers and cognition.
Conclusions: Our study highlights compromised mitophagy in the AD continuum reflected by increased levels of PINK1 and BNIP3L (mitophagy activators) and reduced levels of TFEB (a master regulator of lysosomal biogenesis) in biofluids of AD individuals, suggesting an impairment in the final stage of autophagy. We also found a significant increase in ULK1 and TFEB in FTLD compared to AD, suggesting a different role of mitophagy in the sub-type of neurocognitive disorders. Moreover, our data indicate that mitophagy impairment is associated with advanced AD pathology demonstrated by increased positivity of AD biomarkers, severity of ATN profile, and cognitive impairment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0477 / #1455

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

UNDERSTANDING THE IMPLICATIONS OF DYRK1A OVEREXPRESSION FOR ALZHEIMER'S DISEASE PATHOGENESIS IN PRECLINICAL MOUSE MODELS: A CROSS-SECTIONAL AND LONGITUDINAL STUDY

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Daniella Victorino, Idil Yuksekel, Domitille Des Robert, Jean Delabar, Marie-Claude Potier
Paris Brain Institute - ICM, Alzheimer And Prion's Diseases Team, Paris, France

Aims: Individuals with Down syndrome (DS) have an increased risk of early-onset Alzheimer's disease (AD) and dementia. The overexpression of the Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A (DYRK1A) gene, which is located on chromosome 21, has been hypothesized to play a role in this process. We showed that individuals with AD have decreased plasma levels of DYRK1A compared to controls, as well as DS individuals with dementia compared to those without dementia. However, it is not clear yet whether peripheral levels of DYRK1A are modulated by the progression of AD-related processes in the brain.
Methods: To address gaps in knowledge, we crossed AD mouse models with mice overexpressing DYRK1A, wherein wild-type mice, mice expressing either APP23 or P301S mutation only, mice overexpressing DYRK1A only, and mice that express either APP23 or P301S mutation and overexpression of DYRK1A have been studied.
Results: Starting at 5 months of age, mice carrying both APP23 and DYRK1A transgene show decreased body weight compared to those carrying only APP23 transgene. Similar findings were observed for mice carrying both P301S and DYRK1A transgene compared to those carrying only P301S transgene at 6 months of age. From 2 to 10 months of age, mice have been subjected to monthly plasma sampling for the longitudinal characterization of AD biomarkers by using SIMOA (undergoing analysis). Cross-sectional mouse cohorts at different ages will also be used to assess the association between plasma levels of AD biomarkers and AD-related neuropathology, as well as behavioral deficits by using several tasks (undergoing experiments).
Conclusions: A better understanding of AD pathogenesis is of paramount importance to accelerate biomarker discovery for early detection of AD in at-risk individuals and potential identification of pharmacological targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0478 / #2516

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA BD-TAU AS A SPECIFIC CORRELATE OF DISEASE SEVERITY AND DYNAMIC ACROSS THE ALZHEIMER'S DISEASE SPECTRUM

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Giuseppe Piga[1], Fernando Gonzalez-Ortiz[2], Idil Yuksekel[3], Marion Houot[3], Laura Gonzalez Uribe[1], Armelle Rametti Lacroux[3], Marc Teichmann[1], Stephanie Bombois[1], Isabelle Le Ber[1,3], Bruno Dubois[1,3], Richard Levy[1,3], Foudil Lamari[4], Kaj Blennow[3,5], Nicolas Villain[1,3]
[1]Hôpital Pitié-Salpêtrière, Département De Neurologie, Paris, France, [2]Gothenburg University, Psychiatry And Neurochemistry, Göteborg, Sweden, [3]Sorbonne Université, INSERM U1127, CNRS 7225, Paris Brain Institute - Icm, Paris, France, [4]AP-HP.Sorbonne Université, Dmu Biogem-metabolic Biochemistry Department, Neurometabolic And Neurodegenerative Unit - Hôpital Pitié-salpêtrière, Paris, France, [5]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

Aims: The identification of biomarkers for Alzheimer's disease (AD) remains a significant challenge, particularly for the clinical severity of the disease. Recent studies have shown that plasma brain-derived-tau (BD-Tau) could be a promising biomarker for the identification of AD-type neurodegeneration. This study aimed to investigate the potential of BD-Tau in differentiating various clinical stages of AD, ranging from cognitively unimpaired AD to severe dementia AD. Additionally, the study intended to examine the association of BD-Tau with clinical severity and elucidate its dynamic behavior throughout the natural course of AD.
Methods: Cross-sectional and longitudinal EDTA plasma data, along with clinical information, were utilized from the Pitié-Salpêtrière hospital INSIGHT (cognitively unimpaired individuals with amyloid PET) and SOCRATES cohorts (AD and non-AD symptomatic neurodegenerative disease according to up-to-date international criteria). Plasma BD-Tau was analyzed using the Gothenburg University homebrew Quanterix Simoa immunoassay.
Results: The results revealed that BD-Tau is only elevated in individuals with symptomatic AD, whether the primary or secondary neurodegenerative disease, and not in other neurodegenerative conditions. Additionally, BD-Tau follows the clinical dynamics of AD, as it is only elevated in symptomatic AD patients, while individuals with AD biological changes but no symptoms have normal levels of BD-Tau. BD-Tau levels were also found to be significantly correlated with episodic memory scores and global cognitive performance across a wide range of AD severity. Longitudinal analyses further support BD-Tau's potential as an AD-type neurodegeneration biomarker, as it was found to increase over time only in the symptomatic AD group and not in other groups.
Conclusions: These results support the notion that plasma BD-Tau could be a promising specific biomarker for AD staging, as it follows the AD clinical severity spectrum and is not elevated in asymptomatic amyloidosis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0479 / #256

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CSF ERBB4: A CANDIDATE FOR THE SYNAPTIC BIOMARKERS TOOLBOX IN ALZHEIMER'S DISEASE

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Agathe Vrillon[1], François Mouton-Liger[1], Elodie Bouaziz-Amar[1], Nicholas Ashton[2], Kaj Blennow[2], Henrik Zetterberg[2], Jacques Hugon[1], Claire Paquet[1]
[1]Inserm U1144, Therapeutical Optimization In Neuropsychopharmacology, Paris, France, [2]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: The expression of the post-synaptic tyrosin kinase receptor ErbB4 has been shown to be modified in the AD brain. The objective of our study was to explore CSF ErbB4 levels as a synaptic biomarker for AD.
Methods: This retrospective study included 206 patients with AD dementia (n=67), MCI related to AD (AD-MCI) (n=41), non-AD MCI (n=40), non-AD dementia (n=32), and neurological controls (n=26). CSF ErbB4 levels were measured using a commercial ELISA kit. We explored correlations with CSF core AD biomarkers, synaptic markers GAP-43 and neurogranin, and cognitive status evaluated with MMSE, as well as MMSE change over time for a subgroup of cases (n=139).
Results: CSF levels of ErbB4 were significantly increased in AD (mean: 1130 pg/mL, P=0.001) and AD-MCI (mean: 1122 pg/mL, P=0.002) versus neurological controls (mean: 843.7 pg/mL), after adjustment on age and sex. Amyloid positive patients displayed higher CSF ErbB4 levels than amyloid-negative patients (952.4 pg/mL versus 1127 pg/mL, P=0.004). CSF ErbB4 correlated with core AD biomarkers in the whole cohort (Aβ ratio: r=-0.297, p-tau: r=0.491, t-tau: r=0.520) and in the amyloid-positive patients (Aβ ratio: r=-0.241, p-tau: r=0.397, t-tau: r=0.432). CSF ErbB4 levels were associated with CSF GAP-43 and neurogranin levels (r=0.531 and r=0.340 respectively, P<0.001). In a subgroup of n=139 patients, higher CSF ErbB4 concentration at baseline associated with higher MMSE decline over time (P=0.082).
Conclusions: CSF ErbB4 levels were increased in AD and AD-MCI, and were associated with core AD biomarkers, CSF synaptic markers and cognitive decline. Thus, CSF ErbB4 could have potential for monitoring synaptic demise and cognitive status in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0480 / #2436

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

HERITABILITY OF PLASMA BIOMARKERS AND THEIR ASSOCIATIONS WITH ALZHEIMER DISEASE IN THE OLD ORDER AMISH

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ping Wang[1], Yeunjoo Song[1,2], Audrey Lynn[1,2], Kristy Miskimen[1], Michael Prough[3], Daniel Dorfsman[3,4], Renee Laux[1], Sarada Fuzzell[1], Sherri Hochstetler[1], Andrew Zaman[3], Larry Adams[3], Laura Caywood[3], Jason Clouse[3], Sharlene Herington[3], Patrice Whitehead[3], Yining Liu[5], Noel Moore[5], Leighanne Main[2,6], Paula Ogrocki[7,8], Alan Lerner[7,8], Anthony Griswold[3,4], Jeffery Vance[3,4], Michael Cuccaro[3,4], William Scott[3,4], Margaret Pericak-Vance[3,4], Jonathan Haines[1,2]
[1]Case Western Reserve University, Population And Quantitative Health Sciences, Cleveland, United States of America, [2]Case Western Reserve University, Cleveland Institute For Computational Biology, Cleveland, United States of America, [3]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [4]University of Miami Miller School of Medicine, The Dr. John T. Macdonald Foundation Department Of Human Genetics, Miami, United States of America, [5]Case Western Reserve University, Department Of Nutrition, Cleveland, United States of America, [6]Case Western Reserve University, Genetics And Genome Sciences, Cleveland, United States of America, [7]University Hospitals Cleveland Medical Center, Neurology, Cleveland, United States of America, [8]Case Western Reserve University, Neurology, Cleveland, United States of America

Aims: This study aims to examine the heritability of core AD plasma biomarkers in the Old Order Amish, including the 42- and 40-residue forms of amyloid beta (Aβ40, Aβ42), Aβ42/Aβ40, total tau (tTau), and phosphorylated tau 181 (pTau181), and the association of these plasma biomarkers with AD in the Old Order Amish.
Methods: Plasma biomarker concentrations were measured for 1,169 Old Order Amish individuals from Ohio and Indiana using Simoa™ Neuro-3Plex, 4Plex, and pTau181 Advantage V2 assays. Logistic regression was applied to model each plasma biomarker's effect on AD phenotype, adjusting for study center, age, sex, and APOE4 allele count. Controlling for the same covariates and diagnosis, a variance component model was used to calculate pedigree-based heritability. SNP-based heritability was estimated by QuantHer using individual-level genotype data with covariates as above.
Results: Compared to unimpaired individuals, individuals with AD had lower plasma Aβ42 (6.5 ± 3.8 pg/mL, $p = 0.014$) and higher plasma pTau181 levels (2.3 ± 1.3 pg/mL, $p = 0.01$). In multivariate regression models, decreasing plasma Aβ42 (OR = 0.52, $p < 0.001$) and increasing pTau181 (OR = 1.86, $p = 0.001$) were associated with AD risk. Pedigree-based heritability estimates were: Aβ40 = 23.2%, Aβ42 = 26.2%, Aβ42/40 = 20.8%, tTau = 5.7%, pTau181 = 29.3%. The SNP-based approach yielded lower heritability for all biomarkers (Aβ40 = 16.4%, Aβ42 = 12.5%, Aβ42/40 = 7.4%, tTau = 2.4%, pTau181 = 19.4%).
Conclusions: Plasma Aβ42 and pTau181 are associated with the risk of AD in the Old Order Amish. We found plasma biomarkers are highly heritable and may serve as surrogate markers of AD pathology to study the genetics of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0481 / #225

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

TARGETED MASS SPECTROMETRY ASSAY FOR STAGING AND PREDICTING PROGRESSION OF ALZHEIMER'S DISEASE USING A NOVEL CEREBROSPINAL FLUID PROTEIN PANEL

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Caroline Watson[1], Eric Dammer[1], Rafi Haque[1], Jiaqi Liu[1], E. Carter[2], Duc Duong[2], Aliza Wingo[3], Thomas Wingo[1], Erik Johnson[1], Andrew Saykin[4], Leslie Shaw[5], Blaine Roberts[2], James Lah[1], Allan Levey[1], Nicholas Seyfried[1,2]
[1]Emory University School of Medicine, Neurology, Atlanta, United States of America, [2]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [3]Emory University School of Medicine, Department Of Psychiatry, Atlanta, United States of America, [4]Indiana University School of Medicine, Radiology And Imaging Sciences, Indianapolis, United States of America, [5]University of Pennsylvania, Pathology And Laboratory Medicine, Philadelphia, United States of America

Aims: To demonstrate the utility of selected reaction monitoring mass spectrometry (SRM-MS) for clinical assessment of cerebrospinal fluid (CSF) proteins reflective of Alzheimer's disease (AD).
Methods: We developed an SRM-MS method with isotopically labeled standards for relative protein quantification in CSF to find protein biomarkers that are robustly measured and related to AD. Two pools of CSF were generated based on Amyloid-Beta and Tau immunoassay levels to create AD-positive and AD-negative quality control (QC) standards. The QC pools were processed and analyzed identically to the CSF clinical samples reported. CSF samples from two separate cohorts, Emory Goizueta ADRC and affiliated Emory Healthy Brain Study (EHBS; 133 controls, 127 asymptomatic AD, 130 symptomatic AD) and Alzheimer's Disease Neuroimaging Initiative (ADNI; N=706), were analyzed using SRM-MS to examine the clinical utility of targeting a novel CSF protein panel.
Results: We found approximately 50 proteins in each cohort that were precisely measured (coefficient of variation <20%). The EHBS cohort was used to determine which proteins could distinguish CSF biomarker positivity (SMOC1, GDA, 14-3-3 proteins, glycolysis-involved proteins) and cognitive impairment (neuronal proteins; VGF, NPTX2, NPTXR, SCG2). Utilizing the power of ADNI as a longitudinal study, we found that the SRM biomarker proteins could independently predict Amyloid-Beta and Tau status, and disease state with 97% and 94% accuracy, respectively. Furthermore, by combining Amyloid-Beta, Tau, and SRM biomarkers, we improve the prediction accuracy for cognition, disease severity, and neurodegeneration compared to either measure alone.
Conclusions: We demonstrate the ability to use high-throughput, targeted MS to quantify CSF proteins as different stages of AD and show the targeted CSF protein panel complements existing AD CSF biomarkers to significantly improve diagnosis and predict future cognitive decline and dementia severity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0482 / #2557

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

SHORT AB(1-38) PEPTIDES ARE ASSOCIATED WITH DISEASE PROGRESSION IN AD: LONGITUDINAL DATA FROM THE DELCODE COHORT

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Luisa Schneider[1], Louise Droste Zu Senden[1], Michael Wagner[2], Jens Wiltfang[3], Frank Jessen[4,5], Annika Spottke[5], Robert Perneczky[6], Stefan Teipel[7], Michael Heneka[8], Josef Priller[9], Anja Schneider[10], Katharina Buerger[11], Matthias Schmid[2], Oliver Peters[1]
[1]Charité—Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Psychiatry And Neurosciences, Berlin, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Neuropsychology, Bonn, Germany, [3]University Medical Center Göttingen, Psychiatry And Psychotherapy, Göttingen, Germany, [4]University Hospital of Cologne, Department For Neurology And Psychiatry, Köln, Germany, [5]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Clinical Dementia Research, Bonn, Germany, [6]German Center for Neurodegenerative Diseases (DZNE), Dzne, Munich, Germany, [7]Deutsches Zentrum für Neurodegenerative Erkrankungen, Deutsches Zentrum Für Neurodegenerative Erkrankungen, Rostock, Germany, [8]Université du Luxembourg, Lcsb, Belvaux, Luxembourg, [9]German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany, Department Of Psychiatry And Psychotherapy, Berlin, Germany, [10]German Center for Neurodegenerative Diseases (DZNE), Translational Dementia, Bonn, Germany, [11]German Center for Neurodegenerative Diseases (DZNE, Munich), Stroke Research, Munich, Germany

Aims: Short amyloid beta (Aβ) peptides such as Aβ(1-38) appear to be less neurotoxic in Alzheimer's disease (AD), and may counteract AD neuropathology. However, their effect on AD pathophysiology and disease progression in humans in vivo remains unclear. We investigated whether higher baseline concentrations of CSF Aβ(1-38) compared to Aβ(1-40), Aβ(1-42) and pTau181 are associated with slower cognitive decline and lower risk of conversion to AD dementia within six years.
Methods: 177 participants from the longitudinal, multicenter German DELCODE study with a pathological CSF Aβ42/pTau181 ratio (> 9.68) at baseline were included. Conversion to AD dementia was assessed with the CDR and NINCDS-ARDA criteria and analysed using Cox regression. Cognitive performance was assessed annually for six years with the MMSE and the PACC5. Data on cognitive performance were analysed using model fitting procedures for mixed linear regression (MLR) models, i.e., Likelihood Ratio (LR) testing.
Results: MLR analyses yielded that higher Aβ(1-38) baseline levels were associated with higher PACC scores after three years ($p = .009$) and higher MMSE scores after five years ($p = .003$). Cox regression showed a reduced AD dementia conversion risk ($HR = 0.12$, $p = .037$) for those with higher Aβ(1-38) baseline levels within six years.
Conclusions: Across the AD spectrum, higher Aβ(1-38) levels are associated with slower cognitive decline. This could inform individual risk prediction in memory clinic patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0483 / #1292

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DIRECT COMPARISON OF THE DIAGNOSTIC PERFORMANCE OF PLASMA P-TAU SPECIES MEASURED BY MASS SPECTROMETRY AND SIMOA PLATFORMS

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Yara Yakoub[1], Laia Montoliu-Gaya[2], Nicholas Ashton[2,3,4], Andréa L. Benedet[2], Joseph Therriault[5], Nesrine Rahmouni[5], Stijn Servaes[5], Jenna Stevenson[5], Johan Gobom[2], Henrik Zetterberg[2,6,7,8], Sylvia Villeneuve[1,9], Kaj Blennow[2], Pedro Rosa-Neto[5,9]
[1]Douglas Mental Health University Institute, Centre For Studies On The Prevention Of Alzheimer's Disease (stop-ad), Montreal, Canada, [2]Department of Psychiatry and Neurochemistry, Institute Of Neuroscience & Physiology, University Of Gothenburg, Göteborg, Sweden, [3]Stavanger University Hospital, Centre For Age-related Medicine, Stavanger, Norway, [4]NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia, South London And Maudsley Nhs Foundation, London, United Kingdom, [5]Translational Neuroimaging Laboratory, Mcgill Research Centre For Studies In Aging, Montreal, Canada, [6]UCL Queen Square Institute of Neurology, Department Of Neurodegenerative Disease, London, United Kingdom, [7]School of Medicine and Public Health, Uw Department Of Medicine, Madison, United States of America, [8]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [9]McGill University, Montreal Neurological Institute, Montreal, Canada

Aims: A large body of research has elucidated the potential utility of blood-based biomarkers in Alzheimer's disease (AD). Some studies have investigated the performance of various plasma pTau isoforms utilizing different assays on the Simoa or mass spectrometry (MS) platforms, but only few studies evaluated the performance of both techniques across various tau species. Our aim was to compare the performance of different tau species, measured by both MS and Simoa, in predicting Aβ and tau-PET pathologies
Methods: We included 44 older participants from the TRIAD cohort who underwent Aβ- and tau-PET imaging as well as plasma measurements. We performed receiver operating characteristic curve analyses followed by DeLong test to compare the performance of various p-tau species, including the accuracy of the ratio phosphorylated/non-phosphorylated peptides for p-tau217 and p-tau205, in distinguishing Aβ -and tau-PET positivity
Results: Pearson correlation analyses revealed strong correlations across plasma p-tau231(r = 0.679), p-tau181 (r = 0.637), and p-tau217 (r = 0.587) between Simoa and MS platforms. Plasma p-tau217/non-p-tau (with non-p-tau refers to non-phosphorylated form of the same tau peptide; tau212-221) exhibited the highest AUC, surpassing plasma p-tau217 alone measured through either assay. This marker demonstrated superior performance in predicting Aβ (AUC = 0.955), and tau-PET (AUC = 0.945). Among markers measured using both immunoassays (p-tau181, p-tau231, and p-tau217), there were no significant differences in AUC values, indicating comparable performance between both assays. We also assessed plasma p-tau205, a marker believed to increase along the AD continuum, and found no such differences when using Aβ or tau-PET as outcomes.
Conclusions: Plasma p-tau217/non-p-tau ratio showed a slightly superior performance in predicting AD-related pathologies, as compared with p-tau217 alone, followed by plasma p-tau217 that exhibited comparable accuracy on both Simoa and MS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0484 / #1530

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

TIME COURSE OF NEUROFILAMENT-LIGHT CHAIN PROGRESSION IN MURINE MODELS OF NEURODEGENERATIVE AND RARE DISEASES

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Tina Loeffler, Magdalena Daurer, Livia Breznik, Roland Rabl, Stefanie Flunkert, Manuela Prokesch
QPS Austria GmbH, Neuropharmacology, Grambach, Austria

Aims: As an amyotrophic lateral sclerosis (ALS) biomarker, NF-L levels can forecast the conversion from presymptomatic to symptomatic stage and time of survival by analyzing patients CSF or plasma. Recently, first drugs were approved relying on changes in peripheral NF-L levels as primary read-out. Additionally, NF-L can act as translational marker, being a valuable tool in preclinical mouse models of ALS, Alzheimer's (AD), and Parkinson's disease (PD) as well as lysosomal storage diseases. However, a detailed time course analyses of NF-L progression in these mouse models in relation to other disease-relevant markers are still missing.
Methods: We first focused on the analysis of NF-L levels in the plasma and CSF of the ALS mouse model SOD1-G93A low expressor as well as SOD1-G93A high expressor mice bred on a C57BL/6 background at various time points and correlated data with other disease-relevant read-outs such as motor deficits or oxidative stress. Furthermore, also plasma and CSF of the 5xFAD AD model, the Line 61 PD model and the Gaucher disease model 4L/PS-NA was assessed for NF-L at various ages using commercially available ELISA kits, including those from UmanDiagnostics.
Results: NF-L levels are highly increased in the plasma of ALS, AD and Gaucher disease mouse models, while NF-L plasma levels barely changed in the analyzed PD model. Most of the analyzed models show a progressive increase of NF-L levels with age.
Conclusions: NF-L measurements in mouse models of ALS and AD are thus a good tool to evaluate disease progression. Compared to results in human tissues our results suggest that murine NF-L levels and their progression have a high translation value. Furthermore, our data indicate that NF-L might be a good biomarker for diseases with a neuronal component.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0485 / #1568

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

EXPLORING ELECTROENCEPHALOGRAPHIC (EEG) CONNECTIVITY CHANGES IN HEALTHY AGING AND ALZHEIMER'S DISEASE

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Ángel Blanco[1], Ioannis Kompatsiaris[2], Spiros Nikolopoulos[2], Ioulietta Lazarou[2], Kostas Georgiadis[2], Vangelis Oikonomou[2], Anthoula Tsolaki[3], Magda Tsolaki[2], Víctor Fernández[1], Claire Braboszcz[1], Aureli Soria-Frisch[1]
[1]STARLAB BARCELONA S.L., Neuroscience Business Unit, Barcelona, Spain, [2]ITI, Center For Research And Technology Hellas, Thessaloniki, Greece, [3]Greek Association of Alzheimer's Disease and Related Disorders, Gaadr, Thessaloniki, Greece

Aims: The preclinical phase of AD is characterized by a non-linear evolution of brain connectivity. Our study aimed to investigate alterations in connectivity measures within EEG activity during the process of healthy aging and to understand the connectivity alterations linked to Alzheimer's disease (AD).
Methods: We conducted this exploratory analysis using two different data sets, where we applied Phase-locking value and Magnitude-Square Coherence analysis to resting-state EEG data. The first data set denoted as LEMON dataset (N=162) included participants aged between 20 and 80 years with no disease diagnosis. Furthermore, we applied the same analysis on resting-state EEG recordings (N=220) from individuals aged 60 years and older, categorized into healthy, subjective cognitive decline, mild cognitive impairment, and those diagnosed with AD.
Results: It was observed that healthy aging was linked to heightened connectivity in the Delta and Theta bands, along with diminished connectivity in the Alpha band. On the contrary, individuals with AD exhibited more substantial increases in connectivity across all three bands—Delta, Theta, and Alpha—compared to their cognitively healthy counterparts. Individuals with Mild Cognitive Impairment (MCI) displayed more pronounced increases in connectivity within the Delta and Theta bands than healthy controls, whereas those with subjective cognitive decline shew heightened connectivity only in the Theta band.
Conclusions: These findings collectively suggest the potential of the analyzed connectivity metrics for differentiating among various stages of the disease. Its non-linear nature presents a challenging but exciting opportunity for a more comprehensive characterization of disease progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0486 / #2348

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

EEG BASED CLASSIFICATIONS OF ALZHEIMER'S DISEASE BY USING MACHINE LEARNING TECHNIQUES

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Nagarathna C R[1], Kusuma M[2]
[1]BNM Institute of technology, Ai And Ml, Bangalore, India, [2]Dsatm, Ise, Bangalore, India

Aims: Using EEG analysis is contemporary even today to identify the characteristics of brain functioning illnesses, although it is unclear how these characteristics relate to AD. EEG provides non-invasive, cost-effective data with great temporal precision on electrical activity in the brain during neurotransmission as compared to other imaging modalities. Using a DWT to decompose the EEG signal into its frequency sub-bands and by extracting a set of statistical features to represent the distribution of wavelet coefficients, the proposed framework undertook the processing and analysis of EEG. Data dimension reduction techniques comprises of PCA and independent components analysis (ICA). Following this, these attributes were sent into MLP and a SVM that could only produce one of the two outcomes: AD or NC. To demonstrate the superiority of the classification process, there was a need to demonstrate and compare the performance of the process based on various approaches. These results serve as an illustration of how to train and test an AD prediction system using data from specific petit mal epileptic patients. Given the diversity of epilepsy, it is likely that these kinds of technologies are crucial to tailor intelligent devices for treating epilepsy to each person's neurophysiology before practically adopting them
Methods: First pre-process the input EEG signals and use the PCA, ICA and DWT approaches to extract the latent components from the pre-processed signals. Next, the model is trained using more extracted features. Last of all, evaluate the model using the test dataset.
Results:

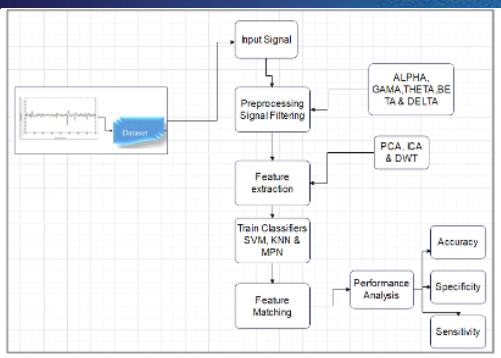


Fig 1 Proposed Model for AD prediction

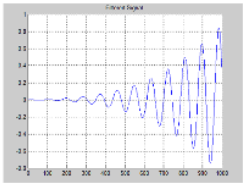


Fig 5 Filtered Signal

The suggested EEG-based AD detection model is depicted in Fig 1.

Conclusions: The proposed model is experimented with SVM, KNN and MLP, among these KNN shows good performance by giving an accuracy of 95%.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0487 / #1925

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

RELEVANCE OF SUBCLINICAL EPILEPTIFORM ACTIVITY IN CLINICALLY HEALTHY ELDERLY POPULATION

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Emoke Anna Csernus[1], Gergő Bolla[2], Viktória Rosenfeld[3], Anita Kamondi[3], Andras Horvath[3]
[1]National Institute of Mental Health, Neurology, Neurosurgery, Neurocognitive Research Center, Budapest, Hungary, [2]Semmelweis University, School Of Phd Studies, Budapest, Hungary, [3]National Institute of Mental Health, Neurology and Neurosurgery, Neurocognitive Research Center, Budapest, Hungary

Aims: Subclinical epileptiform activity (SEA) has been considered of benign etiology and an EEG variant in elderly population. However, epileptiform activity has been associated with decreased cognitive performance, and is a proven marker of progression in Alzheimer's disease. We investigated the relevance of SEA in clinically healthy elderly population with regard to neuropsychological performance and structural neuroimaging.
Methods: We studied 62 elderly subjects determined as healthy based on physical, neuropsychology, neuroimaging(MRI), and serological workup. All subjects underwent 24-h Holter electroencephalography (EEG), visual analysis was conducted by two independent raters. Subjects were classified into EEG positive (EEG+) and negative (EEG-) groups based on detecting epileptiform activity on their EEG. Neuropsychology battery and structural MRI results were compared between the groups.
Results: EEG analysis showed epileptiform activity in 26% of cases. 87% of subjects in the EEG+ group were women (p 0,03). EEG positivity was associated with significantly lower verbal and category fluency subscores on Addenbrook Cognitive Examination (p 0,03 and 0,01). This group also performed worse on both Trail Making A and B Test (p 0,02 and 0,003 respectively). Age and education had a significant effect on neuropsychological performance in both groups. Structural MR analysis showed significant group differences in various areas, particularly in the parietotemporal regions (p 0,001). Interestingly, EEG+ patients had larger temporal brain volume bilaterally (<0,001).
Conclusions: Presence of subclinical epileptiform activity among healthy elderly shows a discrete but significant association with decreased cognitive performance in certain subdomains, as well as bilateral increased brain volume in several temporal areas. Our results underscore the relevance of data suggesting presence of a hippocampal sparing phenotype in Alzheimer's disease and its potential connection to epileptiform activity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0488 / #1563

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

DETECTING COGNITIVE DECLINE IN ELDERLY: AN EEG COMPLEXITY MARKER EVALUATION ON HIGH-DENSITY EEG

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Víctor Fernández[1], Eleni Kroupi[1], Claire Braboszcz[1], Ioannis Kompatsiaris[2], Spiros Nikolopoulos[2], Ioulietta Lazarou[2], Kostas Georgiadis[2], Vangelis Oikonomou[2], Anthoula Tsolaki[3], Magdalini Tsolaki[4], Aureli Soria-Frisch[1]
[1]Starlab Barcelona S.L., Neuroscience, Barcelona, Spain, [2]ITI, Center For Research And Technology Hellas, Thessaloniki, Greece, [3]Greek Association of Alzheimer's Disease and Related Disorders, Gaadr, Thessaloniki, Greece, [4]Aristotle University of Thessaloniki (AUTh), Greek Association Of Alzheimer's Disease And Related Disorders (gaadrd), Thessaloniki, Makedonia, Hellas. 1st Department Of Neurology, School Of Medicine, Macedonia, Greece

Aims: To evaluate the efficacy of electroencephalographic (EEG) complexity markers, namely Higuchi Fractal Dimension (HFD), Waveform Complexity (Cw), Permutation Entropy (PE), Lempel Ziv Welch (LZW) and Weighted Symbolic Mutual Information (wSMI), for cognitive decline detection in the CERTH-GAADRD High-Density EEG Database, which include subjects at different neurodegenerative stages (N=220).
Methods: The validation dataset includes distinct groups of individuals: healthy controls (HC), subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Alzheimer's disease (AD) patients. First, EEG signals were averaged over various cerebral areas. Complexity markers were then computed on this averaged data and the outliers were eliminated using the Tukey method. Lastly, the discrimination capability of the complexity markers among the groups was statistically analyzed.
Results: revealed consistent patterns across several complexity markers. HFD, Cw, and PE markers showed potential to differentiate between various stages of cognitive decline. These markers excelled statistically in the middle-posterior brain region, unlike LZW and wSMI which did not provide statistical significance.
Conclusions: EEG complexity markers, specifically HFD, Cw, and PE, provide discriminatory power in cognitive decline progression. These markers present a nonlinear evolution with respect to the pathological stage. This behavior is analogous to that observed in other EEG markers, such as connectivity ones.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0489 / #429

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

MEG MEASURED CENTRALITY ALTERATIONS ASSOCIATED WITH ALZHEIMER'S DISEASE PATHOLOGY IN HEALTHY INDIVIDUALS

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Alejandra García Colomo[1], David López Sanz[1], Ignacio Taguas[1], Martín Carrasco[2], Alberto Nebreda[1], Fernando Maestú[1]
[1]Universidad Complutense de Madrid, Psicología Experimental, Procesos Cognitivos Y Logopedia, Pozuelo de Alarcón, Spain, [2]Universidad Politécnica de Madrid, Department Of Electronic Engineering, Madrid, Spain

Aims: The preclinical stage of Alzheimer's disease (AD) has gained attention for the window of opportunity it opens for early detection and intervention. However, classically used techniques to measure alterations, such as PET and CSF punctures are too invasive to be good candidates for early detection and disease tracking. In this line, electrophysiology and plasma biomarkers show great promise. The aim of this study is twofold. First, to address the relationship between a compound centrality score (CS; i.e., a measure of the relevance of a region within the network) and plasma pathology markers of AD in unimpaired individuals with elevated neurofilament-light chain (NfL) and phosphorylated tau 231 (p-tau231). Lastly, to evaluate whether this association is greater in hubs.
Methods: 33 individuals with available MEG recordings and over-the-median plasma NfL and p-tau231 levels were included. A compound CS for each 1210 brain sources of every subject was calculated combining node strength, betweenness centrality and eigenvector centrality. Spearman correlations were carried out to address the association between each node's CS and plasma biomarkers. Next, to test whether greater associations were found in hubs (i.e., highly central sources) a correlation between the obtained rho and the grand-average of the CS was carried out.
Results: Increasing concentrations of p-tau231 were associated with greater relevance of posterior areas through their theta oscillations and lower relevance of left areas through their gamma oscillations. The most relevant areas are also the ones that present the greatest association between their CS and p-tau231.
Conclusions: The results of this pioneering study are consistent with previous literature and demonstrate early alterations in network communication associated to elevated plasma biomarkers in cognitively unimpaired individuals, particularly in vulnerable areas to AD pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0490 / #810

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

AN APPLE A DAY KEEPS ALZHEIMER'S DISEASE AWAY

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Alejandra García Colomo[1], Alfredo Trabado-Fernández[2], María Dolores Salas-González[2], Ana Lorenzo-Mora[2], África Peral-Suárez[2], Ester Cuadrado-Soto[2], Aranzazu Aparicio[2], Ana López Sobaler[2], Fernando Maestú[1]
[1]Universidad Complutense de Madrid, Psicología Experimental, Procesos Cognitivos Y Logopedia, Pozuelo de Alarcón, Spain, [2]Universidad Complutense de Madrid, Departamento De Nutrición Y Ciencia De Los Alimentos, Madrid, Spain

Aims: Cognitively unimpaired relatives of Alzheimer's disease (AD) patients are a key population to study the early changes associated with the disease due to the compound risk factors they present. On a related note, lifestyle factors such as nutritional patterns, are being addressed for their interventional potential to change the course of the disease. Despite the broad knowledge of the cardiovascular and brain benefits from adhering to a Mediterranean diet (MeD), no studies have addressed the relationship between this dietary pattern and electrophysiological activity. The aim of this study is to evaluate this relationship within regions of the default mode network (DMN), classically affected in AD, in unimpaired relatives of AD patients and controls.
Methods: 147 individuals with a family history of AD (FH+) and 80 controls (FH-) completed a thorough nutritional questionnaire and a magnetoencephalography recording. The odds ratio of having high or low alpha relative power in relation to the adherence to a MeD was calculated.
Results: High adherence to MeD was associated with high relative power of alpha in the precuneus, inferior parietal lobe and hippocampus in the whole sample. FH- presented an additional benefit from adhering to this diet, while FH+ only showed this association when considering other risk factors such as hypertension or smoking.
Conclusions: The DMN and activity in the alpha frequency range have been extensively studied and are known to be altered from the earliest stages of the AD continuum. The positive relationship observed between the activity of this regions with a good adherence to a MeD could indicate a protective effect of this dietary pattern. Future studies should evaluate further which components of this diet contribute the most to this positive association.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0491 / #924

Poster Topic: *Theme A: β-Amyloid Diseases / A04.g. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

IMPLICATION OF DIABETES MELLITUS IN DEMENTIA A LONGITUDINAL ANALYSIS WITH PLASMA BIOMARKERS IN NEUROPATHOLOGICALLY CONFIRMED PATIENTS.

POSTERS: A04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Maria Ascensión Zea-Sevilla[1], Elisabeth Lucia Valeriano-Lorenzo[2], Belen Frades[3], Meritxell Valenti[4], Alicia Ruiz[5], Andrea Ruiz[6], Ana Pastor[4], Teodoro Del Ser[7], Alberto Rábano[8], Francisco Javier Lopez[9], Pascual Sanchez-Juan[10]
[1]Alzheimer's Centre Reina Sofia Foundation. CIEN Foundation. ISCIII, Clinical Evaluation Platform, Madrid, Spain, [2]Alzheimer's Centre Reina Sofia Foundation. CIEN Foundation. ISCIII., Clinical Evaluation Platform, Madrid, Spain, [3]Alzheimer's Centre Reina Sofia Foundation. CIEN Foundation. ISCIII. ., Clinical Evaluation Platform, Madrid, Spain, [4]Alzheimer's Centre Reina Sofia Foundation. CIEN Foundation. ISCIII, Biomarkers/biochemestry Laboratory And Molecular Genetic., Madrid, Spain, [5]Alzheimer's Centre Reina Sofia Foundation-CIEN Foundation-ISCIII. ., Biomarkers/biochemestry Laboratory And Molecular Genetic., Madrid, Spain, [6]Alzheimer's Centre Reina Sofia Foundation. CIEN Foundation. ISCIII, Biomarkers/biochemestry Laboratory And Molecular Genetic, Madrid, Spain, [7]Alzheimer's Centre Reina Sofia Foundation-CIEN Foundation-ISCIII. ., Clinical Evaluation Platform., Madrid, Spain, [8]Alzheimer's Centre Reina Sofia. CIEN Foundation. ISCIII, Biobank, Madrid, Spain, [9]Alzheimer's Centre Reina Sofia Foundation. CIEN Foundation. ISCIII., Data Manager Department, Madrid, Spain, [10]Alzheimer's Centre Reina Sofia. CIEN Foundation. ISCIII, Scientific Director, Madrid, Spain

Aims: Diabetes mellitus (DM-T2) and Alzheimer's disease (AD) are highly prevalent diseases in elderly and although they have apparently different pathological characteristics.Fluid biomarkers have become potential diagnostic and prognostic tools for neurodegenerative diseases.The aim of this study is to investigate the longitudinal trajectory of 6 blood biomarkers of neurodegenerative disease in patients with AD and DM-T2.
Methods: Cognitive-behavioral variables and blood biomarkers were obtained from 147 dementia patients (80.3% women, 23.6% DM-T2 group, mean age 83.6 ±6.4),residents of the Queen Sofia Foundation Alzheimer Centre and brain donors to the CIEN Foundation Tissue Bank.Patients were followed up during an average of 4.3±3.1 years, and 78% had a main pathological diagnosis of AD.The serum concentrations of GFAP, Nfl, AB40, AB42, tauTotal,and ptau181 were measured using SIMOA technology (Quanterix SR-X) in three timepoints (baseline, intermediate, and last visit before death). The rate of change of each biomarker over time was analysed using linear mixed-effects models (LMM).
Results: The mean survival time of the disease was higher for diabetic patients compared with non-diabetics (DM-T2=9.79; non-DM =12.63; p<0.001). Basal GFAP serum levels were similar in both groups (B=0.002; p=0.985) and the rate of change was significantly higher in subjects with DM-T2 compared to the non-DM (B=0.255; p= 0.048).Serum Nfl levels were similar in both groups (B=0.04; p=0.539), but the rate of change differs from the non-DM to the DM group (B=0.14; p=0.045).
Conclusions: Diabetic patients with dementia show a more aggressive course, with a shorter disease duration and a higher rate of increase in the neurodegenerative marker NfL.Additionally, astrocytic activation, measured by serum GFAP, seems to increase more steeply in diabetic dementia patients during the follow-up period,suggesting a higher inflammatory component in them.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0492 / #2442

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

BRAIN-AGE PREDICTION AS A TRANSDIAGNOSTIC MARKER FOR NEURODEGENERATION

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Gabriel Gonzalez-Escamilla
University Medical Centre, Johannes Gutenberg University Mainz, Department Of Neurology, Mainz, Germany

Aims: N**euroimaging-derived brain-age prediction is increasingly used for the evaluation of brain diseases. We aim to evaluate the set of MRI-derived morphometric variables that maximizes the differences in age prediction accuracy across various neurodegenerative disorders.**
Methods: Brain T1-weighted 3T MRI of participants aged 40-90 years were collected from various databases and preprocessed using FreeSurfer v6 to derive cortical thickness (CT), surface area, cortical volume, and subcortical volume (SubVol). Brains' age was predicted for each morphometric measure by training a support vector regression on healthy participants (HC; n = 816), randomly divided into "training set" (80%) and "test set" (20%). The validation cohorts comprised neurodegenerative patient cohorts within the same age range, particularly patients with advanced Parkinson's disease (aPD; n=66), frontotemporal degeneration (FLD; n=218), Alzheimer's disease (AD; n=85), and late-onset multiple sclerosis (loMS; n=145). Age predictions were evaluated using the coefficient of determination (R^2) computed after cross-validation. Additionally, associations between individual deviations in predicted age (delta-age) and relevant clinical test scores (e.g., disability status and cognition) were evaluated.
Results: Age-prediction accuracy in HC was best using a combination of CT and SubVol (R^2=0.74). In these settings, validation accuracy was lowest in AD, followed by FTD, loMS, and aPD. The delta-age was similar between aPD and AD, while marked differences arose with FTD and loMS. Higher predicted ages associated with worse cognitive functioning in all groups.
Conclusions: Overall, morbidity was associated with elderly appearing brains regardless of the disorder, indicating great utility of MRI-derived morphometric patterns to identify premature brain aging. Comparison of age prediction across diseases may enhance our ability to recognize increased vulnerability and early disease stages, as well as shed light on the disease-specific patterns of neuropathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0493 / #2916

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

THE RATIONALE FOR USING EEG WITH ASSOCIATIVE MEMORY TASKS FOR THE EARLY DETECTION OF ALZHEIMER'S DISEASE.

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Richard Jagger
University of Bolton, Psychology, Bolton, United Kingdom

Aims: Objectives In the asymptomatic stages of Alzheimer's disease there is a progressive pathology within areas of the larger 'episodic memory network'. The lack of symptoms has been postulated to be due to compensatory activity within the prefrontal cortex. EEG can measure prefrontal cortical activity precisely and is non-invasive. As associative memory tasks can be easily manipulated in terms of task difficulty, hypothetically greater input (compensatory) from prefrontal cortical areas due to decreases in the entorhinal cortex signal strength, should be observed.
Methods: Task based approaches have been less forthcoming than so called 'resting state' investigations. Event related potentials and source localisation are powerful tools in the EEG analysis suite. As memory is the primary neurocognitive component affected, due the changes in the episodic memory network, it would seem worthwhile to test and load the network and if compensatory activity is present. A series of associative memory tasks that have increasing task difficulty are currently being developed that can be used in event related potential experiments.
Results: Preliminary data will be available in March 2024 Scores on tests of memory should be equal (compensatory) however the neural response to the tasks i.e. the event related potentials should be quantitatively different, reflecting increasing compensatory activity in the prefrontal cortex.
Conclusions: Recently increasing attention has been given to measurements of non-task activity so called resting states or default mode activity using quantitative EEG methods to detect general changes in the level of activity in a resting state. It is proposed that Associative memory tasks will contribute to the early detection of early Alzheimer's detection using EEG methods. An EEG test battery is proposed.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0494 / #1803

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

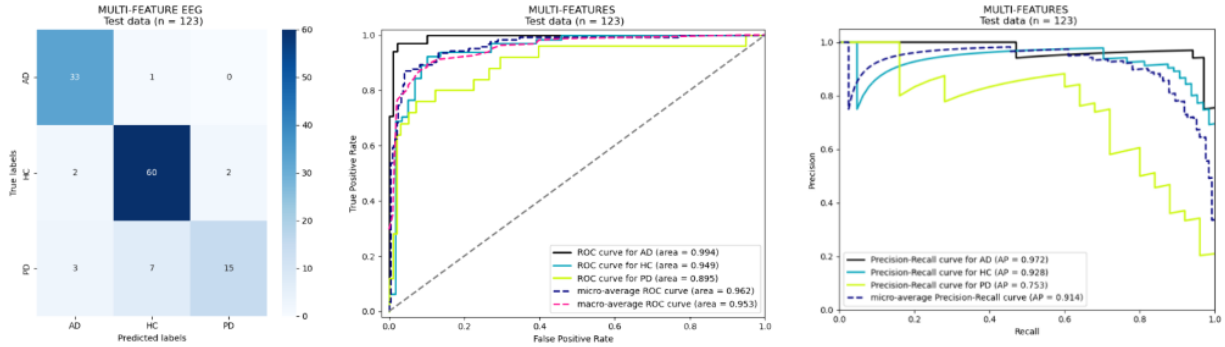
BEYOND POWER: HARMONIZING MULTI-CENTRIC MULTI-FEATURE EEG DATA FOR NEURODEGENERATIVE DISEASES CLASSIFICATION WITH AUTOMATED MACHINE LEARNING

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Alberto Jaramillo-Jimenez[1,2,3,4], Yorguin Mantilla-Ramos[2], Diego Tovar-Rios[1,4,5], John Ochoa[2], Kolbjørn Brønnick[1,4], Dag Aarsland[1,4,6], Laura Bonanni[7]
[1]Stavanger University Hospital, Centre For Age-related Medicine (sesam), Stavanger, Norway, [2]Universidad de Antioquia, Grupo Neuropsicología Y Conducta, School Of Medicine, Medellín, Colombia, [3]Universidad de Antioquia, Grupo De Neurociencias De Antioquia, Medellin, Colombia, [4]University of Stavanger, Faculty Of Health Sciences, Stavanger, Norway, [5]Universidad Del Valle, Grupo De Investigación En Estadística Aplicada - Inferir, Cali, Colombia, [6]Institute of Psychology, Psychiatry & Neuroscience (IoPPN), King's College London, Department Of Old Age Psychiatry, London, United Kingdom, [7]G. d'Annunzio University, Department Of Medicine And Aging Sciences, Chieti, Italy

Aims: Despite the multi-feature richness of resting-state electroencephalogram (rsEEG), power spectrum analysis remains the state-of-the-art approach. Automated machine learning (autoML) performs equal to or better than handcrafted models, even in small samples (n < 1000), but has not been tested on rsEEG for the classification of neurodegenerative diseases (NDD). Also, site-specific "batch" effects are reported in multisite rsEEG studies. The Combining Batches (ComBat) method controls batch effects, preserving biological covariates' variability, but its use in rsEEG data has not been examined. We aimed to evaluate the performance of autoML for classifying NDD from rsEEG features (oscillatory, aperiodic, complexity, connectivity) harmonized using a ComBat variant.
Methods: Signals (n = 410) from Alzheimer's Disease (AD, n = 113), Parkinson's Disease (PD, n = 83), and healthy controls (HC, n = 214) were preprocessed. Oscillatory and aperiodic spectrum, entropy metrics (complexity), and weighted Phase Lag Index connectivity (wPLI) were extracted in sensor space. Datasets (n = 8) harmonization was performed using reComBat, and feature selection using the minimum redundancy – Maximum relevance (mrMR) algorithm. AutoGluon was used to fit models on the training set (n = 287), evaluating the best model on the test set (n = 123).
Results: reComBat mitigated batch effects. Selected features included oscillatory theta-alpha descriptors, aperiodic parameters in anterior-central leads, complexity in posterior derivations, and whole-brain alpha wPLI. Multilayer stacked ensemble achieved a Balanced accuracy (Bacc) of 81.7 % in validation. In the test set **(Figure 1)**, we obtained a Bacc of 83.6 % and a classification of AD (ROC = 0.994), PD (ROC = 0.895), and HC (ROC = 0.949).

Figure 1. Results on the hold-out test set.



Conclusions: Batch harmonization, feature exploitation, and autoML are standardized tools for data integration and improved NDD classification from rsEEG.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0495 / #450

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

NEGATIVE CONNECTIVITY IN ALZHEIMER'S DISEASE: INSIGHTS INTO NETWORK TOPOLOGY AND POTENTIAL IMPLICATIONS

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Ignacio Taguas, David López-Sanz, Fernando Maestú
Complutense University of Madrid, Experimental Psychology, Cognitive Psychology And Speech & Language Therapy, Madrid, Spain

Aims: In recent years, a large body of evidence has underscored the significant impact of Alzheimer's Disease (AD) on the Default Mode Network areas. These areas deactivate during cognitive tasks, which has led numerous authors to speculate that negative functional connectivity might be crucial in AD. However, other studies analyzing BOLD signals suggest that negative correlations can be explained by the patterns of positive connectivity –i.e., there is not an inhibitory force driving negative connectivity– and should therefore be discarded. In this work, we will study if the networks formed by anticorrelations are organized, or if the present a random structure, both in healthy participants and patients.
Methods: The sample consists of 172 cognitively unimpaired participants and 105 patients with amnestic mild cognitive impairment. Using resting-state closed eyes MEG recordings acquired in previous years, we will construct the brain networks of each subject using only the negative functional connectivity values, measured using corrected amplitude envelope correlation. Afterwards, these brain networks will be analyzed and compared between groups in terms of their topological structure –metrics including smallworldness, clustering, and modularity– to test the organization of the structure.
Results: Based on previous literature using fMRI, we expect negative brain graphs to show a random structure, or at least significantly less organized than that of positive networks. However, if we do find an organized structure, we will study the correlation between this organization and the punctuation on neuropsychological tests assessing different cognitive domains.
Conclusions: Functional connectivity is a widespread methodology to assess brain functioning in AD. However, existing results exhibit significant inconsistency, partially attributed to a lack of knowledge of how to handle negative values. Thus, clarifying whether they should be considered will be highly valuable.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0496 / #2270

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

FULLY AUTOMATED SCORING OF AUDIO-VERBAL COGNITIVE ASSESSMENTS DIRECTLY FROM AUDIO RECORDINGS: RESULTS FROM THE AMYPRED STUDIES

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Jack Weston[1], Caroline Skirrow[1], Udeepa Meepegama[1], Michael Ropacki[2], Emil Fristed[1]
[1]Novoic Ltd, R&d, London, United Kingdom, [2]Strategic Global Research & Development, Neuroscience, Temecula, United States of America

Aims: Scoring of cognitive assessments is burdensome, subjective and varies across raters, introducing measurement noise. This study evaluates a fully automated system for scoring audio-verbal cognitive tests.
Methods: Semantic ("animals") and phonemic ("F") fluency tests and Wechsler Logical Memory Test (LMT) from 100 participants (N=48 MCI or mild AD, N=52 cognitively unimpaired) in the AMYPRED studies (NCT04828122, NCT04928976) were administered during supervised assessments. Tests were manually scored by site staff across four sites, and manually re-scored from audio-recordings by one researcher (CS; fluency tests) or consensus scored by two researchers (CS and JW; LMT) to provide a consistent ground truth. Automatic scores were derived from audio files, using a custom transcription model and a fully automated natural language processing system. Reliability of the automated system was evaluated using correlational analyses.
Results: Automated ratings correlated highly with all manual ratings (all $r>0.91$, $p<0.001$). Compared to ground truth scores, correlation coefficients were higher for automated scores than those from site staff, significant for "animals" ($r=0.99$, 95% CI 0.99-0.99; $t=3.59$, $p<0.001$) and LMT consensus scores ($r=0.98$, 95% CI=0.97-0.99, $t=4.28$, $p<0.001$), but not for "F" ($r=0.96$, 95% CI=0.94-0.97, $t=0.39$, $p>0.05$).
Conclusions: The automated rating system demonstrated high convergence with ground truth scores, and equal or better to manual scores by trained raters. Automated scoring could reduce measurement error in outcome assessment, refine detection of group differences and change over time, and/or reduce sample sizes required to detect clinical change in clinical trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0497 / #458

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

COGNITIVE AGING TRAJECTORIES AMONG ENGLISH AND SPANISH TAKERS

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Carlos Araujo Menendez[1], Rubi Carpio[2], Rachel Membreno[2], Armando Lemus[2], Shaun Goycoochea[2], Ursula Saelzler[3], Ariana Stickel[2]
[1]SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, Psychology, San Diego, United States of America, [2]San Diego State University, Psychology, San Diego, United States of America, [3]UC San Diego, Psychiatry, San Diego, United States of America

Aims: Cognitive assessments are typically designed for English speakers, creating a potential disadvantage and misrepresentation of cognitive functioning for non-English testing speakers. We aimed to determine whether English and Spanish test takers have similar or different cognitive trajectories.

Methods: This study included 2,266, Hispanic/Latino adults without dementia, ages 46-104 years (mean = 69.9 years, SD = 8.6), from the National Alzheimer's Coordinating Center (NACC). Mixed-effects regression analyses were used to examine baseline differences and longitudinal changes in immediate and delayed episodic memory, verbal fluency, processing speed and language (confrontation naming) between Spanish- and English-test takers (n=1097 and n=1169, respectively). All models were adjusted for age at baseline, years of education, sex and clinical status [cognitive normal (CN) or mild cognitive impairment (MCI)].

Results: English speakers performed significantly better than Spanish speakers across all cognitive tests at baseline (βs=0.32-0.47, $p < 0.05$). No differences in cognitive trajectories were detected on any tests.
Conclusions: Although both the English and Spanish testing groups began at different levels of cognition, the rates of decline remained similar across all cognitive domains, which may suggest similar cognitive aging trajectories. Differences in cognitive performance cross-sectionally, but not longitudinally, may be due to measurement bias, resulting in underestimation of cognitive abilities of Spanish-speakers, especially those with lower education. Further studies are needed to better understand the mechanisms of how language differentially affects cognitive performance cross-sectionally and longitudinally.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0498 / #2404

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

APPLICATIONS OF MACHINE LEARNING BASED POSE ESTIMATION IN BEHAVIORAL DATA ANALYSIS

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Riccardo De Feo, Timo Bragge, Taneli Heikkinen, Johanna Uhari-Väänänen, Jussi Rytkönen, Artem Shatillo, Susanne Bäck
Charles River, Discovery, Kuopio, Finland

Aims: Behavioral readouts are essential for preclinical research on neurodegenerative disorders. The pathological changes are typically manifested with gradual changes in animal movement and/or in social behavior. Traditionally, the observation and recording of behavioral assays has relied on a human observer, subjecting the collected data to variability and possibly bias. Additionally, the required human resource needed to analyze large data sets can be overwhelming.
Methods: Novel machine learning approaches to image and video analysis open up new possibilities to behavioral data analysis with its speed, more objective detection of behavior and improved quality of data. DeepLabCut (DLC) is a software package for markerless 2D and 3D pose estimation based on transfer learning with deep neural networks (Lauer *et al*. 2022, Nat Methods 19, 496-504). In this study DLC was used to analyze video recordings of typical behavioral assays utilized in Parkinson's disease and Alzheimer's disease animal model research.
Results: We implemented automated analysis pipelines for the tapered beam balance test and Barnes maze, enabling reliable and objective assessment of the readouts of these tests.
Conclusions: As summary, machine learning does not just streamline and enhance the repeatability of scientific studies, it also allows us to scale up the amount of data that we can process in an efficient manner. Machine learning can be utilized in all behavioral analysis where there is a need to track the animals' movement.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0499 / #1514

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

ALTERATION OF VISUOSPATIAL SYSTEM IN MCI – UNDERLYING STRUCTURAL AND FUNCTIONAL CHANGES

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Dalida Berente[1,2], Andras Horvath[2,3], Gergő Bolla[1], Mate Kiss[4], Anita Andrassy[2], Anita Kamondi[2,5]
[1]Semmelweis University, School Of Phd Studies, Budapest, Hungary, [2]National Institute of Mental Health, Neurology and Neurosurgery, Neurocognitive Research Center, Budapest, Hungary, [3]Semmelweis University, Department Of Anatomy Histology And Embryology, Budapest, Hungary, [4]Siemens Healthcare, Siemens Healthcare, Budapest, Hungary, [5]Semmelweis University, Department Of Neurology, Budapest, Hungary

Aims: Alzheimer's Disease (AD) is the most common cause of major neurocognitive disorders in the elderly, preceded by a prodromal phase called Mild Cognitive Impairment (MCI). Despite the urgent need for early diagnosis, optimal screening methods for considerable patient groups are yet to be developed. Recent literature highlights that assessing visuospatial function might be an ideal candidate. In our study, we detected a significant association between our participants' cognitive performance and hand movement characteristics measured by a computer mouse with the Precognize paradigm. Our objective was to identify the underlying structural and functional changes in the brain.
Methods: 44 individuals participated in this study, 28 healthy controls and 16 MCI patients. They underwent comprehensive neurological and neuropsychological evaluation, structural- and functional MRI acquisition (sMR, fMR) and executed tasks with the Precognize paradigm. MRI images were analyzed using Freesurfer 6.0 software and the CONN Toolbox. Meticulous statistical analysis was completed for all data.
Results: Significant correlations were found between the computer mouse movement parameters derived from the Precognize parading and the sMRI and fMRI data. For sMRI, the most significant correlations were detected between the speed of movements by the right hand and cortical thickness of the right fusiform ($r=0.54$, $p<0.001$) and lingual ($r=0.37$, $p=0,01$) gyri. For the fMRI BOLD signal, the most significant correlation was found between the intrinsic connectivity of the right middle temporal gyrus and the speed of the right hand's movements ($r=0.53$, $p<0,001$).
Conclusions: Based on the Precognize paradigm's association with neuropsychological test results and cortical areas relevant for the Trail Making Test and AD, hand movement analysis by the Precognize paradigm seems a promising candidate for an automatic, digital screening method for MCI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0500 / #2313

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

CLINICAL MEANINGFUL CHANGES IN ALZHEIMER'S DISEASE: CDR PROGRESSION AND EFFECT ON MMSE, ADAS-COG, RBANS AND ADC ADLI

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Catarina Cunha[1], Raymond Blattner[2], Selam Negash[2], Silvia Gamazo Navarro[1], Barbara Echevarria[1], Christopher Randolph[3]
[1]WCG Clinical Research Solutions, Clinical Science, Munich, Germany, [2]WCG Clinical Research Solutions, Clinical Data Analytics, Princeton, United States of America, [3]WCG Clinical Research Solutions, Chief Scientific Officer, Princeton, United States of America

Aims: The Clinical Dementia Rating (CDR) is commonly used to characterize Alzheimer's disease (AD) and disease progression. CDR Global score (GS) determines cognitive impairment/dementia and quantifies disease severity from very mild to mild, moderate, and severe. Identifying clinically meaningful changes in cognitive/functional tests is essential when cognition is an outcome in clinical trials. We aimed to establish clinically important differences for commonly cognitive/functional tests when subjects progress from very mild to mild AD stage (CDR0.5 to 1) and from mild to moderate AD stage (CDR1 to 2)
Methods: Effect sizes (ES) were calculated to estimate clinically important changes on the MMSE, ADAS-Cog, RBANS and ADCS ADLI when subjects progressed from very mild AD to mild AD and from mild AD to moderated AD. Clinically important changes were defined as mean change of MMSE, ADAS-Cog, RBANS and ADC ADLI in subjects rated for the first time CDR GS1 and CDR GS2 at 6 and 12 months since baseline. Data from these scales was analyzed for baseline, 6/12 months for 466 subjects with AD enrolled in four multinational double-blind, placebo controlled clinical trials.
Results: The mean changes for CDR rated first time mild (CDR0.5 to 1) in the MMSE, ADAS-Cog, RBANS and ADCS ADLI were respectively: -2.34±3.77 (d=-0.72), 2.83±7.35 (d= 0.43), -4.23±11.58 (d=-0.38) and -3.90±6.78 (d=-0.65). The mean changes for CDR rated first time moderate (CDR1 to 2) in the MMSE, ADAS-Cog, RBANS and ADCS ADLI were respectively: -5.07±3.99 (d=-1.45), 5.61±8.77 (d= 0.68), -4.23±6.96 (d=-0.55) and -14.22±12.00 (d=-1.29).
Conclusions: All scales captured worsening effectively when AD progressed from mild to moderate stage but the MMSE and the ADCS ADLI demonstrated being more sensitive to capturing worsening when AD progressed from very mild to mild stage.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0501 / #331

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

PREDICTION OF ALZHEIMER'S DISEASE USING VOCAL BIOMARKERS: AN AI APPROACH

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Young Chul Youn[1], Sangyun Kim[2], Hotae Jeong[1], Hyunjoo Choi[3], Nayoung Ryoo[4], Minsu Kim[5]
[1]Chung-Ang University Hospital, Neurology, Seoul, Korea, Republic of, [2]Seoul National University Bundang Hospital, Neurology, Seongnam-si, Korea, Republic of, [3]Korea Nazarene University, Communication Disorders, Cheonan, Korea, Republic of, [4]The Catholic University of Korea Eunpyeong St. Mary's Hospital, Neurology, Seoul, Korea, Republic of, [5]Baikal AI, Research And Development, Seoul, Korea, Republic of

Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that significantly impacts memory and cognitive abilities. Early and accurate diagnosis of AD is crucial for effective therapeutic interventions. In this study, we propose an innovative approach that utilizes Artificial Intelligence (AI) to predict AD using vocal biomarkers.
Methods: We recruited participants with varying degrees of cognitive impairment and collected voice recordings during specific tasks designed to elicit speech patterns affected by AD-related cognitive decline. Several AI models were trained on the collected voice data, including spectrograms, 1D & 2D Convolutional Neural Networks (CNNs), Audio Spectrogram Transformer (AST), and Wav2vec 2.0. These models underwent various transformations and augmentations to enhance their robustness and generalization capabilities.
Results: Our study demonstrated the effectiveness of the Wav2vec2 model as the most accurate across all categorizations, closely followed by the AST model. These models exhibited high efficiency in both binary and multi-class audio classifications related to cognitive impairments associated with AD.
Conclusions: The findings suggest that leveraging vocal biomarkers in combination with AI algorithms holds promise for early detection of AD. The non-invasive nature of vocal biomarker analysis makes it a potentially accessible tool for widespread screening and monitoring within communities.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0502 / #1342

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

EYE-TRACKER ASSESSMENT OF THE IMPACT OF DONEPEZIL ON VISUOSPATIAL ABILITIES IN MILD COGNITIVE IMPAIRMENT: PRELIMINARY FINDINGS

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Ko Woon Kim, Qi Wang, Eunsu Lee, Byoung-Soo Shin
Jeonbuk National University, Neurology, Jeonju, Korea, Republic of

Aims: Cholinesterase inhibitors (ChEIs) have been shown to reduce cognitive decline over the long term in patients with Alzheimer's disease (AD). However, there is limited evidence to suggest that ChEIs influence cognitive test results in patients experiencing mild cognitive impairment (MCI) due to AD. Traditional evaluation criteria, including cognitive tests may not be sufficiently responsive to detect subtle therapeutic effects in MCI patients. We propose a randomized controlled trial to assess the effect of donepezil with MCI due to AD.
Methods: Our study enrolled 16 participants with MCI (8 in each arm, donepezil vs. control), who had amyloid positron emission tomography (PET)-positive results. We employed eye-tracking metrics and digital pen data during the execution of the simplified Rey Complex Figure (RCFT). Eye-tracking was recorded during the copying of the simplified RCFT. After standard gaze mapping, we quantified eye-tracking metrics such as the number and duration of fixations in the perception and working areas. The primary outcome measure involves evaluating alterations in the ratio of the number of fixations (working space/perceptual space) using the simplified RCFT, from baseline to the 12-week mark, as evaluated through eye-tracking metrics. Statistical analyses for primary outcome was applied on the donepezil and control groups between the baseline session and follow-up session using paired-Wilcoxon test.
Results: Eye-tracking metrics showed that the ratio (working space/perceptual space) of the visit count (P=0.036), total visit duration (P=0.025), total fixation duration (P=0.036), and first fixation duration (P=0.025) were significantly increased in the follow-up visit compared to the baseline visit in the donepezil group. And the metrics in the control group showed no significant changes.
Conclusions: This research suggests the potential utility of eye-tracking metrics as valuable digital biomarker for detecting subtle alteration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0503 / #2817

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

ASSESSING THE UTILITY OF MINI-COG© FOR DEMENTIA AND COGNITIVE FUNCTION SCREENING IN JAPAN: STUDY RESULTS

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Shinichiro Maeshima[1], Aiko Osawa[2], Chisato Kamizato[1], Shinitaro Nakarai[1], Naoki Itoh[1], Hidenori Arai[3]
[1]National Center for Geriatrics and Gerontology, Education And Innovation Center, Obu, Japan, [2]National Center for Geriatrics and Gerontology, Department Of Rehabilitation Medicine, Obu, Japan, [3]National Center for Geriatrics and Gerontology, President, Obu, Japan

Aims: The Mini-Cog© assessment was developed to aid in the early detection of dementia; however, its adoption in Japan remains limited. The aim of this study was to assess the effectiveness of Mini-Cog© in the context of cognitive screening.
Methods: The study included 170 older participants (76 men and 94 women) attending the Memory clinic, ranging in age from 66 to 94 years, with an average of 11.4 ± 2.7 years of education. Among the participants, 100 were diagnosed with dementia, 53 with mild cognitive impairment (MCI), and 17 exhibited normal cognitive function. Mini-Cog© scores were evaluated to determine sensitivity and specificity for dementia and mild cognitive impairment.
Results: Among the 36 patients with total scores in the normal range (≥4 points) on the initial Mini-Cog© assessment, 5 (13.9%) had dementia, 17 had MCI (47.2%), and 14 were cognitively normal (38.9%). In contrast, of the 134 patients with abnormal total scores (3 or less), 95 (70.9%) had dementia, 36 (26.9%) had MCI, and only 3 (2.2%) were cognitively normal. The sensitivity and specificity for dementia were 0.95 and 0.44, respectively, while those for cognitive decline (dementia and MCI) were 0.86 and 0.82, respectively. The agreement between the Mini-Cog© scores obtained at the first and second visits was 44.4%.
Conclusions: These findings suggest that Mini-Cog© represents a convenient and efficient tool for screening cognitive decline in primary care and health checkup settings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0504 / #1939

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

TECHNICAL AND CLINICAL VALIDATION OF NOVEL COGNITIVE TESTS FOR REMOTE SAMPLING OF MEMORY AND EXECUTIVE FUNCTION

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

John Dyer[1], Alison Buick[1], Laura Rueda-Delgado[2], Md. Nurul Islam[2], Judith Jaeger[3], Niamh Kennedy[4], James Rowe[5], Brian Murphy[2]
[1]Cumulus Neuroscience, Science, Belfast, United Kingdom, [2]Cumulus Neuroscience, Science, Dublin, Ireland, [3]CognitionMetrics LLC, Science, Stamford, United States of America, [4]University of Ulster, Psychology, Coleraine, United Kingdom, [5]University of Cambridge, Clinical Neurosciences, John Van Geest Centre For Brain Repair, Cambridge, United Kingdom

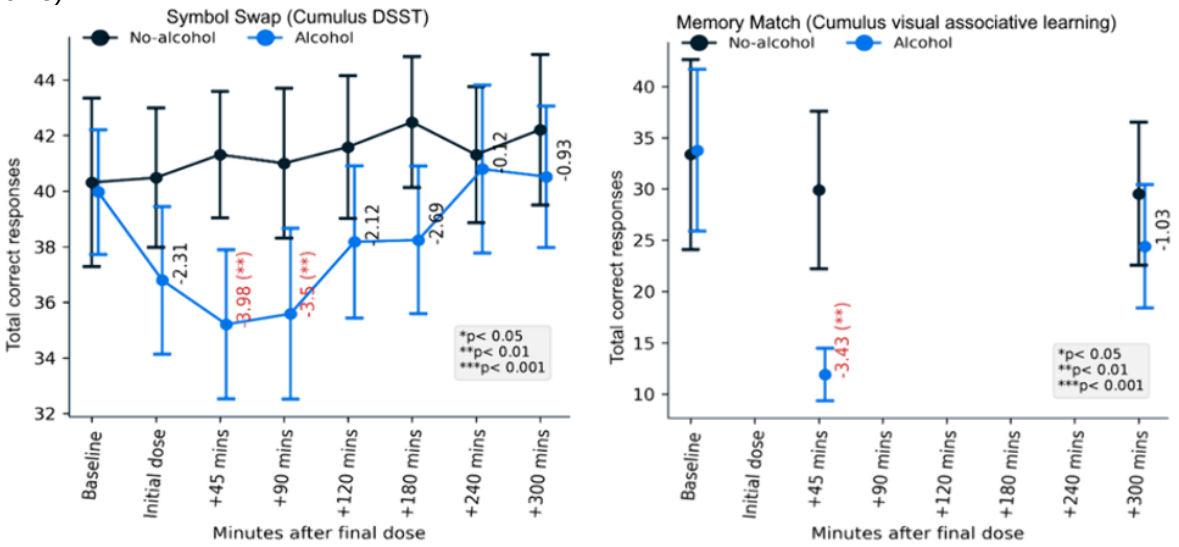
Aims: Frequently repeatable and valid measures of disease-relevant cognitive functions can be used in aggregate to increase the precision of measurement in dementia. This could enable earlier detection of the disease, and also the streamlining of clinical trial designs. We here present data from the validation of two novel assessments in the Cumulus Neuroscience platform, suitable for at-home use by patients, in terms of sensitivity to change in cognitive impairment.
Methods: Tablet-based assessments covering episodic memory and executive function were developed in collaboration with a panel of dementia stakeholders (N = 10), representing patients, carers and practitioners in the field. “Symbol Swap” is a symbol-coding task, related to the classic DSST. “Memory Match” is a visual associative learning paradigm, designed to test recollection memory. These underwent technical validation in a small (N=30) alcohol challenge lab study to evaluate sensitivity to subtle cognitive impairment. The tasks were also deployed in a longitudinal field study involving 59 participants living with mild AD dementia and 60 matched healthy control participants, for which we report cross-sectional

Task screenshots from Cumulus tasks Symbol Swap (top) and Memory Match (bottom). In Symbol Swap, tiles must be dragged (using a stylus or finger) to the next open slot in the row. In Memory Match, the position of abstract patterns must be recalled, with the number of patterns to be remembered growing at an ever-increasing rate.

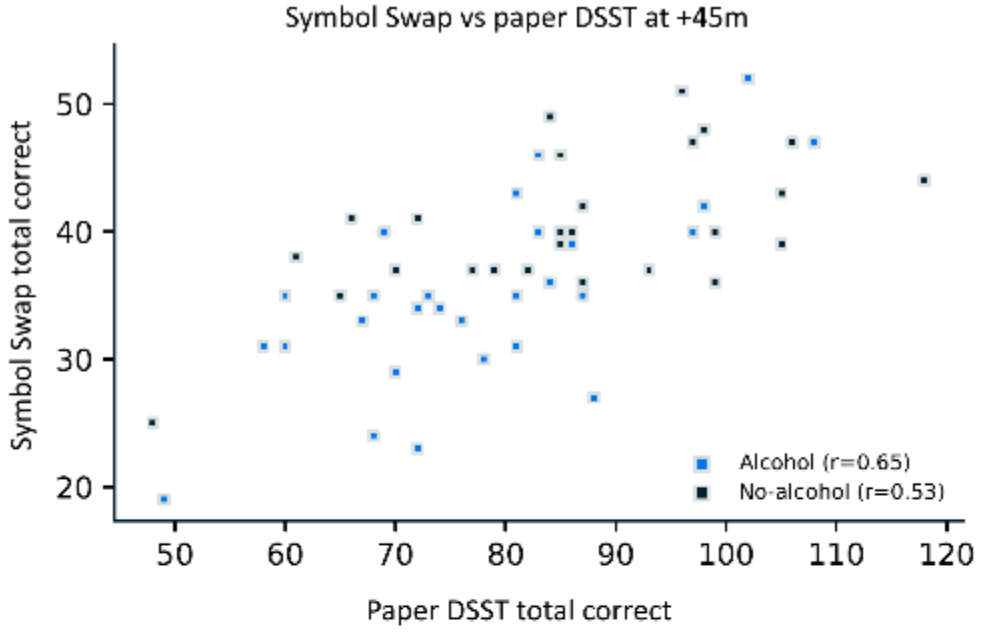
analyses.

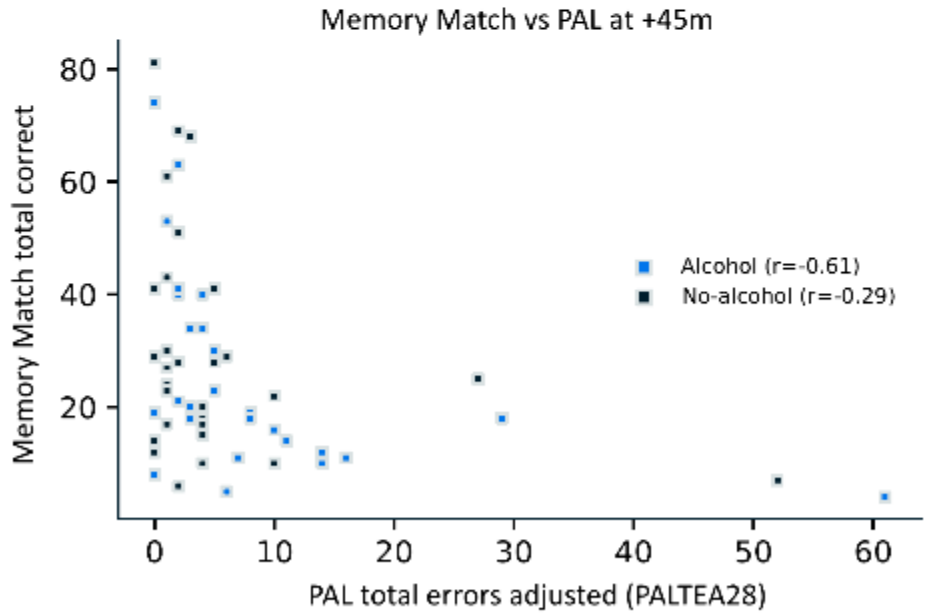
Results: In the alcohol study practice effects were small, and performance demonstrated a curve of impairment and return to baseline with intoxication. Correlations with benchmark measures were high (r > 0.61). In the patient study both tasks strongly differentiated AD status with equivalent or greater sensitivity

than ADAS-Cog (Symbol Swap: t(98) = 10.32, p=4.8e-17; and Memory Match: t(98) = 8.11, p= 2.4e-11). Furthermore, strong correlations with benchmark measures were found (r > 0.75).

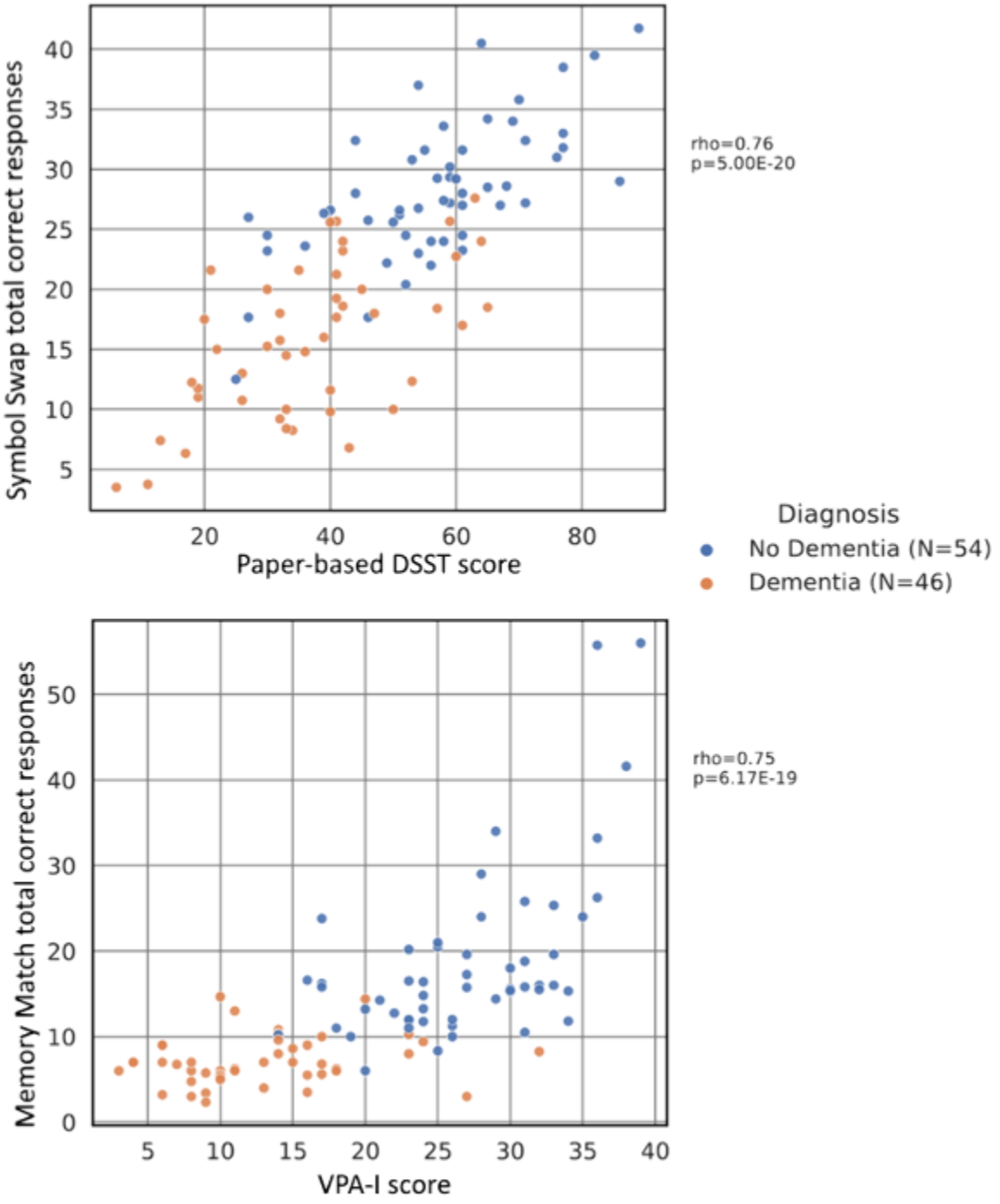


Timecourse of alcohol-induced impairment over the experiment, for the alcohol and placebo arms. Error bars are 95% confidence intervals. t values are shown for the interaction of session type (alcohol/placebo) and session timepoint, with significant interactions highlighted (Holm-Bonferroni corrected). Left: Alcohol vs placebo performance data over time for Symbol Swap. Right: Alcohol vs placebo performance data over time for Memory Match (note that Memory Match was administered at baseline, peak intoxication and finish only, due to time constraints).

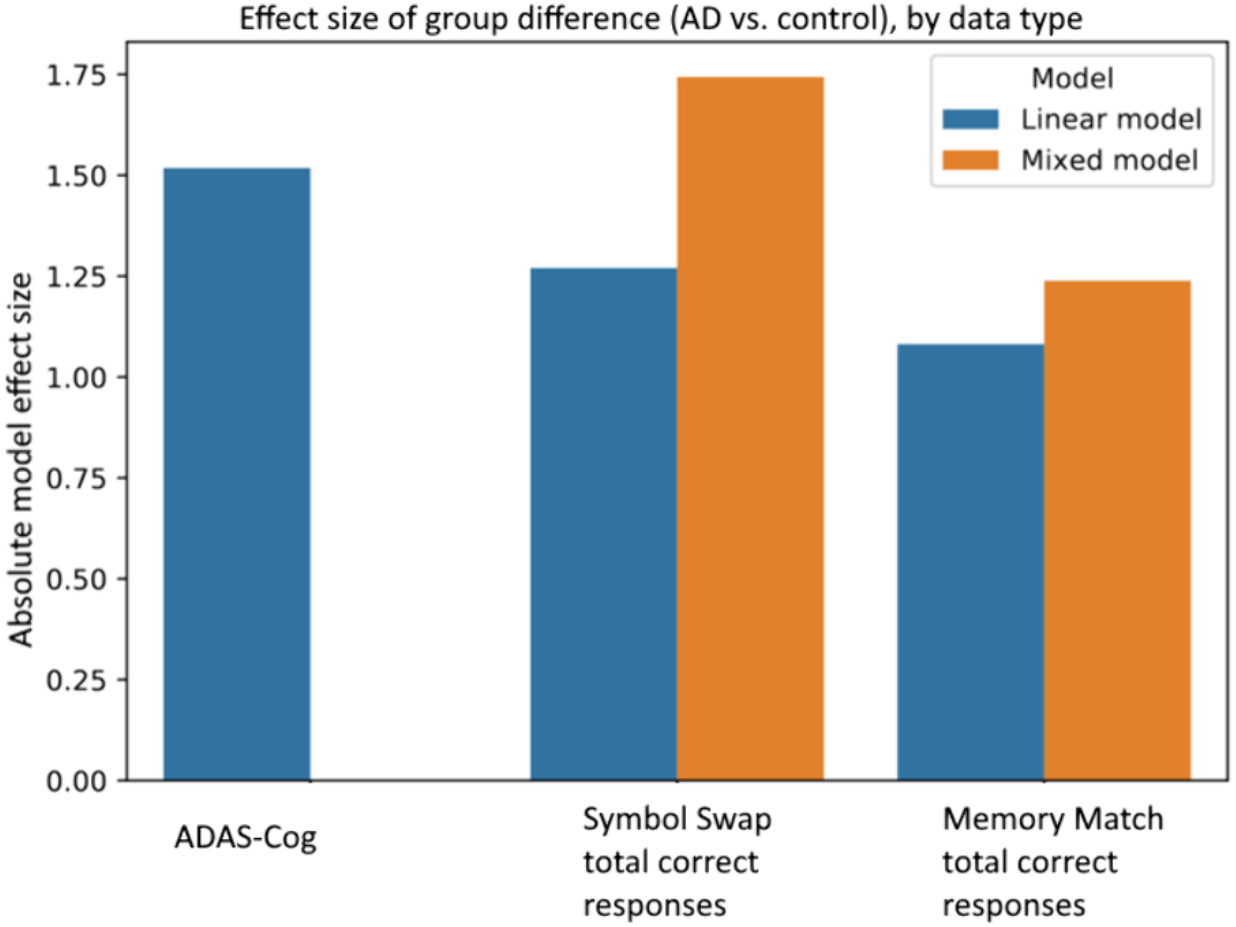




Scatterplots showing scores for Cumulus tasks against benchmark comparators with Spearman rank correlation. Top: Cumulus Symbol Swap vs paper DSST. Bottom: Cumulus Memory Match vs PALTEA28 (one of two primary metrics from PAL). Data here are taken from 45 minutes after final dose of alcohol or placebo (peak intoxication where applicable).



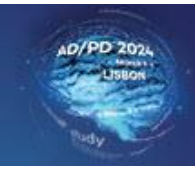
Scatterplots of Cumulus variables against paper-based benchmarks. Top: Symbol Swap showed a correlation with the paper-based DSST 0.76 (p=5e-20). Bottom: Memory Match task showed a correlation with the Verbal paired associates (VPA-I)of 0.75 (p=6.2e-19).



Group effect size of selected Cumulus variables and the ADAS Cog 13. Using the average of Cumulus sessions results in a lower effect size than the one obtained from the ADAS Cog. With mixed models, we exploit the within-user variability and obtain an effect size higher than the ADAS Cog.

Conclusions: These studies demonstrate that the novel tasks are usable by patients, and sensitive to impairment – making them suitable for use in modern clinical trials where individual-level precision measurement is required.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0505 / #1329

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

A DETECTION MODEL OF COGNITIVE IMPAIRMENT VIA THE INTEGRATED GAIT AND EYE MOVEMENT ANALYSIS FROM A LARGE CHINESE COMMUNITY COHORT

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Bin Jiao[1], Jingyi Lin[2], Tianyan Xu[1], Lu Shen[1]
[1]87 Xiangya Road Xiangya Hospital, Central South University, Department Of Neurology, Changsha, China, [2]Xiangya Hospital Central South University, Hunan International Scientific And Technological Cooperation Base Of Neurodegenerative And Neurogenetic Diseases, Changsha, China

Aims: Whether the integration of eye-tracking, gait, and dual-task analysis can distinguish cognitive impairment (CI) patients from controls has been elusive.
Methods: 1481 participants, including 724 CI and 757 controls, were enrolled in this study. Eye movement and gait, combined with dual-task patterns were measured. The LightGBM machine learning models were constructed.
Results: A total of 105 features of gait and eye-tracking were extracted. 46 parameters, including 32 gait and 14 eye-tracking features, showed significant differences between two groups ($p<0.05$). Among them, the Gait_3Back-TurnTime and Dual-task cost-TurnTime patterns were correlated to plasma p-tau 181. The model based on dual-task gait, dual-task smooth pursuit, prosaccade and antisaccade achieved the best AUC of 0.987 for CI detection, while combined with p-tau181, the model could discriminate mild cognitive impairment (MCI) from CN with an AUC of 0.824.
Conclusions: Combining dual-task gait and dual-task eye-tracking analysis has the feasibility in non-invasive detection of CI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0506 / #1465

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

CORRELATION ANALYSIS OF APOB, APOA1, AND APOB/APOA1 WITH CORTICAL MORPHOLOGY IN PATIENTS WITH MEMORY COMPLAINTS

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Wang Jiayu[1], Wang Ziqi[2], Duan Mingjun[2]
[1]Zunyi Medical University, Nursing, Zunyi, China, [2]the Fourth People's Hospital of Chengdu, Geriatrics, Chengdu, China

Aims: To examine whether apolipoprotein B (ApoB), apolipoprotein A-1 (ApoA1), and their ratio (ApoB/ApoA1) are associated with early changes in cortical morphology in patients with memory complaints.
Methods: A total of 100 patients from two centers were grouped based on recruitment location, and underwent neuropsychological tests, plasma Alzheimer's biomarker assessments, apolipoprotein E (ApoE) genotyping, and 3T magnetic resonance imaging. The CAT12 toolbox (SPM12) was used to measure cortical morphology.
Results: Significant positive correlations were found between ApoB and sulcal depth in the occipital cortex for both individual groups (p=0.001 and p=0.002) and the total combined group (p=0.000). Sulcal depth showed negative correlations with time measurements from the Shape Trails Test Part A and B in the total combined group (β=-0.336, p=0.001 and β=-0.228, p=0.023), the first group (β=-0.49, p=0.002 and β=-0.251, p=0.031), and the second group (β=-2.79, p=0.007 and β=-0.452, p=0.001). In the second group, positive associations were identified between sulcal depth and scores on the Montreal Cognitive Assessment Basic (β=0.407, p=0.002), Animal Fluency Test (β=0.392, p=0.007), and Boston Naming Test (β=0.407, p=0.006). No correlations were found between other cortical shapes and ApoB, ApoA1, or ApoB/ApoA1.
Conclusions: ApoB influences the sulcal depth in the lateral occipital cortex, potentially impacting executive function in individuals with memory complaints.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0507 / #1574

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

DIFFERENCES IN COGNITIVE TRAJECTORIES OF DEMENTIA SUBTYPES: ALZHEIMER'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Bang-Hoon Cho[1], Seong-Min Choi[2], Min-Kyung Song[3], Sujeong Jang[4], Han-Seong Jeong[4], Byeong C. Kim[2]
[1]Korea University Anam Hospital, Korea University College of Medicine, Neurology, Seoul, Korea, Republic of, [2]Chonnam National University Medical School & Hospital, Neurology, Gwangju, Korea, Republic of, [3]Chonnam National University Hospital, Neurology, Gwangju, Korea, Republic of, [4]Chonnam National University Medical School, Physiology, Jellanamdo, Korea, Republic of

Aims: Prediction of the dementia progression is important for patient's management. We aimed to investigate the cognitive trajectories of Alzheimer's disease dementia (ADD) and dementia with Lewy bodies (DLB) according to the initial structural change measured by comprehensive visual rating scales (CVRS).
Methods: We retrospectively included the patients who initially visited the Dementia Clinic of Chonnam National University Hospital between 2010 and 2012. All patients underwent dementia work up including neuropsychological battery (Seoul Neuropsychological Screening Battery, SNSB). We recruited the participant who underwent SNSB annually for three years successively. Total 136 patients of ADD and 63 patients of DLB were included for analyze. We analyzed the decline pattern of cognitive profile according to the initial brain structural changes.
Results: The general cognitive trajectories between ADD and DLB patients were not different. However, DLB patients showed more rapid decline of cognitive function in language and related function, visual memory function, and frontal executive function. The scores were lower in participants with DLB without atrophic group in attention, visuospatial function, and frontal executive function. In analysis of the cognitive trajectories, the visual memory domain declined rapidly in DLB without atrophy group compared with the ADD without atrophy group.
Conclusions: We founded that the differences in visual cognitive profile in ADD and DLB patients in serial follow up of neuropsychological tests. It is prominent in the mild structural change group of ADD and DLB.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0508 / #2752

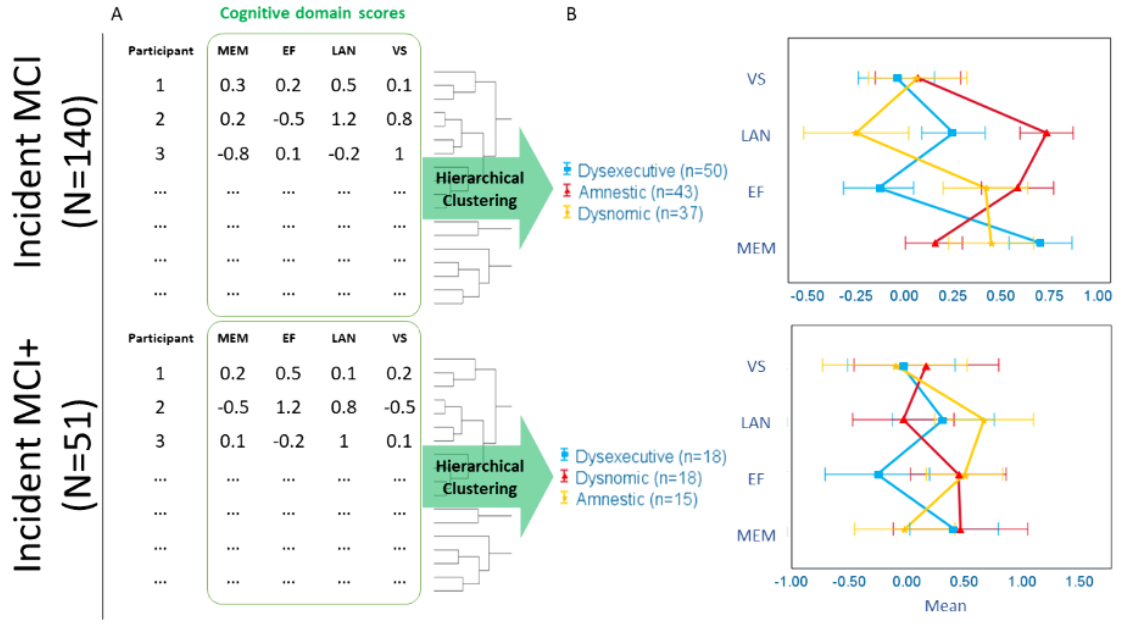
Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

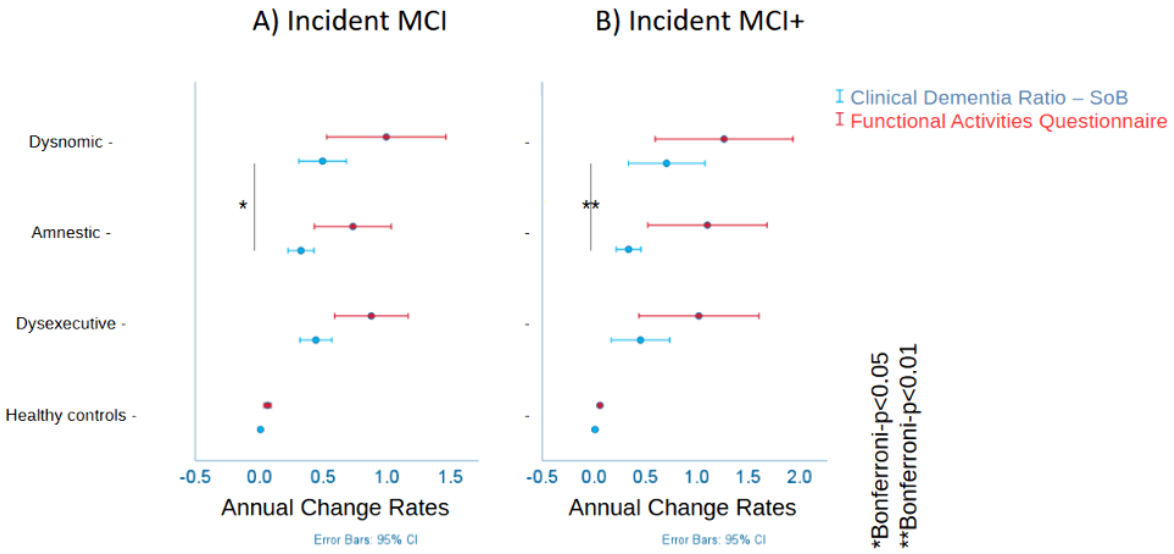
COGNITIVE SUBTYPES DIFFER IN CLINICAL PROGRESSION IN BETA-AMYLOID POSITIVE INDIVIDUALS WITH INCIDENT MILD COGNITIVE IMPAIRMENT

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Ersin Ersözlü[1], Alzheimer'S Disease Neuroimaging Initiative (Adni)[2]
[1]Charité, Campus Benjamin Franklin, Department Of Psychiatry And Psychotherapy, Berlin, Germany, [2]University of Southern California, Neurology, Los Angeles, United States of America

Aims: Alzheimer's disease (AD) is proven to cause heterogeneous clinical manifestations. The recent studies identified clinical phenotypes, including the amnestic, dysexecutive and dysnomic, using neuropsychological test batteries in mild cognitive impairment (MCI). However, the studies did not consider the biological definition, i.e., abnormal β-amyloid (Aβ), while defining disease groups. We aim to explore possible clusters of neuropsychological domain scores in Aβ+ patients with MCI and their relations to cognitive trajectories.
Methods: We included n=180 cognitively normal participants without abnormal Aβ, phosphorylated-tau or total-tau and n=130 patients with an incident MCI (iMCI) and n=51 patients with abnormal Aβ and iMCI (iMCI+). iMCI was defined as the first diagnosis of MCI after at least one prior visit without a diagnosis of MCI. A hierarchical clustering approach was used on the cognitive composite scores of memory, executive functions and language domains to determine three clusters in iMCI and iMCI+ groups. We defined a priori the three-cluster solution and compared the clusters' baseline characteristics and cognitive trajectories.
Results: The clustering method classified the disease group into three clusters and showed similar phenotypes in iMCI and iMCI+, presenting amnestic, dysexecutive and dysnomic clusters (**Fig. 1**). The baseline demographics and global cognition did not differ among clusters, while amnestic and dysnomic clusters were more likely Apolipoprotein E ε4-allele-carriers. The dysnomic cluster revealed a higher annual change rate of the Clinical Dementia Ratio - Sum of Boxes than the amnestic cluster, adjusted for confounders (**Fig. 2**).





Conclusions: Our results demonstrate that identifying MCI subtypes might enhance the accuracy of prognostic predictions for clinical progression. Moreover, the consistency of iMCI subtypes within the iMCI+ group indicates that the observed clusters may be a part of the biologically defined AD continuum.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0509 / #2058

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

AUDITORY COGNITION IS RELATED TO NEUROIMAGING MARKERS OF ALZHEIMER'S DISEASE

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Meher Lad, Tim Griffiths
Newcastle University, Auditory Laboratory, Newcastle upon Tyne, United Kingdom

Aims: Hearing loss is related to an increased risk of dementia but the reasons for this are unclear. Poor central hearing has previously been shown to increase risk of Alzheimer's disease dementia. Poor performance on these tests have also shown associations with greater rates of temporal lobe atrophy. This study tested whether two types of central hearing: speech-in-noise perception ability and auditory memory could differentiate groups with or without Alzheimer's disease dementia and whether performance on these tests was associated with morphometric measures in regions that are specifically associated with risk of the condition. These included region thickness and volume in Alzheimer's disease signature regions, medial temporal lobe and auditory processing areas.
Methods: 50 participants (25 Cognitively normal, 10 Mild Cognitive Impairment and 15 Alzheimer's disease dementia) underwent a battery of auditory tests including speech-in-noise perception (digits-in-noise and sentence-in-babble perception) ability and auditory memory. 3T structural MR imaging for T1-weighted and T2-weighted imaging was conducted on a Philips Acheiva scanner. All scans were preprocessed using sMRIprep and underwent a full recon-all surface reconstruction using Freesurfer 7.0. Normalised volumetric measures and mean cortical thickness values for Alzheimer's disease signature regions, medial temporal lobe structures and auditory processing regions were used for group-level analysis.
Results: All regions of interest showed group-level differences in volume and cortical thickness with lower values progressing from cognitively normal, mild cognitive impairment due to Alzheimer's disease to Alzheimer's disease dementia. Effect sizes were stronger for auditory memory rather than speech-in-noise perception measures.
Conclusions: This study presents cross-sectional evidence linking auditory behavioural performance to neuroimaging markers related to neurodegeneration in AD, suggesting a direct link between central hearing and neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0510 / #2383

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

CAN COGNITIVE CHARACTERISTICS AND AGE OF HEALTHY PEOPLE BE PREDICATED BY WHOLE BRAIN STRUCTURAL CONNECTOME?

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Yong Li[1], Sebastian Kopetzky Kopetzky[1], Markus Butz-Ostendorf[1], Marcus Kaiser[2]
[1]Labvantage - Biomax GmbH, Product Management, Planegg, Germany, [2]University of Nottingham, Precision Imaging Beacon, School Of Medicine, Nottingham, United Kingdom

Aims: The ability to predict cognitive states and age of healthy people via whole brain structural connectome alone is highly challenging but extremely meaningful in identifying individuals at high-risk in presympotomatic neurodegenerative diseases stage within healthy people. This study provides a plausible option, which employs a simple machine learning model, an automated imaging processing pipeline and whole brain structural connectome features extracted by the pipeline, to predict changes in crystallized intelligence, fluid intelligence and age based on limited brain image modality alone.
Methods: Our in-house automated brain imaging processing pipeline was applied for the healthy subjects from the Human Connectome Project Young Adult (HCP, N=1048) and ANDI-3 study (N=94) to extract whole brain probabilistic tractography-based connectome features. To predict crystallized and fluid intelligence as well as age, we used the correlation-based regression algorithm (Han et al. 2014) with a 10-fold cross-validation for each data set.
Results: For the HCP subjects, predictability of crystallized intelligence was better than that of fluid intelligence in all investigated conditions (Wilcoxon signed-rank test, P_{Total}=1.38e-10, P_{Male}=3.26e-06, P_{Female}=2.18e-06, Benjamini-Hochberg multiple testing correction FDR=0.05). Our results well predicted age for ADNI-3 subjects (r=0.57, NMAE=0.14), whereas it was less profound for the HCP subjects (r=0.21, NMAE=0.20) under all conditions.
Conclusions: Our study provides a realistic attempt to explore different predictabilities of cognitive assessments as well as age in healthy people by using a simple machine learning approach constructed based on limited brain imaging data features.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0511 / #2769

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

SPEECHDX: A HARMONIZED SPEECH DATASET FOR ALZHEIMER'S DISEASE BIOMARKER DEVELOPMENT

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Melissa Lee[1], Lampros Kourtis[1,2], Rhoda Au[3], David Bartrés-Faz[4], Edgar Buloz[4], Gabriele Cattaneo[4], Lakita Cavin[1], Matthew Clement[5], Ileana De Anda-Duran[6], Sherral Devine[3], Juan Domingo Gispert[7], Simon Fankhauser[4], Karine Fauria[7], Fernando García-Gutiérrez[8], Felicia Goldstein[9], Oriol Grau-Rivera[7], Ashita Gurnani[3], Karen Harris[1], Kristi Ho[3], Akwaugo Igwe[3], Jennifer Jarovslavsky[1], Spencer Low[3], Kristina Malzbender[2], Carolina Minguillón[7], Alvaro Pascual-Leone[4], Zachary Popp[3], Andreea Radoi[7], Salman Rahman[3], Robin Romback[6], Gonzalo Sánchez-Benavides[7], Javier Solana Sánchez[4], James Snider[1], Marc Suarez-Calvet[7], Aishwarya Sukumar[2], Preeti Sunderaraman[3], Sergi Valero[8], Laura Nisenbaum[1], Niranjan Bose[2], Howard Fillit[1]
[1]Alzheimer's Drug Discovery Foundation, Science, New York, United States of America, [2]Gates Ventures, Health & Life Sciences, Kirkland, United States of America, [3]Boston University Chobanian & Avedisian School of Medicine, Department Of Anatomy And Neurobiology, Boston, United States of America, [4]Institut Universitari de Neurorehabilitació adscrit a la UAB, Institut Guttmann, Barcelona, Spain, [5]Alzheimer's Disease Data Initiative, Addi, Kirkland, United States of America, [6]Tulane University School of Public Health and Tropical Medicine, Department Of Epidemiology, New Orleans, United States of America, [7]BarcelonaBeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain, [8]Ace Alzheimer Center Barcelona, Universitat Internacional De Catalunya, Barcelona, Spain, [9]Emory University School of Medicine, Department Of Neurology, Atlanta, United States of America

Aims: Effective treatment of Alzheimer's disease and related dementias (ADRD) relies on the availability of scalable biomarkers that enable early detection, prognosis, and monitoring of AD. Biomarkers generated from speech have high potential to meet this need, but their development has been restricted by the size of speech and language datasets with requisite clinical data. SpeechDx aims to enable AD speech biomarker development and validation through (1) generation of a large volume of speech and language data samples across partner clinical sites, (2) pairing of each individual's speech and language data with their clinical data gathered at each site, and (3) harmonization of paired speech-clinical data across all sites.
Methods: SpeechDx is a 3-year observational study enrolling 2,650 participants spanning the full AD spectrum. Quarterly, each participant will remotely complete a brief battery of speech- and language-eliciting tasks via a custom-built SpeechDx app installed onto a study-provided tablet. Tasks included have been selected to elicit semi-constrained and unconstrained speech. SpeechDx clinical sites were selected to ensure reliable longitudinal clinical data collection, which may include blood and CSF ADRD biomarkers, MRI and PET imaging, and neuropsychological testing data. Clinical data across participating sites will be paired with individuals' speech and language data to serve as ground truth for machine learning training and validation. These data will be de-identified and harmonized across clinical sites to form the unified SpeechDx Dataset, accessible via the ADDI AD Curation Studio.
Results: SpeechDx is currently enrolling across 7 clinical sites in the US, Australia, and Spain, with full dataset completion anticipated by the 2028.
Conclusions: SpeechDx enables ADRD speech biomarker development via the creation of a new, gold-standard database of paired, harmonized speech and clinical data.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0512 / #2858

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

MINIMUM MMSE INCLUSION CRITERIA AND RELATION TO SUBSEQUENT COGNITIVE CHANGE

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Cai Gillis[1], Jin Wang[1], John O'Gorman[1], Wenting Cheng[1], Shardae Showell[1], Philip Montenigro[1], Nancy Maserejian[1], Sharon Cohen[2], Paul Aisen[3], Jennifer Murphy[1]
[1]Biogen Inc., Medical Affairs, Cambridge, United States of America, [2]Toronto Memory Program, Neurology, Toronto, Canada, [3]Keck School of Medicine, University of Southern California, Department Of Neurology, San Diego, United States of America

Aims: Better understanding of the impact of MMSE inclusion criteria on disease progression rates would help inform clinical trial design. In this work we explore differences in progression on clinical and cognitive measures comparing those with a baseline MMSE=22 to those with MMSE=21 or with MMSE=20, the minimum MMSE criteria often used in modern early AD trials.
Methods: NACC participants with AD dementia and evidence of amyloid-positivity were eligible for inclusion. Included participants were required to have a clinical dementia diagnosis, a CDR global score of 0.5 or 1.0, and a minimum MMSE score of 20, 21, or 22 all at the same visit. Additionally, at the time of MMSE index baseline, participants were required to be 60-85 years, have ≥6 years of education, and at least one additional follow-up visit with cognitive scores available. Linear mixed effect models adjusted for age, sex, years of education, and APOE ε4 status were examined to estimate mean annualized change in cognitive score (MMSE or CDR-SB) by baseline MMSE score for up to 5 years post-baseline.
Results: In adjusted-models, those with baseline MMSE=20 (n=116) had marginally greater annual progression compared to those with baseline MMSE=22 (n=159) on CDR-SB (0.03 points/year, p=0.13) and MMSE (-0.05 points/year, p=0.13) over follow-up. However, there were no differences in progression rates comparing those with index MMSE=22 (n=159) to those with baseline MMSE=21 (n=116) on CDR-SB (0.01 points/year, p=0.52) or MMSE (-0.02 points/year, p=0.39).
Conclusions: While there was suggestion of marginal differences in progression among baseline MMSE=20 compared to MMSE=22, differences were small and may be potentially relevant statistically but not clinically. Successful measurement of treatment effect in neurologically progressive disease requires a granular understanding of population differences in disease progression rate.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0513 / #2866

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

ASSESSING FINGER IMITATION TESTS FOR DEMENTIA AND MCI SCREENING IN CLINICAL PRACTICE

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Shintaro Nakarai[1], Shinichiro Maeshima[2], Aiko Osawa[1], Hitoshi Kagaya[1]
[1]National Center for Geriatrics and Gerontology, Rehabilitation Medicine, Obu, Japan, [2]National Center for Geriatrics and Gerontology, Education And Innovation Center, Obu, Japan

Aims: In the context of an increasingly elderly population, the prevalence of dementia and mild cognitive impairment (MCI) is on the rise, underscoring the importance of early detection and intervention. The aim of this study is to elucidate the utility of the finger construction imitation test (Fox and Reverse Fox) conducted in routine clinical settings.
Methods: We studied 170 patients attending a memory clinic. They consisted of 100 dementia patients, 53 MCI patients, and 17 cognitively normal individuals. During their initial consultation, patients were asked to imitate the shapes created with their fingers, such as the Fox and the combination of left and right fingers. The study also evaluated the sensitivity and specificity of this test for screening dementia and MCI.
Results: Concerning the imitation of the Fox shape, 121 patients (67 dementia, 44 MCI, 17 cognitively normal) were able to successfully imitate it, while 49 patients (40 dementia, 9 MCI) were not. The imitation of left and right finger combinations was achieved by 27 individuals (10 healthy, 9 MCI, 8 dementia). Significant differences were observed in the success rates of both Fox shape imitation and combination imitation. The sensitivity of Fox shape imitation for dementia and MCI was 0.4 and 0.32, which is relatively low, but the specificity was 1, indicating a high likelihood of success when cognitive function is normal. In contrast, finger combination (Reverse Fox) imitation showed good sensitivity for dementia and MCI, with values of 0.92 and 0.89, but the specificity was somewhat lower at 0.27 and 0.58.
Conclusions: The finger imitation task used in this study is simple and can be performed in a short time, even by non-specialists, suggesting its potential to identify cognitive decline.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0514 / #837

Poster Topic: *Theme A: β-Amyloid Diseases / A04.h. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

IMPAIRED DYNAMICS OF GLOBAL BRAIN COUPLING AND INHIBITORY SIGNALS PREDICT NEURAL OSCILLATIONS IN ALZHEIMER'S DISEASE

POSTERS: A04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Parul Verma[1], Benjamin Sipes[1], Kamalini Ranasinghe[2], Faatimah Syed[2], Bruce Miller[2], Katherine Rankin[2], Srikantan Nagarajan[1], Ashish Raj[1]
[1]University of California San Francisco, Radiology And Biomedical Imaging, San Francisco, United States of America, [2]University of California San Francisco, Memory And Aging Center, Department Of Neurology, San Francisco, United States of America

Aims: Recent neuroimaging findings indicate that the brain's functional activity does not remain static even while resting. Instead, it constantly switches between "micro-states", which are dynamic fluctuations of functional activity. We quantify micro-state dynamics in Alzheimer's disease (AD) using a biophysical model that predicts brain function from its structural network.
Methods: The model is characterized by global parameters that describe the coupled excitatory and inhibitory mesoscopic activity and the long-range excitatory macroscopic activity. We aimed to use the dynamic profiles of these parameters to classify AD patients versus a cohort of age-matched controls. Accordingly, we generated time-frequency spectrograms from a 1 min MEG recording with ~0.5s intervals. We then fit the model to each interval across subjects to obtain estimates of the biophysical model parameters, and we used sample entropy as a measure of model parameter temporal dynamics (Fig.1A). We hypothesized that the global coupling parameter, which can reflect microstates of whole-brain integration from those of segregated activity, would be less dynamic in AD.
Results: We indeed found that the global coupling parameter has significantly less dynamics, measured by the lower sample entropy, in AD ($p < 0.001$). We also found that another parameter reflecting inhibitory neural gain had significantly higher entropy in AD ($p < 0.05$; Fig.1B). Further, we found that the sample entropy of these model parameters was useful in classifying AD from controls (AUC = 0.86, Fig.1C), with the most important dynamic feature being global coupling (Fig.1D).

Conclusions: These results indicate that, in addition to biophysical parameters associated with static spectral changes observed previously, we can identify biophysical parameters associated with abnormal micro-state behavior in AD. Lower global coupling entropy indicates less dynamic switching between

integrative and segregated states in

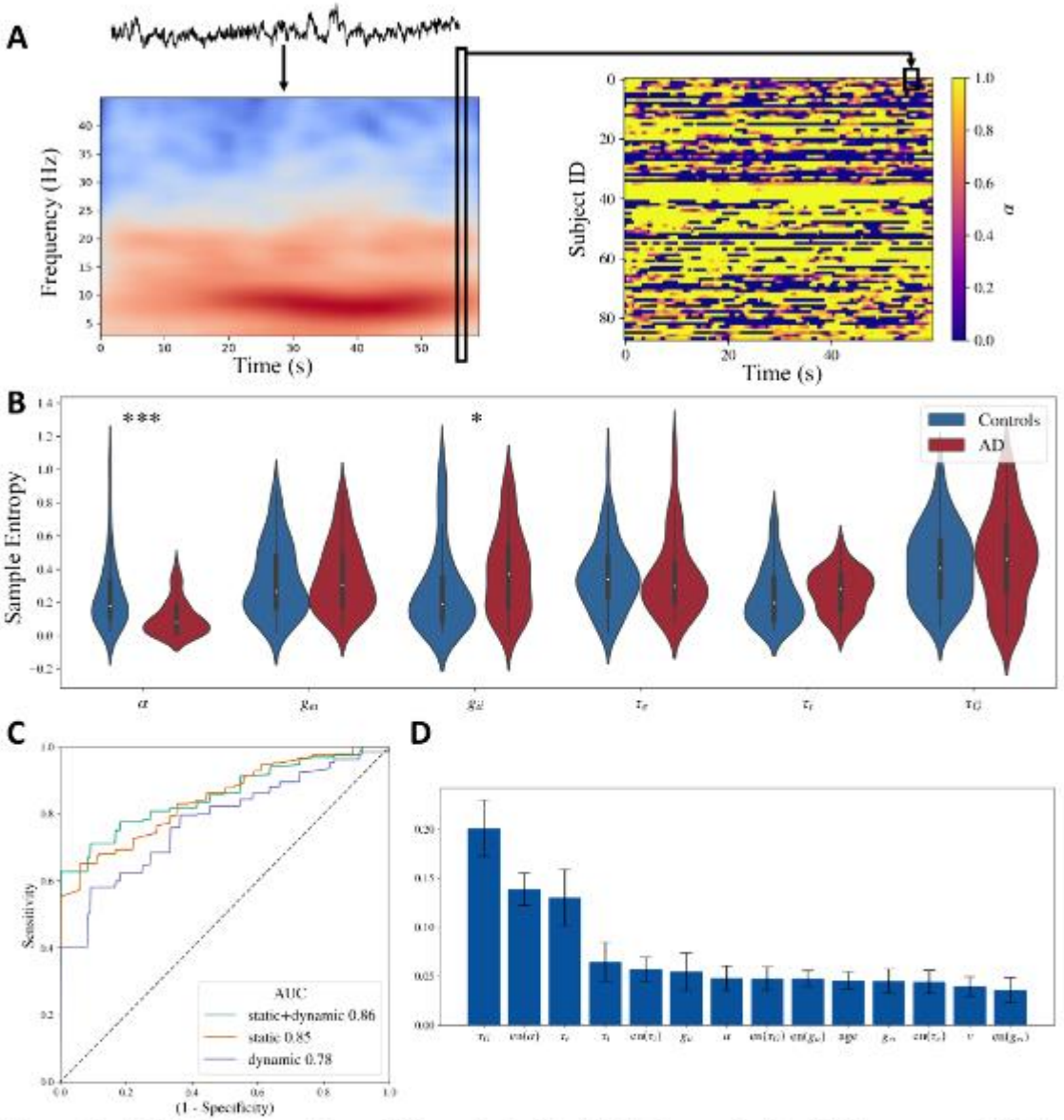


Figure 1: **A**) Illustrative workflow of the method. The MEG time series (top left) are converted into spectrogram (bottom left). We extract frequency spectra every 0.5s and then infer model parameters for each frequency spectra (right). The parameter plot shown on right is for the coupling parameter α. **B**) Sample entropy of parameters α: coupling among brain regions, g_{ei}: mesoscopic neural gain of signals coupled between excitatory and inhibitory populations, g_{ii}: mesoscopic neural gain of inhibitory population signals, τ_e: mesoscopic excitatory signal time constant, τ_i: mesoscopic inhibitory signal time constant, τ_G: macroscopic long-range excitatory time constant (***:p<0.001, *:p<0.05). **C**) Receiver operating characteristics curve obtained with entropy of parameters (purple), model parameters obtained by fitting to static frequency spectra (orange), and both entropy and static parameters (green) as features of a random forest classifier. **D**) Feature importance plot with both static parameters and entropy of dynamic parameters as features of the classifier. en() stands for entropy; v stands for speed parameter.

AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0515 / #439

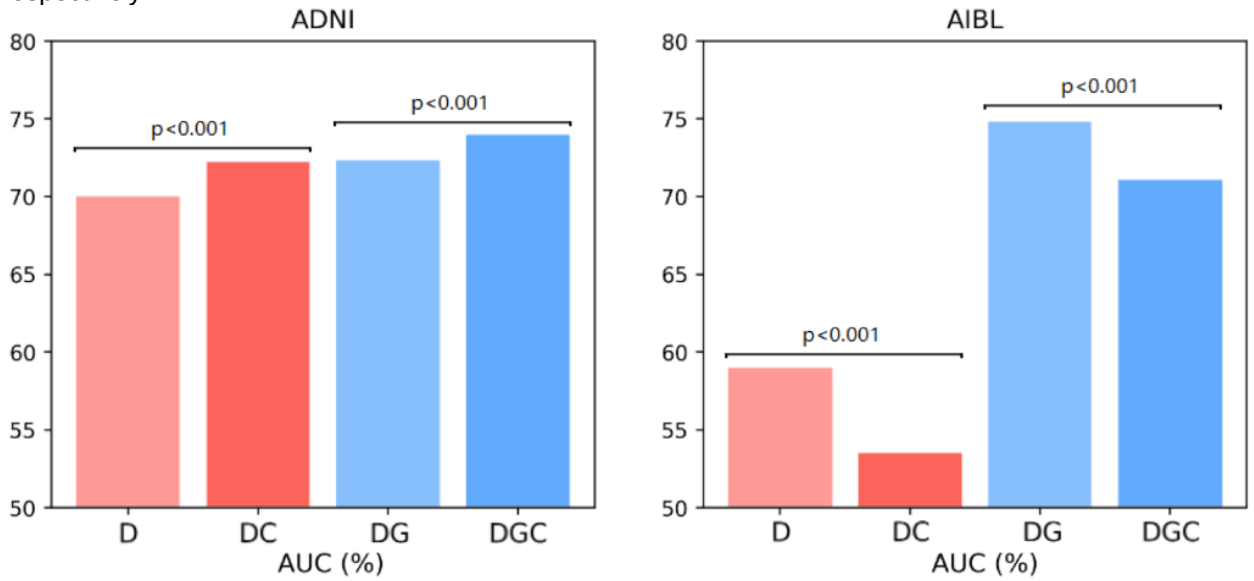
Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

CLASSIFYING BETA-AMYLOID POSITIVITY USING COGNITIVE ASSESSMENTS IN COGNITIVELY UNIMPAIRED COHORTS

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Shu Liu[1], Benjamin Goudey[1], Victor Fedyashov[1], Paul Maruff[1,2]
[1]University of Melbourne, Florey Institute Of Neuroscience & Mental Health, Carlton, Australia, [2]Cogstate, Cogstate, Melbourne, Australia

Aims: For preclinical Alzheimer's disease (Pre-AD), individuals with Beta-amyloid (Aβ) deposition do not meet criteria for cognitive impairment, there is evidence of subtle cognitive impairment. Therefore, cognitive tests may improve the prediction of Aβ status based on established demographic and genetic risk factors. This study aimed to quantify the benefit of cognitive measures when predicting Aβ status among cognitively unimpaired individuals beyond established risk factors.
Methods: Data came from 65-85 years old cognitively unimpaired individuals of the anti-amyloid treatment in asymptomatic Alzheimer's disease (A4) (n=4,036), the Alzheimer's Disease Neuroimaging Initiative (ADNI) (n=400), and the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) cohorts (n=141). Aβ-PET+ status was defined as a Centiloid score>30 based on florbetapir or florbetaben PET imaging. A Ridge regression was trained in the A4 using variables including demographics (D: age, sex, education), genetics (G: APOEe4 status), and cognition (C: CogState Brief Battery, PACC). The performance was evaluated in the AIBL and the ADNI using Area under ROC (AUC).
Results: In AIBL, cognitive measures significantly improved AUC by 2.22% and 1.65% beyond models with D and DG models. In the ADNI, cognitive measures significantly reduced sensitivity by 5.66% and 3.66% vs. age with and without APOE4
respectively.



Conclusions: Cognitive measures designed to be sensitive to AD showed limited or even reduced

sensitivity to Aβ+ compared to age with and without APOE4, motivating the development of Pre-AD specific cognitive tests.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0516 / #1498

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

LEVERAGING SPEECH PRODUCTION AS A PHYSIOLOGICAL MARKER OF COGNITIVE DECLINE: DEMONSTRATION OF THE ROLE OF TIMING AND SYNTACTIC CHANGES

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Jennifer Sorinas[1], Kristin Hannesdottir[1], Jessica Robin[2], William Simpson[2], Neva Coello[1], Angelika Caputo[1], Marie-Emmanuelle Riviere[1], Jelena Curcic[1]
[1]Novartis, Institutes For Biomedical Research, Basel, Switzerland, [2]Cambridge Cognition, Clinical Science, Toronto, Canada

Aims: Sensitive, easy to use, and meaningful markers of early cognitive decline are essential to AD drug development. We examined how audio recordings of the Clinical Dementia Rating (CDR) Scale interview could be used as objective measures of early cognitive decline.
Methods: We analyzed audio recordings of the CDR from 75 English-speaking participants at risk of developing AD enrolled in the Alzheimer's Prevention Initiative Generation Program. All participants were cognitively healthy at baseline. Recordings were processed using the Winterlight speech analysis platform; producing an array of objective speech features. We applied different machine learning strategies to examine which groups of features were predictive of the emergence of clinically significant cognitive decline.
Results: 52% of the participants showed cognitive decline over the course of the study (assigned via expert clinicians at each visit). Examination of classifier learning curves highlighted the recent experience task, and the memory repetition task as showing the strongest association with cognitive decline. Complexity of speech (represented by timing and syntactic features) within the recent experience task showed the strongest effect, predicting a transition to cognitive impairment with 70% accuracy. Other informative categories included acoustic (spectral properties of the sound wave, 69%), morphological (inflection, case and tense changes, 69%) and discourse (organization and repetitiveness, 68%). Sentiment (emotional content) and lexical (types of words used) features performed above chance but were less informative.
Conclusions: These results further support the growing literature linking measurable changes in speech to cognitive decline. New measures are needed to stage and monitor patient cohorts in the earliest phases of disease. These results highlight the utility of speech in these cases and support future validation and use of these tools in clinical trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0517 / #996

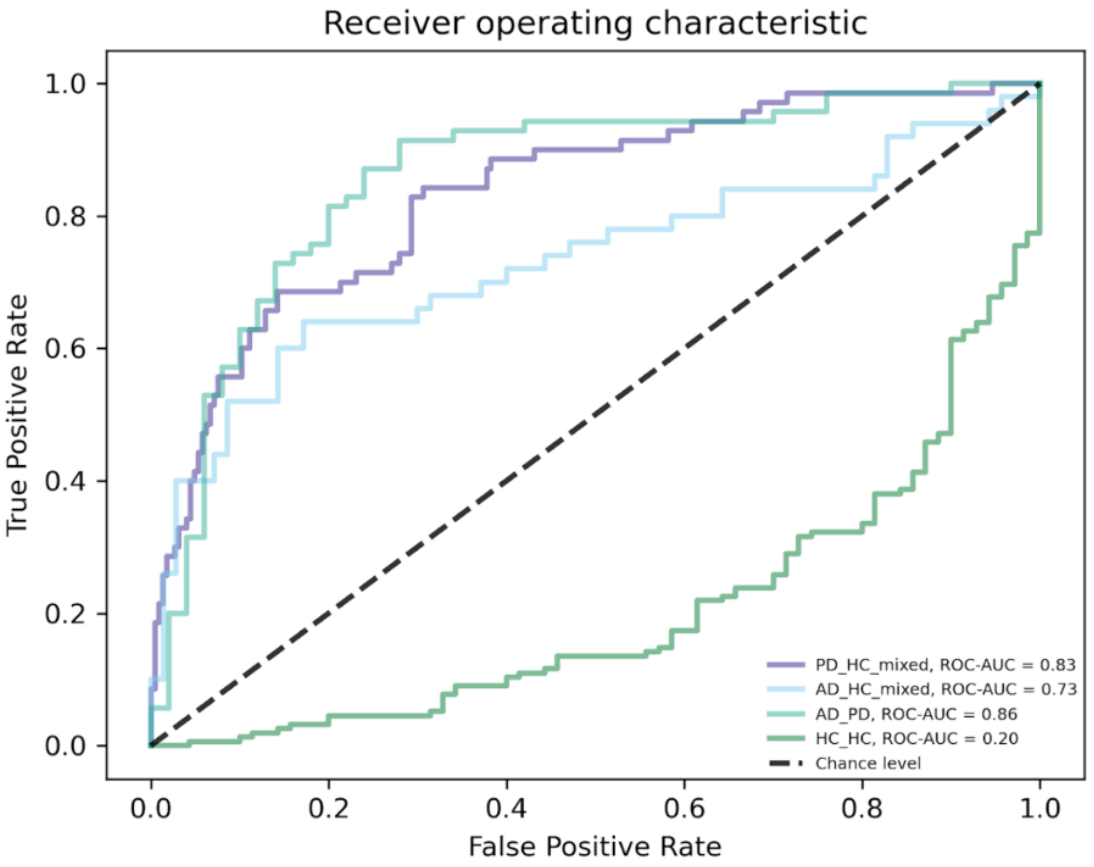
Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

DISTINCT ACOUSTIC SPEECH PROFILES DIFFERENTIATING AD AND PD FROM A READING PASSAGE IN SPANISH

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Johannes Tröger[1], Elisa Mallick[1], Felix Dörr[1], Alexandra König[2,3], Ebru Baykara[2], Nicklas Linz[1], Juan Rafael Orozco-Arroyave[4]
[1]ki:elements, Research, Saarbrücken, Germany, [2]ki:elements, Clinical, Saarbrücken, Germany, [3]inria, Cobtek, Sophia Antipolis, France, [4]Universidad de Antioquia, Gita Lab, Medellín, Colombia

Aims: The aim of this work is to investigate whether acoustic speech biomarker profiles from a standardized reading passage speech task can differentiate Alzehimer's from Parkinson's disease and associated behavioral clinical symptoms.
Methods: This feasibility research is based on two different Spanish reading speech data sets—the Dementia Bank IVANOVA (Ivanova et al., 2022) and the PC-GITA (Orozco-Arroyave et al., 2014). Both data sets recorded patients and matched healthy controls: IVANOVA (AD_dementia 54/ HC 155) and PC-GITA (PD 70 / HC 70). From the recordings, we extracted acoustic features using the ki:elements speech extraction library SIGMA. We normalized acoustic features for potential cohort effects (loudness normalization) and subsequently preselected acoustic features that do not show significant differences on their distributions when comparing the respective HC groups using p = 0.20 as cutoff on the Two Sample Smirnov Test. We then combined those features in logistic regression models using 10-fold x-validation for better generalisability to simulate downstream clinical utility.
Results: After preprocessing set of acoustic features remained significant measuring temporary aspects of speech, voice quality as well as prosodic aspects. Those features have been traditionally associated with symptoms in PD such as aprosodia or dysphonia as well as apathy in AD dementia. The logistic regression models were able to differentiate between PD and AD with a balanced accuracy of .81. The Receiver Operating Characteristics of all models evaluated can be seen in Figure
1.



Conclusions: The results show that acoustic speech biomarker profiles can indeed differentiate AD and PD. A limitation of these results is that patient groups stem from different cohorts. However, both are Spanish and we conducted a series of preparatory steps ensuring that speech features are not significantly different between the cohorts per se.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0518 / #499

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

ACTIGRAPHY AND SLEEP-MONITORING DEVICES HELP TO DIFFERENTIATE BETWEEN ALZHEIMER'S DISEASE AND DEMENTIA WITH LEWY BODIES.

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Debby Tsuang[1], Karl Brown[2], Sarah Payne[3], Andrew Shutes-David[2], Victoria Orr[2], Kevin Vintch[1], Pamela Dean[1], Katherine Wilson[2], Yeilim Cho[3], Daniel Levinowski[4], Edmund Seto[5]
[1]University of Washington, Psychiatry And Behavioral Sciences, Seattle, United States of America, [2]Seattle Institute of Biomedical and Clinical Research, Va Puget Sound, Seattle, United States of America, [3]VA Puget Sound, Research And Development, Seattle, United States of America, [4]Applied Brain Monitoring, Inc, N/a, Carlsbad, United States of America, [5]University of Washington, Environmental Health, Seattle, United States of America

Aims: To identify actigraphy and sleep differences between Alzheimer's disease (AD) and dementia with Lewy bodies (DLB).
Methods: Participants with probable AD (n=8) and DLB (n=12) wore triaxial wGT3X-BTs actigraphy devices on their non-dominant wrists for 2 weeks and Sleep Profiler X8 EEG devices on their foreheads for 2 consecutive nights. Raw actigraphy data were converted into daily activity counts (ACs) using activityCounts R with fragmentation calculated using ActFrag R.
Results: AD participants were ~10 years older than DLB participants, but other demographics and cognitive scores were similar. AD participants had shorter sedentary bouts (mean minutes [SD]=4.30 [0.85] vs 5.44 [1.34]) and slightly higher ACs (mean [SD]=$1.45x10^6$ [$5.82x10^5$] vs $1.38x10^6$ [$6.99x10^5$]) than DLB participants (Fig. 1a/1b). A threshold of 200 counts/minute showed the most separation between groups, with AD participants spending more time above the threshold (mean minutes [SD]=657 [89] vs 550 [161]; Fig. 1c). AD participants spent more time in REM sleep (mean [SD]=17.8% [4.51] vs 6.89% [7.19]) and less in NRH (mean [SD]=5.03% [4.95] vs 12.8% [11.3]) than DLB participants (Fig. 2).

Figure 1a: Sedentary bout duration

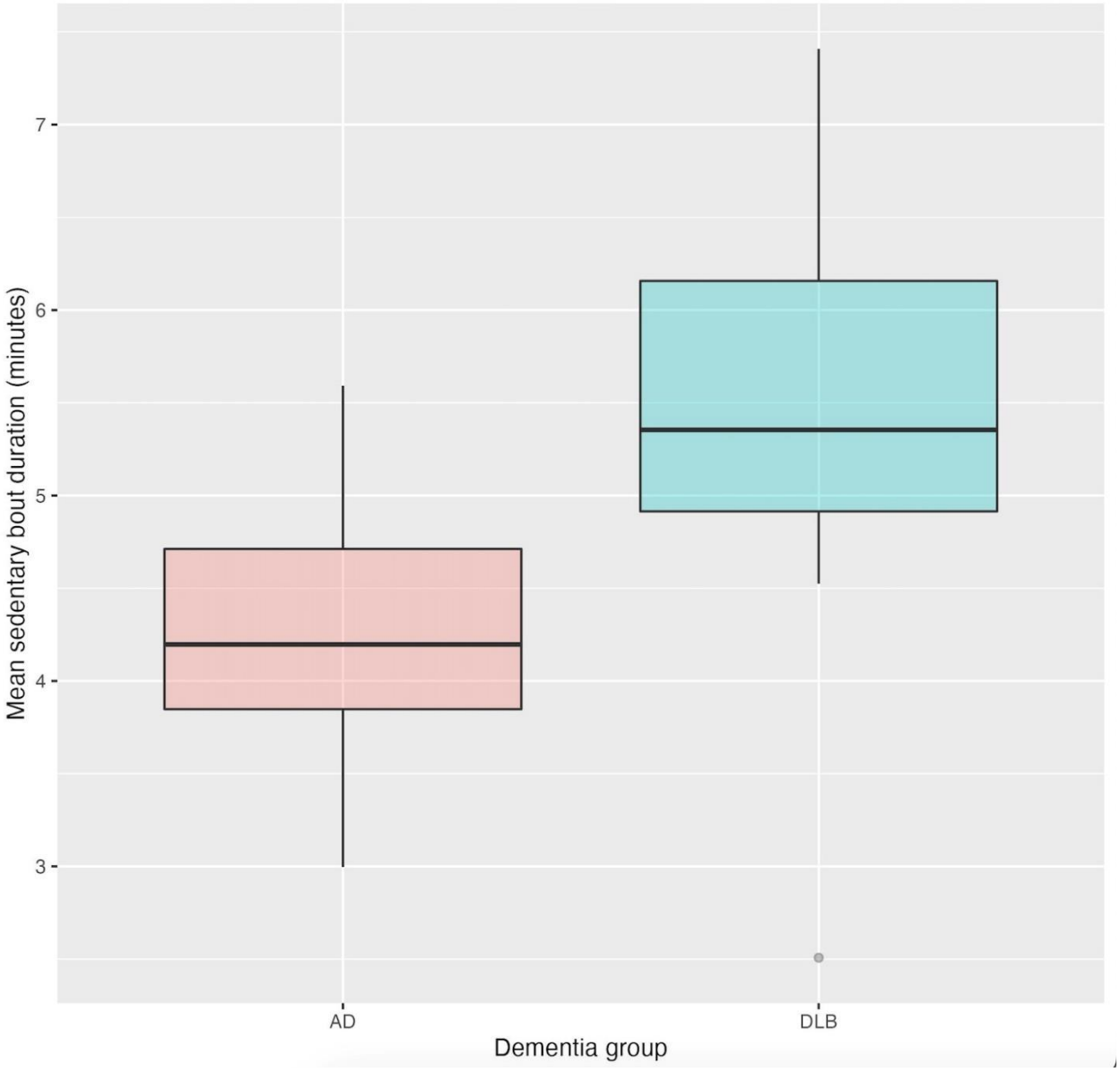


Figure 1b: Total activity

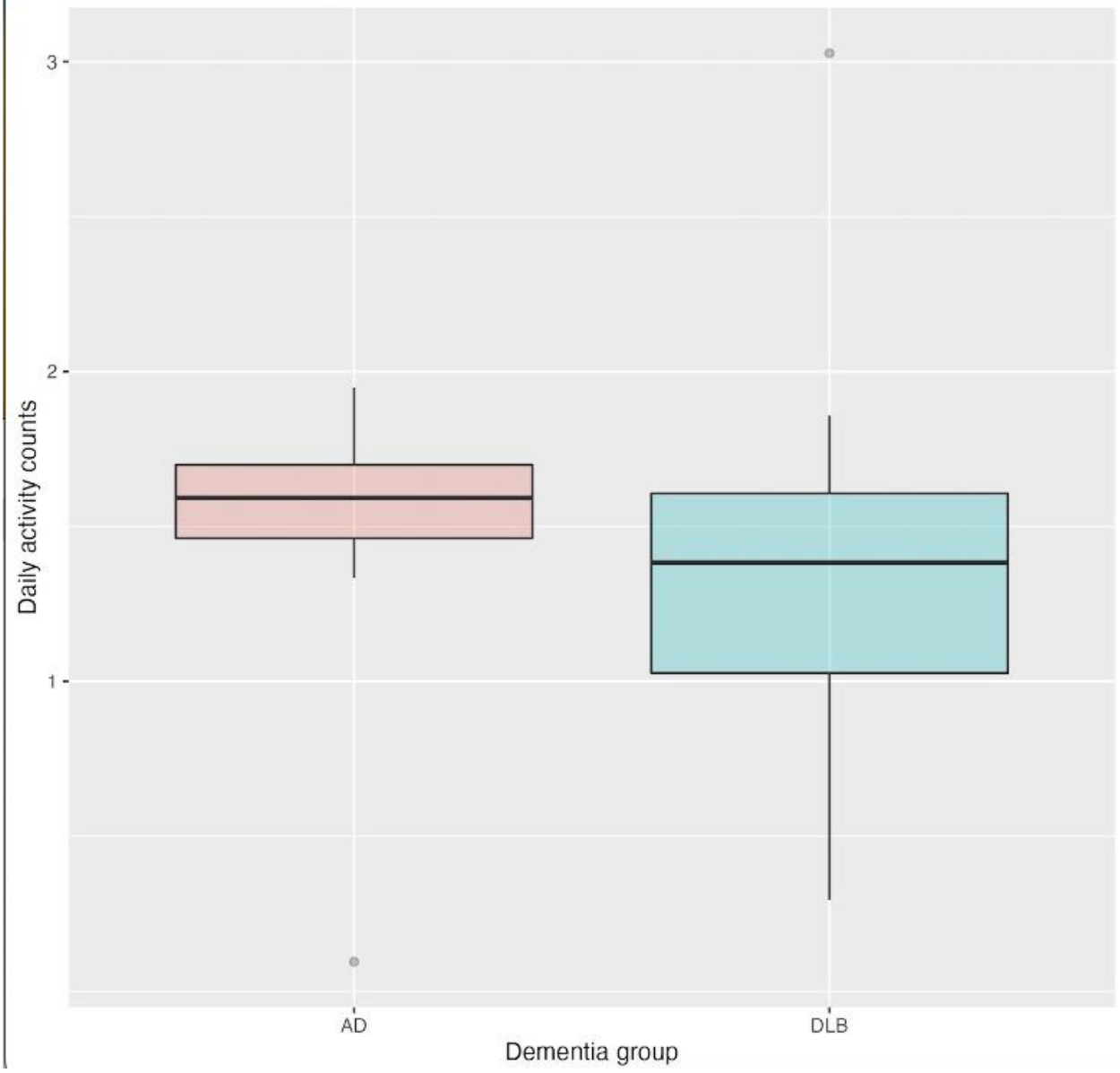


Figure 1c: Activity count cutpoint thresholds

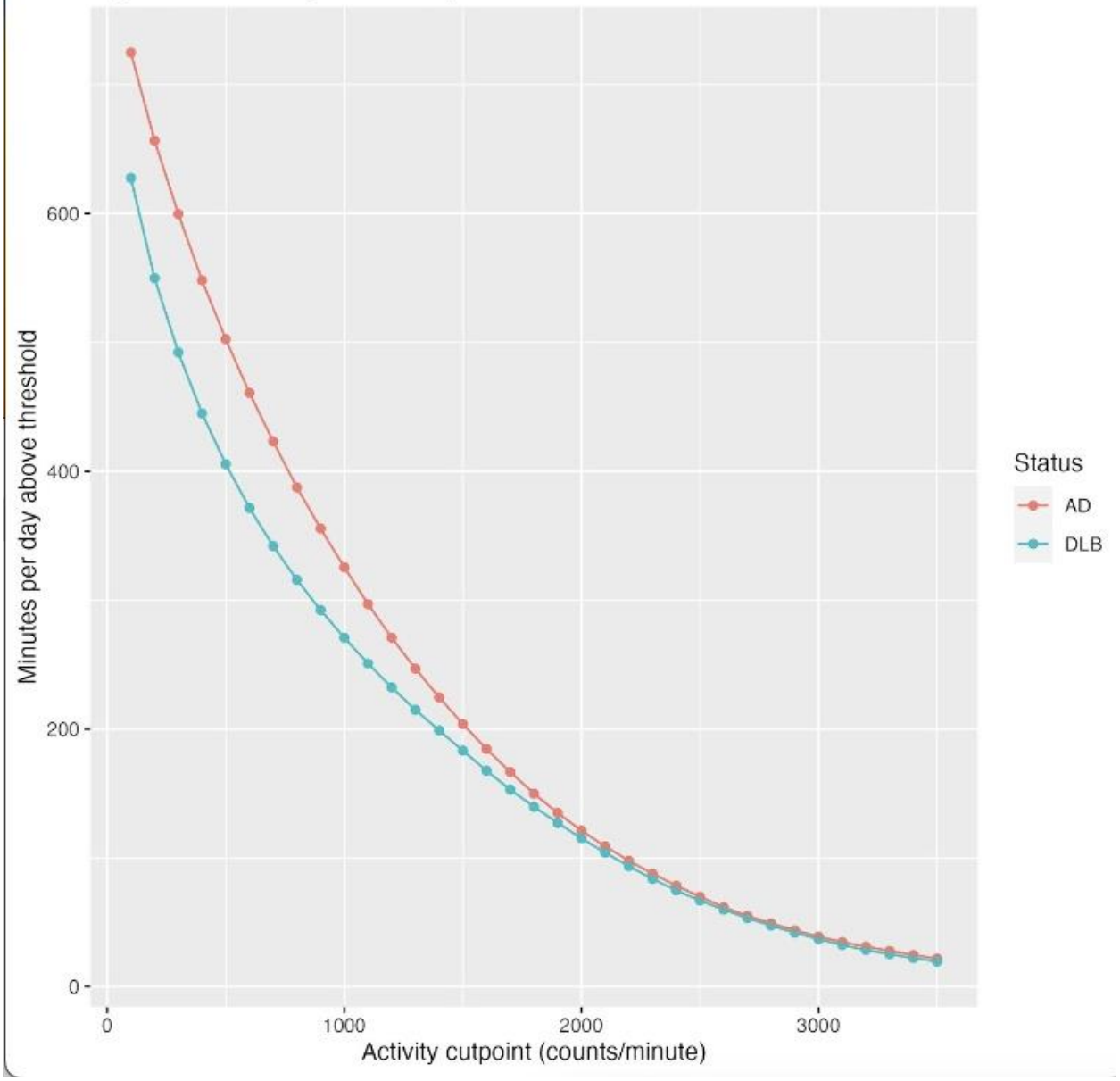
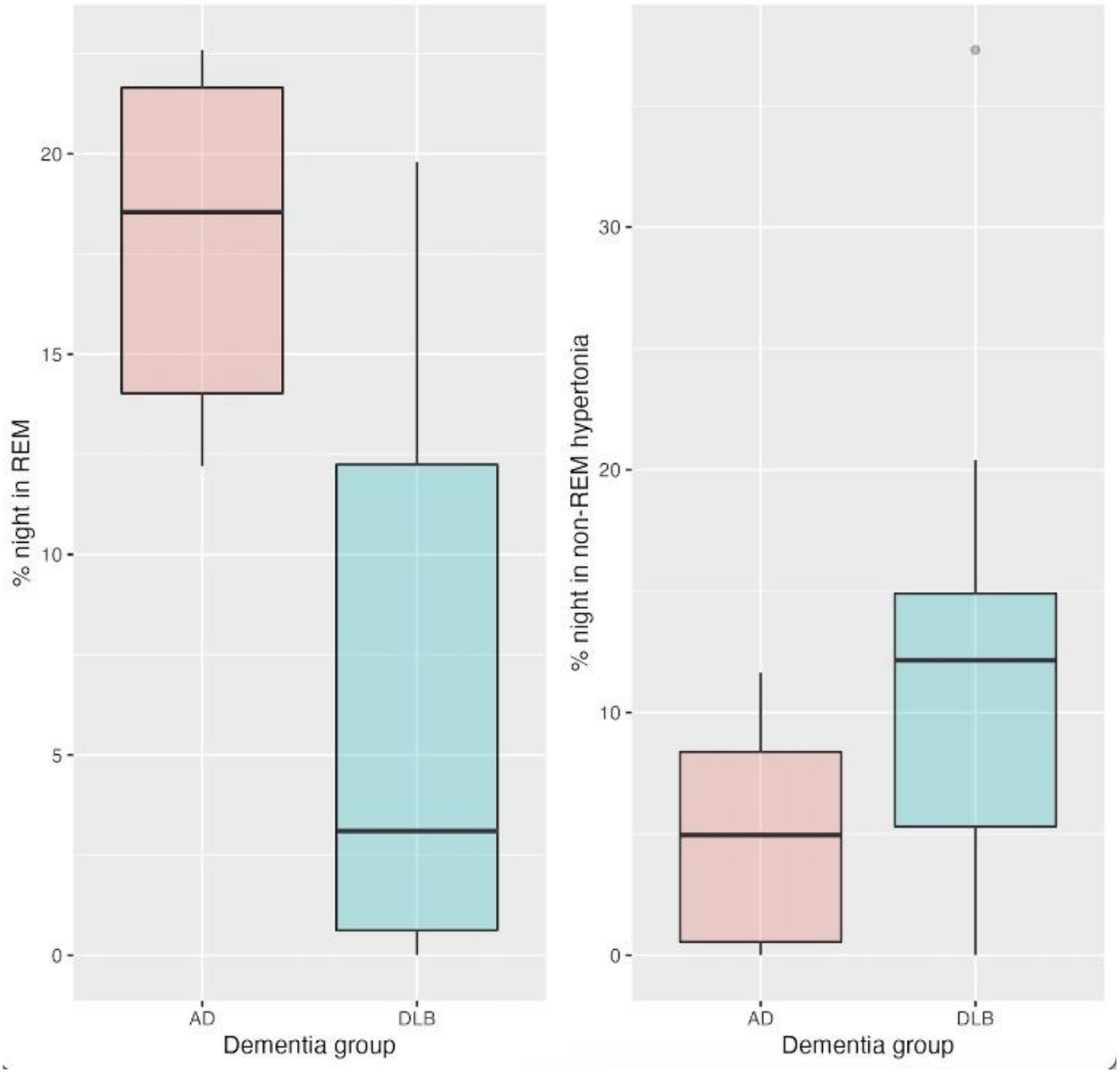


Figure 2: Sleep metrics



Conclusions: Actigraphy and sleep-monitoring devices can elucidate potential differences between AD and DLB in REM and NRH time, sedentary bout duration, and activity at low-activity thresholds.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0519 / #2913

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

EXPLORING THE EFFECT OF AMYLOID BETA ON EXECUTIVE FUNCTIONS IN COGNITIVELY UNIMPAIRED ADULTS: A REPLICATION AND EXTENSION STUDY USING THE DELCODE COHORT

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Louise Droste Zu Senden[1], Luisa Schneider[1], Michael Wagner[2], Josef Priller[3], Anja Schneider[4], Jens Wiltfang[5], Frank Jessen[6], Emrah Düzel[7], Katharina Bürger[8], Robert Perneczky[8], Stefan Teipel[9], Christoph Laske[10], Annika Spottke[6], Michael Heneka[11], Matthias Schmid[11], Oliver Peters[1]
[1]Charité—Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Psychiatry And Neurosciences, Berlin, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Neuropsychology, Bonn, Germany, [3]German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany, Department Of Psychiatry And Psychotherapy, Berlin, Germany, [4]DZNE, Translational Dementia Research, Bonn, Germany, [5]German Center for Neurodegenerative Diseases (DZNE), German Center For Neurodegenerative Diseases (dzne), Goettingen, Germany, [6]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Clinical Dementia Research, Bonn, Germany, [7]German Center for Neurodegenerative Diseases, -, Magdeburg, Germany, [8]German Center for Neurodegenerative Diseases (DZNE), Dzne, Munich, Germany, [9]Deutsches Zentrum für Neurodegenerative Erkrankungen, Deutsches Zentrum Für Neurodegenerative Erkrankungen, Rostock, Germany, [10]German Center for Neurodegenerative Diseases, Dzne, Tübingen, Germany, [11]German Center for Neurodegenerative Diseases, Dzne, Bonn, Germany

Aims: Previous studies suggest that in prodromal Alzheimer's disease (AD) stages, AD pathology (i.e., deposition of Aβ(1-42) and p-tau181) may be differentially associated with different cognitive function domains. Precisely, one study showed that abnormal CSF Aβ(1-42) status predicts executive function decline, and abnormal CSF p-tau181 status predicts memory decline in cognitively unimpaired (CU) individuals with AD neuropathology. Here, we aimed to validate and extend these previous findings.
Methods: CU participants from the German DELCODE cohort with available CSF biomarker data (p-tau181, Aβ(1-42) and total tau) and neuropsychological test data on executive functions, memory, visuospatial functions and verbal fluency (i.e., TMT, Delayed Recall, Clock Copying, Animal Fluency Task) were included. Additionally, analyses were conducted not only for single test scores but also for cognitive domain composite scores. Analyses were performed using Multiple linear regression models.
Results: 287 participants were included. Aβ(1-42) was associated with executive functions as measured by the TMT (β=0.12, p=0.043). However, no association was found between Aβ(1-42) and the executive functions composite score. P-tau181 was associated with memory (i.e., ADAS Delayed Recall test; β=0.16, p=0.005), but not with the memory composite score. None of the predictors were associated with verbal fluency or visuospatial function. In a second step to investigate the prodromal AD stages, participants were classified in A+/A- and T-/ N- biomarker profiles. Again, Aβ(1-42) was associated with executive function (β=0.12, p=0.047) but not with memory. No association was found for the executive functions composite score.
Conclusions: In line with previous findings, Aβ(1-42) was associated with worse executive function performance, while p-tau181 was associated with worse memory performance. However, no effect of Aβ(1-42) on executive functions was found using composite scores, which ultimately warrants additional research into this topic.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0520 / #2793

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

LONGITUDINAL IN VIVO MICROSCOPIC IMAGING OF AB PATHOLOGY IN A NOVEL HUMANIZED APP KNOCK-IN MOUSE MODEL (APPSAA)

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Evgeny Pryazhnikov[1], Ulrika Julku[1], Tamas Kopcsanyi[1], Tom Cornelissen[2], Wannes Dejonckheere[2], Sofie Carmans[2]
[1]Neurotar LtD, Neurotar Ltd, Helsinki, Finland, [2]reMYND, Cro, Leuven, Belgium

Aims: *In vivo* two-photon imaging of cerebral Aβ deposits is an invaluable tool for studying these hallmarks of Alzheimer's disease (AD) and evaluating the efficacy of disease-modifying treatments. We present the results of the first-time *in vivo* assessment of the growth patterns of parenchymal and perivascular Aβ plaques in a new humanized APP knock-in mouse model (APPSAA) which endogenously expresses APP with three clinical mutations.
Methods: We used longitudinal *in vivo* two-photon imaging to follow the growth of Aβ plaques in the somatosensory cortex of 6.5 months old humanized APPSAA knock-in mice. The plaques were labeled using a Methoxy-XO4 tracer 24 hours before the start of imaging.
Results: Initial observations revealed a moderate density of Methoxy-XO4-labeled plaques with a small dense core surrounded by fibrillar Aβ. This is in line with previously observed Aβ staining by immunohistochemistry. Follow-up imaging sessions revealed an increase in density of cortical plaques primarily due to the emergence of new small Aβ cores, rather than the expansion of pre-existing plaques. Notably, perivascular amyloid deposition escalated after 7 months of age. In 80% of the mice, the cranial windows remained clear, permitting the longitudinal tracking of individual deposits over multiple sessions. No behavioral abnormalities linked to anesthesia were observed in these subjects.
Conclusions: This first *in vivo* pathological characterization of the APPSAA model underscores its potential for *in vivo* testing of compounds aimed at slowing AD progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0521 / #1689

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

THE GAIT PATTERN OF ALZHEIMER'S DISEASE IS ASSOCIATED WITH THE REGIONAL BETA-AMYLOID DEPOSITION AND CORTICAL ATROPHY

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Min Seok Baek[1], Dong Ho Kim[2]
[1]Wonju Severance Christian Hospital Yonsei University Wonju College of Medicine, Department Of Neurology, Wonju, Korea, Republic of, [2]Korea University, 1department Of Artificial Intelligence, Seoul, Korea, Republic of

Aims: To investigate the association between gait patterns and neuroimaging biomarkers in Alzheimer's disease.
Methods: We prospectively included 33 cognitively unimpaired (CU) individuals, 20 patients with MCI due to AD, and 43 patients with AD dementia at the Memory Disorder Clinic of Wonju Severance Christian Hospital between January 2022 and May 2023. Participants underwent brain magnetic resonance imaging (MRI), ^{18}F-florbetaben PET, neuropsychiatric tests, and APOE genotyping. Gait was evaluated using a 5.79-m long walkway. We conducted a comparative analysis using Pearson correlation to examine the relationships between gait parameters and several variables, including cortical thickness and regional Standardized Uptake Value Ratios (rSUVR).
Results: After controlling for age, sex, and duration of education, the MCI group exhibited distinct gait patterns compared to the CU group. Specifically, the MCI group displayed lower velocity, reduced step length, and decreased swing %. The gait patterns of the Dementia (DEM) group were characterized by even more pronounced decreases in velocity, step length, and swing percentage in comparison to the CU group. Decreased gait velocity and step length was associated with greater Aβ burden in prefrontal, sensorimotor, parietal, lateral temporal, occipital, and anterior cigulate cortices and precuneus. Decreased step length was associated with greater Aβ burden in the prefrontal, inferior parietal, lateral temporal, occipital, anterior cingulate cortices and precunes after multiple region-wise correction. Gait velocity and step length was associated with cortical thickness in the lateral temporal, inferior parietal, entorhinal, parahippocampus, insular cortices and
precuneus.

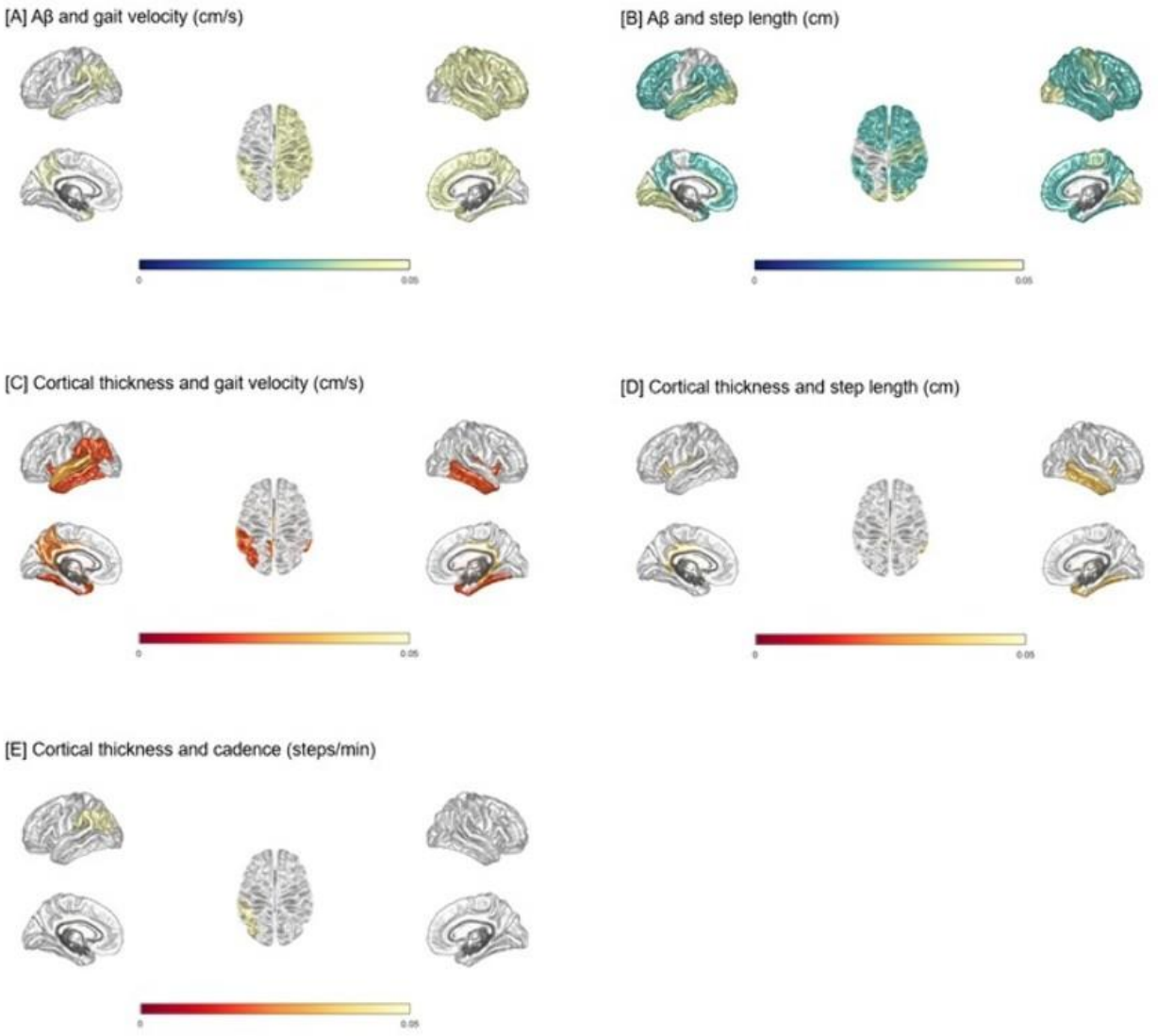


Figure 1. Association of gait parameters with ^{18}F-florbetaben SUVR (A, B), and cortical thickness (C, D, E) after adjustment for age, sex, and duration of education.

Conclusions: Our study has revealed significant correlations between gait parameters and Aβ, and cortical thickness in AD. T

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0522 / #1849

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

UNBIASED CLASSIFICATION RESOLVES DISTINCT SUBTYPES ASSOCIATED WITH CLINICAL AND PATHOLOGICAL PHENOTYPES IN THE ELDERLY HUMAN BRAIN PROTEOME

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Kathleen Carter[1,2], Lenora Higginbotham[2,3], Anantharaman Shantaraman[1], Lingyan Ping[1], Duc Duong[1], Philip De Jager[4], David Bennett[5], James Lah[2,6], Allan Levey[2], Nicholas Seyfried[2]
[1]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [2]Emory University School of Medicine, Goizueta Alzheimer's Disease Research Center, Atlanta, United States of America, [3]Emory University School of Medicine, Department Of Neurology, Atlanta, United States of America, [4]Columbia University Irving Medical Center, Center For Translational And Computational Neuroimmunology, Department Of Neurology And Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York, United States of America, [5]Rush University Medical Center, Rush Alzheimer's Disease Center, Chicago, United States of America, [6]Emory University School of Medicine, Neurology, Atlanta, United States of America

Aims: Proteomic subtyping is a valuable tool for understanding the biological differences between individuals, regardless of clinical presentation. Our recent proteomic studies of human brain tissues have identified disease subtypes in cognitively impaired individuals linked to distinct biological mechanisms and clinicopathological phenotypes in the aging brain. Here, we extend these analyses by including over 300 new individual samples, which include over 100 African Americans.
Methods: Over 9000 proteins were quantified from more than 900 postmortem brain samples obtained from the Religious Orders Study and Rush Memory and Aging Project using tandem mass tagged mass spectrometry (TMT-MS). Module hub proteins from a recent consensus network analysis of the human brain were utilized to classify samples into subtypes based on patterns in shared biology, using the MONET M1 modularity clustering algorithm. Furthermore, to preserve the effects of demographic factors on proteomic subtyping, age and sex were not regressed. Supervised machine learning approaches were utilized to identify proteins driving subtype distinction.
Results: Unbiased classification of control, mild cognitively impaired (MCI) and Alzheimer's Disease (AD) brain proteomes resolved multiple subtypes with expression differences across numerous cell-types and biological ontologies. Each subtype differs in their clinical and pathological presentation and demographics (e.g., age, sex, race). One subtype enriched with MCI and AD presented with atypical proteomic features associated with clinical and pathological hallmarks of cognitive resilience.
Conclusions: Unbiased clustering can resolve pathological and cellular phenotypes linked to cognitive impairment. Further investigation of these distinct subtypes promises to meaningfully impact diagnostic, prognostic, and therapeutic precision.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0523 / #2862

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

A NOVEL APPROACH TO DETECT ABERRENT TRIGLYCERIDES IN AD TRANSGENIC MOUSE BRAIN USING MALDI-2 MASS-SPECTROMETRY IMAGING

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Bandana Bera[1], Daniela D'Amico[1], Prem Shankar[1], Eliseo Eugenin[1], Giulio Taglialatela[2], Brendan Prideaux[1]
[1]University of Texas Medical Branch, Department Of Neurobiology, Galveston, United States of America, [2]University of Texas Medical Branch, Neurology, Galveston, United States of America

Aims: Neutral storage lipids, such as triacylglycerides (TAGs) and cholesteryl esters (CEs), accumulate as lipid droplets (LDs) within tissues and cells in multiple neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis. Due to their poorer ionization efficiencies than other abundant lipids visualization of TAGs and CEs in brain is challenging using traditional MALDI-1 MSI techniques. A modified MALDI-2 MSI imaging approach has been developed with improved sensitivity to detect and visualize the distribution of neutral lipids in brain tissues to elucidate their role in AD pathogenesis.
Methods: MALDI-2 MSI was applied to examine neutral lipid distribution such as triglycerides accumulation within the subventricular zone (SVZ) in brain tissue obtained from 5 and 17 months old 3xTGAD mice and wild type controls. A combination of lipidomic MALDI-2 MSI assessment, immunofluorescence (IF) analysis, and histological staining for morphological evaluation were used for a direct co-localization of lipid/metabolite with protein signals at a single cell spatial resolution.
Results: We have found that MALDI-2 increases the sensitivity of TAG analysis when spiked onto brain tissue sections. MALDI-2 ionization also enhances TAG imaging in 3xTG mouse brain tissues, more interestingly we found that TAG accumulate within the SVZ early period of disease pathogenesis in the 3xTg mouse model (~ 5 months) and the accumulation increased with disease progression. Moreover, we also found that our MALDI-2 methods produce IF equivalent image quality.
Conclusions: Our optimized MALDI-2 MSI approach enables imaging of TAGs in 3xTG mice brain tissues at the single cell spatial resolution. This characterization can be translated to other neurodegenerative diseases to elucidate potential targets for new pharmacological therapies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0524 / #1403

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

NEW INSIGHTS INTO ETIOLOGY OF ALZHEIMER'S DISEASE: THE ROLE OF DIACYLGLYCEROL KINASE Θ (DGKΘ)

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Giovanna Casili, Marika Lanza, Laura Cucinotta, Rossella Basilotta, Irene Paterniti, Salvatore Cuzzocrea, Salvatore Oddo, Emanuela Esposito
University of Messina, Chemical, Biological, Pharmaceutical And Environmental Sciences, Messina, Italy

Aims: Objectives. Diacylglycerol kinase (DGK) is a key enzyme in regulating diacylglycerol turnover and is involved in various physiological functions. The isoform DGKθ has a unique domain structure, and it is predominantly expressed in excitatory neurons throughout all parts of the mammalian brain. This study aimed to reveal the involvement of DGKθ in neurodegenerative diseases, highlighting its role in Alzheimer's disease (AD).
Methods: Methods. The evaluation of DGKθ was verified in brains of APP/PS1 and control mice (4-5 and 12-18 months of age) through western blot analysis. Immunohistochemistry analysis was used to reveal b-amyloid depots and glial fibrillary acid protein (GFAP) immunostaining. Statistical correlations between DGKθ expression, inflammatory markers and autophagy activation were also performed.
Results: Results. In older APP/PS1 mice (12-18 months of age), DGKθ levels were significantly higher compared to control mice and positively correlated with b-amyloid deposit. In addition, GFAP immunoreactivity and mTOR activation positively correlated with DGKθ levels. Interestingly, the absence of DGKθ modulation in control APP/PSN1 mice at 4-5 months of age, supports the idea that the AD disease triggers the increase in DGKθ.
Conclusions: Conclusions. These results suggest that DGKθ may play a significant role in AD, potentially serving as a crucial diagnostic biomarker and offering valuable insights into its use as a pharmacological therapeutic target.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0525 / #1357

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

ASSOCIATION BETWEEN CSF AB42/40 RATIO AND AMYLOID DISCRIMINABILITY OF ATN CLASSIFICATION IN ODOR IDENTIFICATION IN ALZHEIMER'S DISEASE

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Yukifusa Igeta[1], Isao Hemmi[2], Kohei Yuyama[3], Yasuyoshi Ouchi[1]
[1]Toranomon Hospital, Department Of Dementia, Minato-ku, Tokyo, Japan, [2]Japanese Red Cross college of Nursing, Faculty Of Nursing, Shibuya-ku, Tokyo, Japan, [3]Hokkaido University, Faculty Of Advanced Life Dcience, Kitaku,Sapporo, Japan

Aims: Screening tests are necessary to identify patients who are suitable for Alzheimer's disease (AD) disease-modifying therapies. We studied whether odor identification scores can identify patients at each stage of the ATN classification system.
Methods: This study included 132 Japanese participants, with 49 having AD, 23 having mild cognitive impairment (MCI), and 60 normal controls. Participants underwent comprehensive medical evaluations, including neuropsychological tests, imaging studies, and CSF biomarker assessments. ELISA was used to measure Aβ42, p-Tau181, and t-Tau in CSF. ROC analysis was performed to determine cutoff values for each biomarker for diagnosing AD. Based on this index, ATN classification was performed. The discriminative ability of odor identification scores was evaluated among four ATN subgroups, which included the normal biomarker group and the AD continuum, after removing the SNAP group. The correlation between odor identification scores and various CSF biomarkers and neuropsychological tests were also examined.
Results: The odor identification scores correlated significantly with major neuropsychological scores, regardless of apolipoprotein E(APOE)4 status. They also correlated with effective cerebrospinal fluid (CSF) biomarkers (amyloid β(Aβ)42 ($p=0.0005$) and the Aβ42/40 ratio($p=0.0001$) and phosphorylated Tau (p-Tau)/Aβ42 ratio ($p<0.0001$) but not ineffective biomarkers (Aβ40($p=0.813$) and the p-Tau/total Tau (t-Tau) ratio($p=0.262$). Covariate analysis showed a slight positive correlation between the odor identification scores, and CSF Aβ42 ($\rho=0.230$; $p=0.043$) and the Aβ42/40 ratio ($\rho=0.292$; $p=0.010$). Conclusively, according to the ATN classification, the odor identification scores demonstrate excellent discriminative power for amyloid deposition but are unsuitable for differentiating between the p-Tau accumulation and neurodegeneration stages.
Conclusions: The odor identification scores show a mild association with CSF Aβ42 and the Aβ42/40 ratio and is a potential screening parameter for preclinical AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0526 / #358

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

EXPLORATORY ANALYSIS OF 3000 PROTEINS IN POSTMORTEM HUMAN BRAIN TISSUE LYSATES USING PROXIMITY EXTENSION ASSAY

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Anne-Li Lind[1], Christoffer Cambronero[2], Ryan Lamers[1], Mariana Fontes[1], Tarif Awad[1]
[1]Olink Proteomics, Scientific Affairs, Uppsala, Sweden, [2]Olink Proteomics, Data Science, Uppsala, Sweden

Aims: The development of effective management strategies of neurological disorders is challenging, in part because of the complexity and inaccessibility of the affected systems and tissues. Omic, and multi-omic analyses of bio-banked postmortem donor brain tissues offer a unique opportunity to map complex mechanisms in the actual tissue affected by neurological disease. In this study we aimed to evaluate the matrix compatibility and technical performance of a new Olink® Proximity Extension Assay (PEA) technology measuring 3000 proteins in human brain tissue lysates.
Methods: In this exploratory technical study, we examined, for the first time, the detectability of 3,000 human proteins in 15 postmortem human brain tissue lysate samples using PEA technology. The study protocol and platform performance were evaluated for data quality and technical reproducibility.
Results: The results showed robust detectability for the neat dilution of this complex sample matrix for the majority of assays, including hundreds of proteins relevant for neurological conditions.
Conclusions: We conclude that the PEA proteomic platform can serve as a valuable tool for neurological studies involving brain tissues. Leveraging recent technological advances in sample-sparing scalable proteomic methods, such as the PEA, can accelerate insights into pathophysiological mechanisms and the identification of novel drug targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0527 / #1383

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

NON-DESTRUCTIVE SYNCHROTRON X-RAY IMAGING OF METAL LEVELS IN HUMAN HIPPOCAMPUS FOR CONTROL, MCI AND ALZHEIMER'S

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Yunxing Ma[1], Joanna Collingwood[2], Natalie Arigundiya[2], Kalotina Geraki[3]
[1]University of Warwick, Engineering, Coventry, United Kingdom, [2]University of Warwick, School Of Engineering, Coventry, United Kingdom, [3]Diamond Light Source, I18 Beamline, Didcot, United Kingdom

Aims: Synchrotron X-ray fluorescence (SXRF) imaging is non-destructive and provides excellent sensitivity and specificity for trace metals. The objective is to understand the evolution of metal element levels and distributions through the development from healthy control to advanced Alzheimer's, as this has implications for pathogenesis and therapeutic interventions.
Methods: SXRF imaging and subsequent elemental quantification was performed at 30μm resolution for human hippocampus sections from 6 cases with clinical diagnoses of control, mild cognitive impairment (MCI), and AD (healthy or Braak stage I&II, III&IV, V&VI respectively). Corresponding adjacent H&E stained sections informed segmentation of hippocampal subfields.
Results: Detailed evaluation by hippocampal subfield revealed some metal elements unchanged as a function of disease status, whereas others differed. For example, iron clusters were prominent in the region between the cornu Ammonis (CA) pyramidal cell layer and dentate gyrus (DG) granule layer. AD cases had lower average iron levels (35 ppm, n=2) in this region compared to MCI (39 ppm, n=1) and healthy control (46 ppm, n=3). CA4 had the highest level of zinc among the hippocampal subfields evaluated, regardless of disease status. The average and standard deviation for zinc in CA4 was 35 ppm +/- 6 ppm. Zinc contrast clearly highlighted the boundary between CA4 and DG.
Conclusions: Metal-ion distributions in human hippocampus subfields were quantified at high resolution with excellent sensitivity and specificity. Correlation with optical microscopy and adjacent stained sections permitted unprecedented non-destructive investigation of the elemental properties, with scope for further evaluation of pathological hallmarks in the XRF-imaged human brain tissue sections.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0528 / #2880

Poster Topic: *Theme A: β-Amyloid Diseases / A04.i. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

IDENTIFYING PERSONS AT RISK OF COGNITIVE DECLINE USING DIGITALLY OBTAINED VOICE: AN AUTOMATED ANALYSIS OF ACOUSTICS

POSTERS: A04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Stina Saunders[1,2], David Libon[3,4], Rodney Swenson[5], Russ Banks[1,6], Daniel Schulman[1], Connor Higgins[1], Jeffrey Pobst[1], Claudio Toro-Serey[1], Ali Jannati[1,7], Joyce Gomes-Osman[1,8], Stephanie Cosentino[9], Catherine Price[10], Melissa Lamar[11], Sean Tobyne[1], Alvaro Pascual-Leone[1,7,12]
[1]Linus Health, Product, Medical And Analytics Department, Boston, United States of America, [2]University of Edinburgh, Centre For Clinical Brain Sciences, Edinburgh, United Kingdom, [3]Rowan University, School Of Osteopathic Medicine, New Jersey Institute For Successful Aging, Stratford, United States of America, [4]Rowan University, Department Of Psychology, Glassboro, United States of America, [5]University of North Dakota, School Of Medicine And Health Sciences, Grand Forks, United States of America, [6]Michigan State University, Department Of Communicative Sciences & Disorders, College Of Arts & Sciences, East Lansing, United States of America, [7]Harvard Medical School, Department Of Neurology, Boston, United States of America, [8]University of Miami Miller School of Medicine, Department Of Neurology, Florida, United States of America, [9]Columbia University Irving Medical Center, Department Of Neurology, NEW YORK CITY, United States of America, [10]University of Florida, Department Of Clinical And Health Psychology, Gainesville, United States of America, [11]Rush University Medical Center, Rush Alzheimer's Disease Center And The Department Of Psychiatry And Behavioral Sciences, Chicago, United States of America, [12]Hebrew Senior Life, Hinda And Arthur Marcus Institute For Aging Research And Deanna, Sidney Wolk Center For Memory Health, Boston, United States of America

Aims: We conducted a study to assess which acoustic variables related to prosody were most associated with intact neuropsychological test performance in a group of community dwelling research participants.
Methods: Community dwelling participants (n= 245) were assessed with a 10-minute digitally administered and scored neuropsychological protocol encompassing verbal memory (6-word Philadelphia [repeatable] Verbal Learning Test [P(r)VLT]), working memory (backward digit span), and lexical access (semantic fluency) abilities. Cluster analysis using standard test scores classified participants into cognitively normal (CN), dysexecutive (dMCI), and amnestic mild cognitive impairment (aMCI) groups. Linear regression analyses of standardized residuals created a single residual acoustic score (RAS) for each test. Acoustic analyses measuring decibel, speech duration/total syllables, and variations in signal frequency (jitter) and amplitude (shimmer) were obtained from the P(r)VLT-delay free recall and semantic ('animals') fluency tests.
Results: Nominal regression analysis (CN reference group) using the P(r)VLT-delay free recall and 'animal' fluency RAS were able to classify participants into their respective groups ($p < 0.016$, all analyses). Between-group analyses examining the P(r)VLT delay free recall test revealed that the aMCI group had greater attenuated voice volume range than other groups ($p < 0.016$, both analyses); shorter speech duration ($p < 0.005$) than CN participants; and greater jitter ($p < 0.010$, both analyses) than other groups. Between-group analyses examining the semantic fluency test revealed that dMCI participants had attenuated voice volume range ($p < 0.029$); shorter speech duration ($p < 0.001$); and greater jitter ($p < 0.003$) than CN participants.
Conclusions: Results revealed a double dissociation between clustered groups and acoustic variables. These data suggest that digitally obtained voice behavior can provide neurocognitive biomarkers that are sensitive and specific and are potentially scalable for widespread administration to persons at risk for Alzheimer's disease and related dementias syndromes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0529 / #728

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

PROCESS MINING: A POWERFUL TOOL TO STUDY COGNITIVE PATIENT JOURNEYS

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Stefania Orini[1,2], Claudio Singh Solorzano[3], Simona Buscarnera[4], Francesco Rossato[5], Federica Ribaldi[6], Cristina Festari[3], Giovanni Frisoni[6,7], Roberto Gatta[2]
[1]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Alzheimer's Unit, Memory Clinic,, brescia, Italy, [2]University of Brescia, Department Of Clinical And Experimental Sciences,, Brescia, Italy, [3]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Laboratory Of Alzheimer's Neuroimaging And Epidemiology, Brescia, Italy, [4]Università la Sapienza di Roma, Dipartimento Di Neuroscienze Umane, Roma, Italy, [5]University of Padova, Italy, Department Of Neuroscience, Padova, Italy, [6]University of Geneve, Laboratory Of Neuroimaging Of Aging (lanvie), Geneve, Switzerland, [7]University Hospitals of Geneva, Memory Centre, Division Of Geriatrics And Rehabilitation, Geneva, Switzerland

Aims: Process mining is a data science technique that could be used to extract the most frequent diagnostic workup and describe the temporal evolution of patients' diagnostic pathways using an AI-based data-driven approach applied to real-world data. The study aims to explore the diagnostic workup of Mild Cognitive Impairment.
Methods: We analyzed 717 medical charts of consecutive patients who visited the Geneva Memory Clinic for a first visit between June 2021 and December 2022. We utilized a machine learning algoritm for process discovery using pMiner, a R library.
Results: Among the 664 participants meeting the inclusion criteria for this study (syndromic hypothesis of mild dementia or MCI), 32 were excluded because they only completed the first visit and did not continue with the assessments. Out of the remaining 632 selected patients, the most common pathway observed was as follows: an initial visit (330), followed by either neuropsychological assessment (306) or MRI (228), a second visit (290), CSF (123) and the majority of patients reached their diagnosis by the third visit
(fig1).

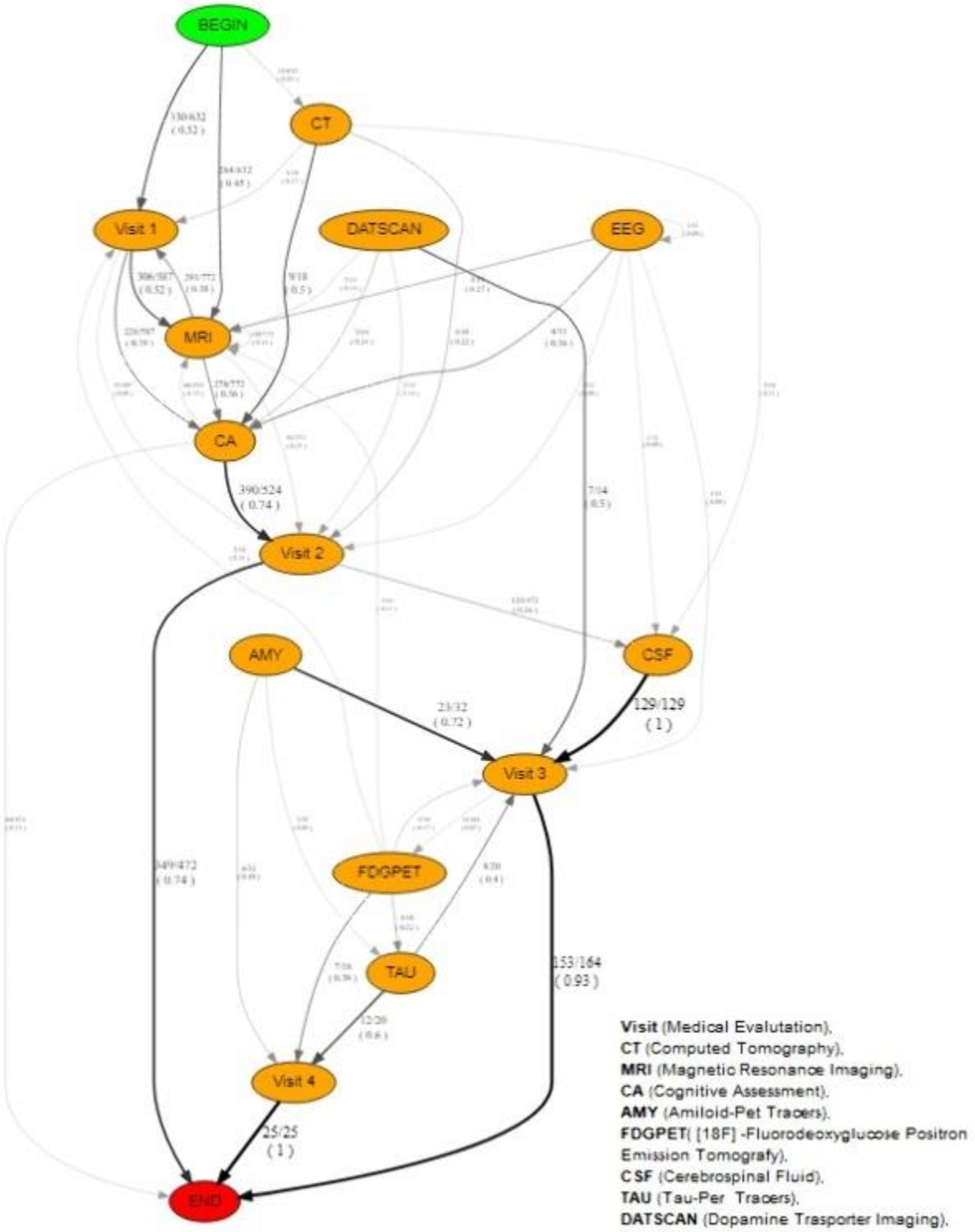


Fig 1. Graphical representation of the diagnostic pathways (without outlier) according a temporal evolution of the diagnostic pathways, the branches and their effects. The numerator of the archs represents the number of transitions to that connection, while the denominator represents the total transitions through

the node, the thickness of each arrow is proportional to the number of transitions.

Conclusions: This study has allowed us to analyse the actual patient's pathways at the Memory Clinic, which are not evident using traditional statistics. Based on this evaluation, it is possible to assess the efficiency of the clinic's diagnostic process, adherence to proposed diagnostic protocols, and potentially address bottlenecks to improve the process.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0530 / #2244

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

MICROSTRUCTURAL ALTERATIONS OF THE LIMBIC SYSTEM IN PERSONS AT GENETIC RISK OF ALZHEIMER'S DISEASE.

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Silvia Saglia[1], Giulia Quattrini[2], Moira Marizzoni[1,3], Ilari D'Aprile[3], Annamaria Cattaneo[3,4], Daniele Corbo[5], Roberto Gasparotti[5], Marta Bortoletto[6], Michela Pievani[1]
[1]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Laboratory Of Alzheimer's Neuroimaging And Epidemiology (lane), Brescia, Italy, [2]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Laboratory Of Alzheimer's Neuroimaging And Epidemiology (lane), BRESCIA, Italy, [3]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Laboratory Of Biological Psychiatry, Brescia, Italy, [4]University of Milan, Department Of Pharmacological And Biomolecular Sciences, Milano, Italy, [5]University of Brescia, Neuroradiology Unit, Brescia, Italy, [6]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Neurophysiology Lab, Brescia, Italy

Aims: The limbic system comprises cortical and subcortical structures functionally integrated by short- and long-range white matter (WM) fibers, involved in memory, emotion and behavioral regulation. The degeneration of limbic structures and related WM connections have been described in Alzheimer's Disease (AD) patients since prodromal stages, but research in cognitively unimpaired at-risk individuals (i.e., APOE ε4 carriers) is currently limited.
Methods: Cognitively unimpaired APOE ε4 carriers (n=22, age=66±6 years, 59% females, MMSE=29±1) and non-carriers (n=35, age=69±6 years, 43% females, MMSE=30±1) underwent 3T MRI exams, including Diffusion-Weighted Imaging (DWI), and neuropsychological assessment. DWIs were pre-processed using the FMRIB's Software Library (FSL) toolbox (*topup, eddy,* and *DTIfit* from FDT toolbox for fractional anisotropy [FA], mean [MD], axial [AxD], and radial [RD] diffusivities measurement). TBSS was used to warp the individual native DWIs to MNI standard space and backward. Limbic tracts (cingulum bundle, fornix, uncinate fasciculus, anterior thalamic radiation) were extracted from JHU atlas, combined, and overlaid to DTI native maps for mean values' extraction. A multivariate GLM, adjusting for age, sex, and education, was used to compare FA, MD, RD, and AxD values between groups. Partial correlations between FA/diffusivities values and RBANS immediate and delayed memory index were explored.
Results: Significantly lower left FA (p=.014) and higher left RD (p=.037) were detected in carriers compared to non-carries. Specifically, carriers showed lower FA in parahippocampal cingulum (p=.033) and anterior thalamic radiation (p=.007), higher RD in fornix (p=.026) and anterior thalamic radiation (p=.022). No significant association emerged between limbic FA/RD and memory.
Conclusions: Our preliminary results suggested that microstructural WM changes of the limbic system are detectable in unimpaired at-risk subjects, suggesting their early involvement in AD pathophysiology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0531 / #1415

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

ASSOCIATION OF CT-BASED VOLUMETRIC MEASURES OBTAINED THROUGH DEEP LEARNING WITH RADIOLOGICAL MARKERS OF IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Meera Srikrishna[1,2], Clara Constantinescu[3,4], Anna Zettergren[5], Silke Kern[5,6], Lars-Olof Wahlund[7], Eric Westman[7], Ingmar Skoog[5], Mats Tullberg[3], Michael Schöll[1,2,8,9]
[1]University of Gothenburg, Wallenberg Centre For Molecular And Translational Medicine, Gothenburg, Sweden, [2]Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [3]Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Department Of Clinical Neuroscience, Gothenburg, Sweden, [4]Sahlgrenska University Hospita, Department Of Neurology, Gothenburg, Sweden, [5]Institute of Neuroscience and Physiology, Sahlgrenska Academy, Centre for Ageing and Health (AgeCap), University of Gothenburg, Neuropsychiatric Epidemiology, Mölndal, Gothenburg, Sweden, [6]Institution for Neuroscience and Physiology, Department Of Neurochemistry And Psychiatry, Gothenburg, Sweden, [7]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, STOCKHOLM, Sweden, [8]Institute of Neurology, University College London, Dementia Research Centre, London, United Kingdom, [9]Sahlgrenska University Hospital, Department Of Clinical Physiology, Gothenburg, Sweden

Aims: Brain computed tomography (CT) is a widely accessible and affordable modality routinely used to assess neuroimaging signatures of idiopathic normal pressure hydrocephalus (iNPH), particularly ventricular enlargement. Previously, we developed deep learning U-Net-based models to segment various brain tissue classes in brain CTs. In this study, we aim to assess the association of CT-based volumetric measures (CTVMs) with radiological markers of iNPH.
Methods: We included 734 (52.6% female, 70.44 ± 2.6 years) CT scans which had paired T1-weighted magnetic resonance images scans from the Gothenburg H70 Birth Cohort collected on the same day. An experienced rater evaluated various iNPH related radiological markers in all T1-weighted images. Our trained U-Net models were used to predict brain volume (BV), intracranial volume (ICV), cerebrospinal fluid (CSF), and ventricular CSF (VCSF) segmentations from input CT scans. Then, we assessed the relationship between CTVMs such as VCSF/ICV, BV/ICV, and VCSF/CSF and standard radiological markers such as Evan's index, Z-Evan's index, and callosal angle using Spearman's rank correlation tests.
Results: CT-based volumetric measures showed good correlation with Evan's index (ρ= 0.64, $p<0.001$) and Z-Evan's index (ρ= 0.8, $p<0.001$). CTVMs had lower but significant correlation with callosal angle (ρ= -0.31, $p<0.001$). CT-VCSF/ICV showed higher correlation with radiological markers of iNPH in comparison to CT-BV/ICV and CT-VCSF/CSF. Higher levels of Evan's index and Z-index associated with higher levels of CT-VCSF/ICV and CT-VCSF/CSF and lower levels of CT-BV/ICV.

Correlation matrix of CT-based volumetric measures and radiological markers of idiopathic normal pressure hydrocephalus in the Gothenburg H70 Birth Cohort (n= 734). Spearman correlation coefficients are plotted. Cells were coloured according to the strength and trend of correlations (shades of blue = positive, shades of red = negative correlations). *Abbreviations: BV- Brain volume; CSF- cerebrospinal fluid; CT- computed tomography; ICV- intracranial volume; VCSF- ventricular CSF*

Conclusions: CT-based volumetric measures correlate with relevant radiological markers of iNPH. This supports the potential application of CTVMs in aiding diagnostics and monitoring the progression of iNPH. Association between CTVMs with diagnosis and other clinical iNPH markers will be further explored in future.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0532 / #547

Poster Topic: *Theme A: β-Amyloid Diseases / A04.j. Imaging, Biomarkers, Diagnostics: Other*

X-RAY BASED BRAIN TISSUE MATERIAL DECOMPOSITION AND QUANTIFICATION OF OLIGOMERIC AND FIBRILLAR AMYLOID-BETA AGGREGATES

POSTERS: A04.J. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Karthika Suresh, Eshan Dahal, Aldo Badano
U.S. Food and Drug Administration (FDA), Division Of Imaging, Diagnostics, And Software Reliability, Office Of Science And Engineering Laboratories, Center For Devices And Radiological Health, Silver SPring, United States of America

Aims: Label free spectral small angle X-ray scattering (sSAXS) is an emerging tool for detecting amyloid-β deposition in the brain in vivo based on the cross-β sheet structure of oligomeric and fibrillar aggregates. We aim at recovering and quantifying X-ray scattering signals of the pathogenic protein aggregates from the cumulative X-ray spectrum contributed by different brain tissue components.
Methods: Brain tissue material decomposition and quantification were performed by scatter specific peak deconvolution on sSAXS spectra followed by integration of deconvolved signal. The method was evaluated for clinically relevant quantities in the microgram (μg) range of amyloid oligomer and fibrillar models embedded in different regions of sheep brain tissues varying from stem to cortex.
Results: The X-ray scattering spectrum of the brain tissue within the wavevector (q) range of 4.5-22 nm^{-1} is primarily dominated by the lipid scattering with q centered between 13-14 nm^{-1} along with minor contribution from water near q=21 nm^{-1}. The X-ray intensities of μg range protein aggregates are significantly lower than lipids and the scattering signals arising from inter- (q=6.7 nm^{-1}) and intra- (q=13.3 nm^{-1}) β-sheet spacings of the amyloid cross-β motifs that are hidden within the broader lipid spectrum. By performing peak deconvolution with component specific peak center, we were able to decompose signals from mixtures of the brain tissue and recover the hidden amyloid signals. Integration of deconvolved peak accurately estimated the amyloid burden. Preliminary investigations show that the Aβ index quantified by q-spectrum normalization is a metric for amyloid burden.
Conclusions: Our findings suggest that the proposed approach would allow amyloid quantification at regional level using sSAXS. This method could also be extended to other neurodegenerative diseases including Parkinson's diseases due to the generalized cross-b structure of pathogens.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0533 / #1031

Poster Topic: *Theme A: β-Amyloid Diseases / A05.a. Genetics, Epidemiology: Whole genome sequencing*

POPULATION-SCALE LONG-READ SEQUENCING TO BETTER UNDERSTAND THE GENETICS OF NEURODEGENERATIVE DISEASES

POSTERS: A05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

Kimberley Billingsley[1], Kensuke Daida[2], Pilar Alvarez Jerez[3], Rylee Genner[3], Andrew Singleton[1], Cornelis Blauwendraat[1]
[1]CARD, NIH, Center Of Alzheimer's And Related Dementias, Card, Nih, Bethesda, United States of America, [2]NIH, Laboratory Of Neurogenetics, Bethesda, United States of America, [3]CARD, NIH, Center Of Alzheimer's And Related Dementias, Card, Nih, Bethesda, United States of America

Aims: We aim to generate a new genetic resource for Neurodegenerative diseases by discovering and genotyping structural variants. Structural variants drive gene expression in the brain and are causative of many neurological conditions. However, most existing genetic studies have been based on short-read sequencing methods which poorly capture these regions.
Methods: We leverage a new scalable wet-lab protocol and computational pipeline (Napu) for Oxford Nanopore Technologies (ONT) and apply it to neurologically normal control samples from the North American Brain Expression Consortium (NABEC) cohort and Parkinson's disease case and control samples from the Parkinson's Progression Markers initiative (PPMI).
Results: Through this work, we present a publicly available long-read resource from hundreds of human brain and blood samples (average N50 ~30kb and ~40X coverage). We discover over 100k structural variants, consisting mainly of insertions and deletions. Utilizing matched expression datasets for these samples including CAGE-seq and bulk and single-cell RNA-seq we apply quantitative trait locus (QTL) analyses and identify structural variants that impact gene expression in post-mortem frontal cortex brain tissue and whole blood. Further, we determine haplotype-specific methylation rates of millions of CpGs and with this data identify cis-acting structural variants.
Conclusions: In summary, these results highlight that long-read sequencing at population scale can identify disease-relevant regulatory loci that were inaccessible using previous technologies. We believe this new resource will provide a critical step toward understanding the biological effects of genetic variation in the human brain. Expanding on this, as part of the NIH's Center of Alzheimer's and Related Dementias (CARD) long-read sequencing initiative, we are currently applying this framework to sequence thousands of human case and control samples to build the first highly accurate catalog of structural variants in Neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0534 / #16

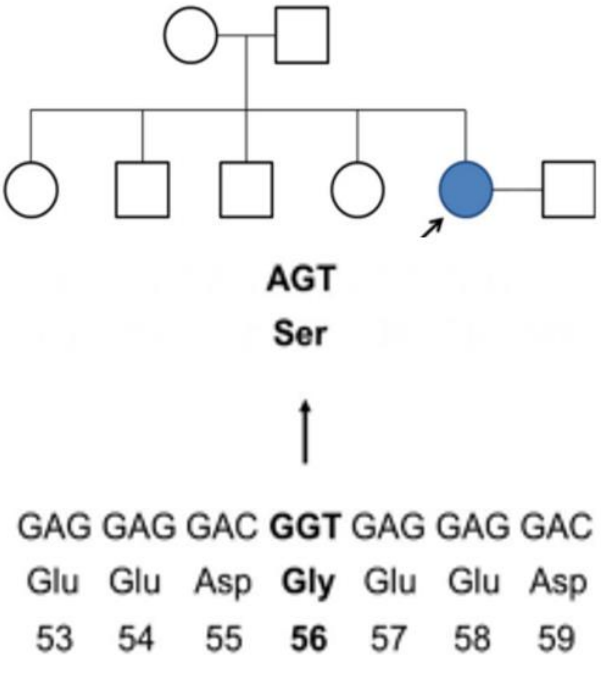
Poster Topic: *Theme A: β-Amyloid Diseases / A05.a. Genetics, Epidemiology: Whole genome sequencing*

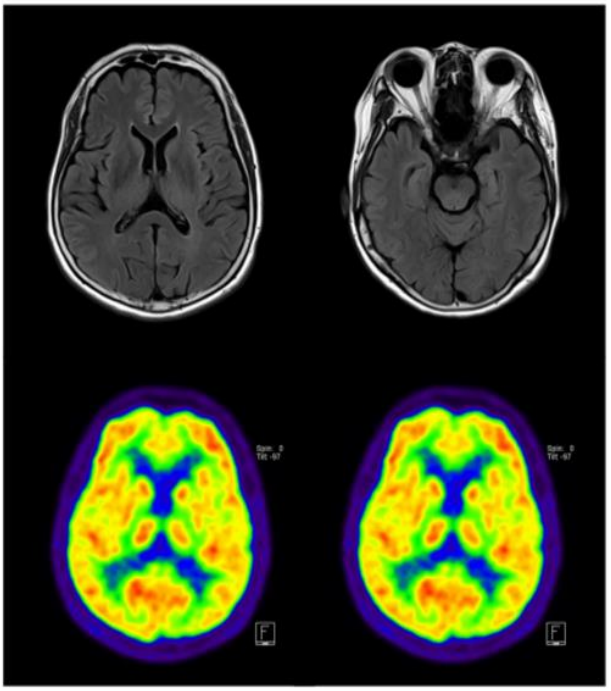
A POSSIBLE PATHOGENIC PSEN2 GLY56SER MUTATION IN A KOREAN PATIENT WITH EARLY-ONSET ALZMEIMER'S DISEASE

POSTERS: A05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

Da Eun Jeong
Central Veterans Hospital, Neurology, Seou, Korea, Republic of

Aims: In this study, we described a clinical data of a Korean EOAD patient with Gly56Ser mutation in PSEN2. To address the pathogenicity of the mutation, in silico analysis and structural predictions were also conducted.
Methods: Patient information A 64-year-old right-handed woman with 12 years of education presented with a 4-year history of progressive cognitive impairment. Her symptoms occurred insidiously, with short-term memory loss and insomnia. The patient scored 24/30 in a Mini-Mental State Examination (MMSE). The subscores seven serial calculations were 3 out of 5 and the delayed word recall score was 0 out of 3, with a 0.5 Clinical Dementia Rating (CDR). Brain magnetic resonance imaging showed that the volume of the bilateral hippocampus was reduced. (Figure 1). 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) showed bilateral temporoparietal association cortices, precuneus, inferiorparietal lobule, and middle temporal gyrus
hypometabolism.





Results: From in silico analysis, the bulkiness score of mutant PS2 was higher than that of the wild-type protein (Figure 2). The hydrophobicity score of the mutant protein was markedly lower than that of the wild-type one. Based on the 3D structural modeling of the secondary structure, the positions of Gly56 and Ser56 of the wild-type and mutant proteins, respectively, were anticipated to be located within loop structures without definite structures. Based on a model of the mutant protein, Ser56 displayed the

potential interactions with Met1, Ala6, Asp8, and Glu54. Interestingly, in mutant model 2, a hydrogen bond formed between Ser56 and Leu396 that reduced the distance between the loop and the helix region in PS2

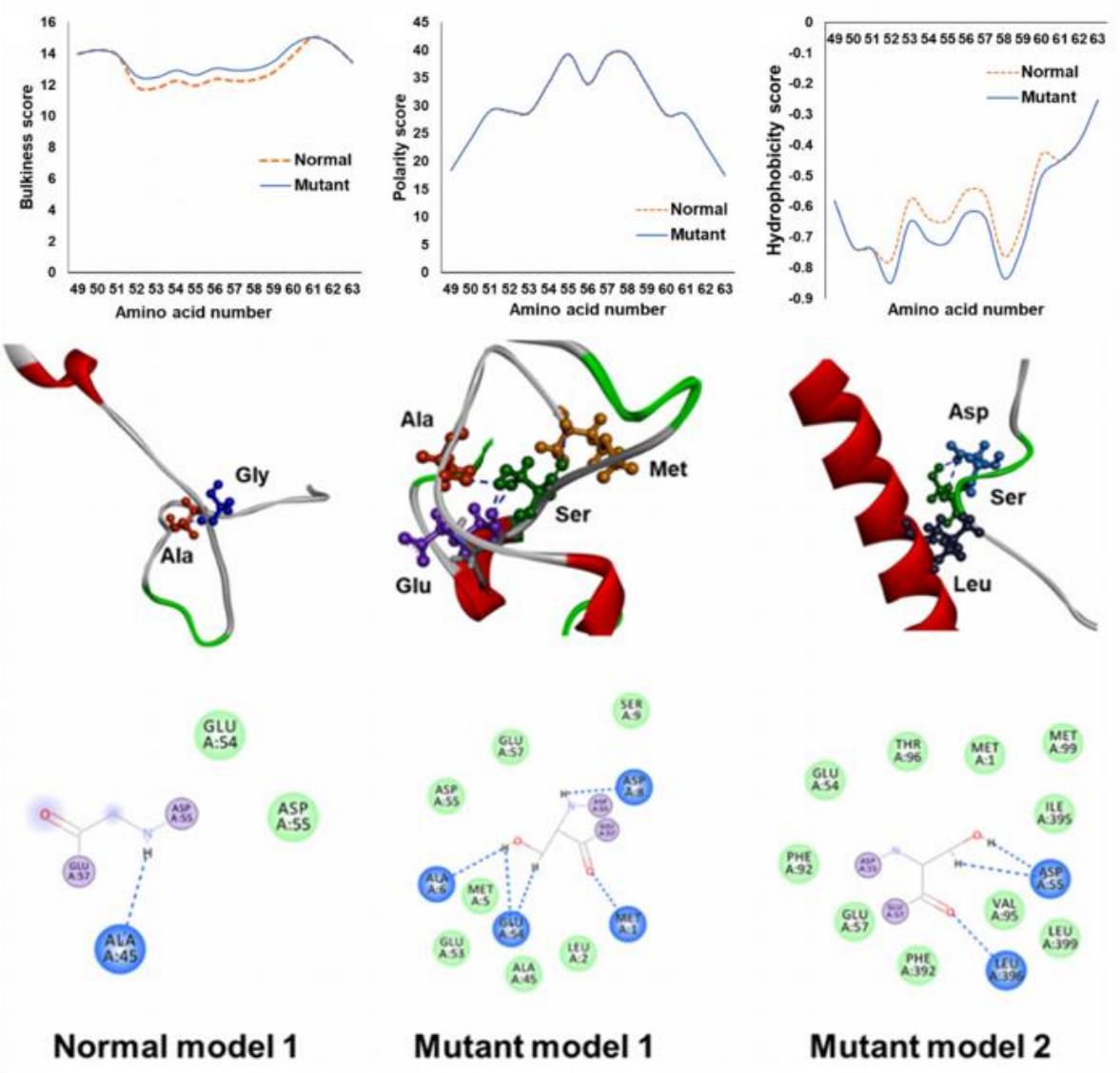


Figure 2. ExPASY scores, 3D predicted structure and possible intramolecular interactions of Gly56Ser PS2.

Conclusions: Substitution with serine may affect interactions with other residues and/or phosphorylation, promoting AD pathogenicity Future functional studies will be required to fully understand disease progression and mechanisms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0535 / #2239

Poster Topic: *Theme A: β-Amyloid Diseases / A05.a. Genetics, Epidemiology: Whole genome sequencing*

WHOLE GENOME SEQUENCING ANALYSIS TO SEARCH FOR PROTECTIVE VARIANTS FOR ALZHEIMER'S DISEASE IN THE AMISH

POSTERS: A05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

Yeunjoo Song[1,2], Weihuan Wang[1], Kristy Miskimen[1], Renee Laux[1], Audrey Lynn[1], Sarada Fuzzell[1], Sherri Hochstetler[1], Leighanne Main[3], Michael Osterman[1], Ping Wang[1], Yining Liu[1], Michael Prough[4], Susan Hackleman[4], Larry Adams[4], Laura Caywood[4], Sharlene Herington[4], Jason Clouse[4], Daniel Dorfsman[4], Jeffery Vance[4], Michael Cuccaro[4], Alan Lerner[5], Paula Ogrocki[5], Margaret Pericak-Vance[4], William Scott[4], Jonathan Haines[1,2]
[1]Case Western Reserve University, Population And Quantitative Health Sciences, Cleveland, United States of America, [2]Case Western Reserve University, Cleveland Institute For Computational Biology, Cleveland, United States of America, [3]Case Western Reserve University, Genetics And Genome Sciences, Cleveland, United States of America, [4]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [5]Case Western Reserve University, Neurology, Cleveland, United States of America

Aims: A shift in focus from risk to resilience for Alzheimer's disease (AD) encourages efforts to uncover novel AD biological mechanisms. We examined whole genome sequencing data from a Midwestern Amish population in a genome-wide search for rare coding protective variants shared only among cognitively unimpaired (CU) individuals and performed a sequence-based genome-wide association study (seqGWAS) of cognitive status, CU vs. cognitively impaired (CI).
Methods: The cognitive status of each individual was assigned via a consensus review of medical history and neuropsychological testing. Allele frequencies were calculated across all samples for all variants. Allele frequencies of rare variants (MAF<0.05) within CU and within CI individuals were compared. Variants with a minor allele count (MAC)>10 in the CU group and 0 in the CI group were annotated to determine likely loss of function. Variants were further filtered to exclude those shared by younger (age < 75) CU individuals. A linear mixed model was used to test for association with common variants (MAF>=0.05).
Results: After extensive QC, 1141 individuals, 549 CU (mean age=80.33±5.71, 62% female) and 432 CI (mean age=83.07±5.60, 56% female) were available for analysis. 3459 rare variants with MAC >10 were found only in CU. There were 31 coding variants (25 *missense*, 1 *inframe_deletion*, 5 *splice donor*) and 11 synonymous variants. 9 missense, 2 splice, and 3 synonymous variants were shared by at least 10 CU with age > 75. No SNPs reached genome-wide significance($p=5\times10^{-8}$) among common variants but 272 variants had suggestive associations ($p=1\times10^{-5}$).
Conclusions: Numerous rare variants potentially impacting gene function were found only in CU individuals, providing a rich resource for further investigation of genes that may provide protection from cognitive impairment. We identified novel common variants in 32 gene regions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0536 / #572

Poster Topic: *Theme A: β-Amyloid Diseases / A05.b. Genetics, Epidemiology: Disease-causing mutations*

CHARACTERISTICS OF TREM2 L15Q MUTATION ON AB-RELATED PATHOGENESIS

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Danyeong Kim[1,2], Kyuhwan Shim[1], Hyewon Yang[1], Heewon Bae[2], Seong Soo A. An[1], Min Ju Kang[2]
[1]Gachon University, Department Of Bionano Technology, Seongnam, Korea, Republic of, [2]Veterans Health Service Medical Center, Neurology, Seoul, Korea, Republic of

Aims: *TREM2* L15Q mutation was found in a 65-year-old AD patient. To assess its pathogenicity, we produced transfected cells and investigated the relationship between the *mutation* with Aβ-related pathology.
Methods: *TREM2* Wild type (WT) and L15Q were transfected onto the HEK 293 by using a plasmid transfection system and selected using geneticin. Gene expression and protein were measured for confirmation of modifying cells. The $A\beta_{42}$ and $A\beta_{40}$ performed commercial kits. In Aβ uptakes, the cells were incubated with $A\beta_{42}$ and then, measured $A\beta_{42}$. Aβ phagocytosis was obtained cell images and video by treating Aβ-labeling pHrodo.
Results: *TREM2* gene and protein were confirmed in *TREM2* WT and L15Q transfected cells. Although both were overexpressed in HEK 293(MOCK), *TREM2* L15Q was a lower protein than in WT. *TREM2* L15Q had a higher $A\beta_{42/40}$ ratio than WT. The $A\beta_{42}$ uptake was relatively lower than WT. In Aβ phagocytosis images and video, *TREM2* L15Q showed lower red fluorescence than WT, but similar to MOCK.
Conclusions: In this study, we investigated the pathogenicity of the *TREM2* L15Q mutation using the generation of mutant cells. Our results revealed that *TREM2* L15Q led to an increase in extracellular Aβ42 levels while reducing Aβ42 uptake. These findings suggest that the mutation impairs the Aβ uptake and elimination functions of *TREM2*, resulting in incomplete Aβ clearance and an increase in extracellular Aβ in mutant cells. Consistent with our confocal images and live cell video analyses, which showed a decreased red fluorescence signal in *TREM2* L15Q cells, we conclude that Aβ phagocytosis is hindered by the *TREM2* mutation. Taken together, *TREM2* L15Q interfered with Aβ phagocytosis and reduced Aβ uptake, which may allow Aβ to accumulate rather than be removed, thereby affecting the pathogenicity of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0537 / #2368

Poster Topic: *Theme A: β-Amyloid Diseases / A05.b. Genetics, Epidemiology: Disease-causing mutations*

EVALUATION OF A NEW STRATEGY TO IDENTIFY PATIENTS AT HIGH RISK FOR UNDERLYING GENETIC CAUSES

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Theresa König, Sara Silvaieh, Tandis Parvizi, Raphael Wurm, Evelyn Berger-Sieczkowski, Helena Untersteiner, Stella Göschl, Alexander Zimprich, Elisabeth Stögmann
Medical University of Vienna, Department Of Neurology, Vienna, Austria

Aims: Pathogenesis, clinical course and pathological processes differ significantly between dementias. However, diagnosis remains challenging and reliable *in vivo* biomarkers are needed for patient stratification and therapeutic intervention. Our objective was to i) assess the extent of putative high genetic risk in our dementia cohort and ii) enhance diagnostic efficacy in clinical whole exome sequencing (WES) routines.
Methods: We retrospectively applied a recently proposed classification scheme (Koriath et al. 2020, Mol. Psychiatry) considering dementia type, family history and age of disease onset (AAO) to evaluate the genetic risk in a well-characterized dementia patient cohort (AD, FTD, and other dementias, n=703). Patients were divided into groups with high, medium and low genetic risk in a blinded approach according to the adapted scheme. If available, WES, as well as *APOE* and *C9ORF72* genotyping data of high-risk patients was analyzed.
Results: 53 high-risk patients were identified. To date, full genetic data was available for 28 patients (53%). 11 individuals were carriers of established pathogenic variants and three were *APOE4* homozygous. Thus, overall, 14 of the 53 patients (26.4%) were carriers of diagnostic relevant, pathogenic variants (*APP, PSEN1, MAPT, PGRN, C9ORF72* and *APOE4/4*). Excluding the 25 patients that have yet to be fully resolved, the diagnostic yield reaches up to 50% (14 out of 28 patients).
Conclusions: Utilizing a classification scheme based on AAO and family history proved effective in increasing the probability of detecting pathogenic variants relevant for diagnosis and patient counseling. This approach significantly enhanced the diagnostic yield of WES in our cohort, demonstrating a marked improvement compared to the previously observed 20% in our clinical setting.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0538 / #2439

Poster Topic: *Theme A: β-Amyloid Diseases / A05.b. Genetics, Epidemiology: Disease-causing mutations*

CHCHD2 AND DNAJC6 DOUBLE GENE MUTATION IN AN ITALIAN PATIENT WITH EARLY-ONSET ALZHEIMER'S DISEASE

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Federico Menegon[1], Francesca Vignaroli[1], Lucia Corrado[2], Fabiola De Marchi[1], Silvio Daffara[3], Fjorilda Caushi[2], Sandra D'Alfonso[2], Cristoforo Comi[4], Giacomo Tondo[4]
[1]University of Piemonte Orientale, Department Of Translational Medicine, Novara, Italy, [2]University of Piemonte Orientale, Department Of Health Sciences, Novara, Italy, [3]Sant'Andrea Hospital, Biology Unit, Vercelli, Italy, [4]Neurology Unit, Sant'Andrea Hospital, Vercelli, University Of Piemonte Orientale, Vercelli, Italy

Aims: Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative diseases (NDDs) share pathological mechanisms, combining genetic and environmental factors.
Methods: Early-onset AD, appearing before age 65, accounts for roughly 10% of all AD cases, and is largely unexplained by known genetic mutations, resulting in a lack of understanding of its molecular etiology.
Results: A 51-year-old female reported a one-year history of progressively worsening memory, attentive and planning disturbances. She had no family history of neurological or psychiatric disorders. Neuropsychological assessment revealed memory, language, and executive function deficits. MRI showed diffuse atrophy and FDG-PET revealed hypometabolism in bilateral temporo-parietal regions and in the left frontal lobe. CSF T-tau and p-tau levels were normal, while amyloid β was markedly reduced. Based on the clinical phenotype, and the exam findings, early-onset AD was diagnosed. The patient has a rapidly progressive worsening of cognitive functions. A genetic analysis testing for the genes associated with AD and other neurodegenerative diseases was performed, and two rare different heterozygous mutations in CHCHD2 and DNAJC6 genes were revealed.
Conclusions: CHCHD2 encodes for protein involved in mitochondrial function. Mutations in this gene have been associated with familial and sporadic PD, but are also described in amyotrophic lateral sclerosis/frontotemporal dementia and AD. DNAJC6 encodes for protein involved in the endo-lysosomal pathway. Mutations of DNAJC6 have been associated with early-onset PD, and only in one study with AD. We present the first Caucasian patient carrying a double gene mutation in CHCHD2 and DNAJC6, manifesting with early-onset and rapidly progressive AD, giving new insight into the pathology and genetics of NDDs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0539 / #1176

Poster Topic: *Theme A: β-Amyloid Diseases / A05.b. Genetics, Epidemiology: Disease-causing mutations*

DISTINCT AMYLOID-B DEPOSITS IN PSEN1 P.G206A MUTATION CARRIERS ASSOCIATE WITH DISEASE DURATION

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Baayla Boon[1], Sarah Lincoln[1], Daniel Wickland[1], Erica Engelberg-Cook[1], Darren Rothberg[1], Michael Deture[2], Nilüfer Ertekin-Taner[2,3], Neill Graff-Radford[3], Dennis Dickson[1], Melissa Murray[1], Cyril Pottier[4]
[1]Mayo Clinic, Neuroscience, Jacksonville, United States of America, [2]Mayo Clinic, Department Of Neuroscience, Jacksonville, United States of America, [3]Mayo Clinic, Department Of Neurology, Jacksonville, United States of America, [4]Mayo Clinic Florida, Neuroscience, Jacksonville, United States of America

Aims: *PSEN1* mutations lead to an increased amyloid-β processing and production, however, even in individuals with the same mutation, there is a large phenotypical variability. We hypothesized that neuropathologic characteristics, cellular and transcriptomic alterations are associated with clinical phenotype. We investigate the association between types of amyloid-β deposits, brain cell type proportion, gene expression, and splicing isoforms with age at onset, disease duration and severity of Alzheimer's Disease (AD) neuropathologic change.
Methods: Histologic stains (hematoxylin-eosin and thioflavin S) as well as immunohistochemistry for phosphorylated-tau (AT8)and amyloid-β (6F/3D) were performed in eight Hispanic *PSEN1 p.G206A* AD cases in the inferior parietal gyrus and motor cortex. Single-nuclei long-read RNA sequencing is being performed on both brain regions. We will stratify our transcriptomic analyses on phenotype and neuropathology.
Results: We observed large variability in age at onset (median = 53 years; range: 42-59 years) and disease duration (median = 10 years; range: 8-17). Disease duration did not correlate with amyloid-β (correlation coefficient = 0.09) and phosphorylated-tau (correlation coefficient = 0.0003) burden. In cases with a shorter disease duration (8-10 years), we observed a high burden for coarse-grained plaques and cerebral amyloid angiopathy, whereas in cases with a longer disease duration (13-17 years) we observed a high burden of classic cored plaques (Fig.1, Table
1).

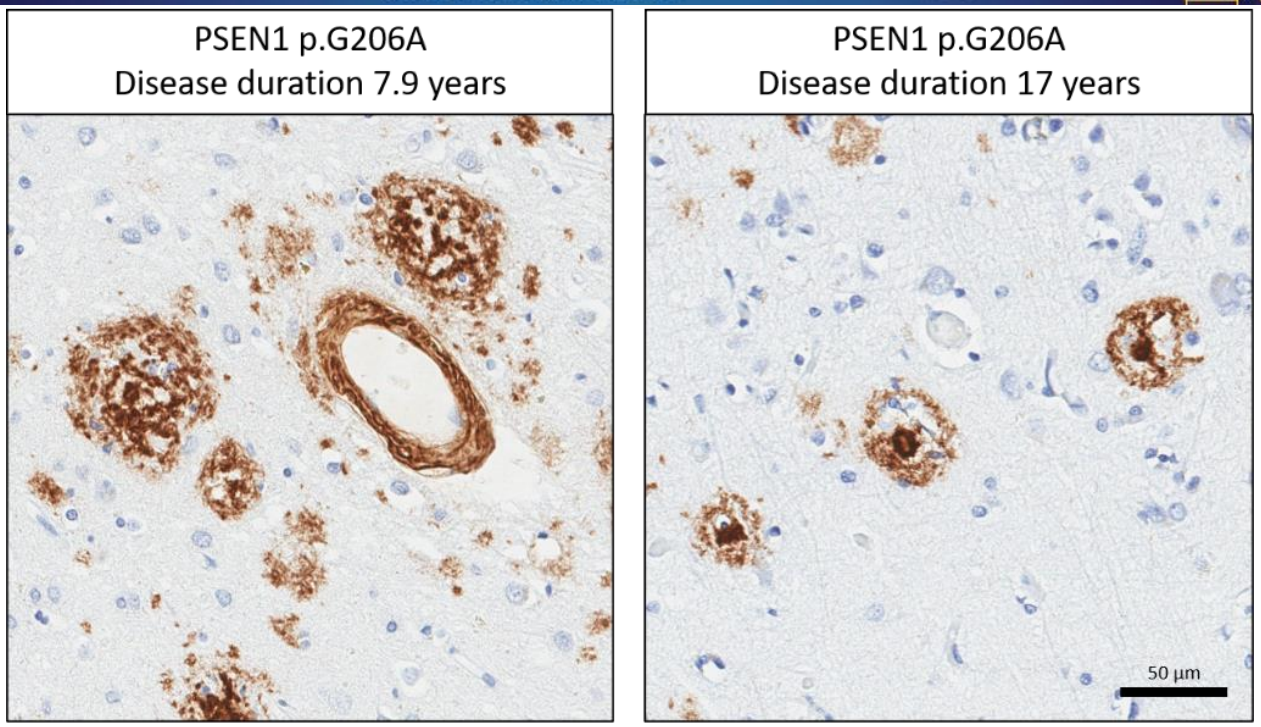


Fig. 1. Amyloid-β (clone 6F/3D) immunohistochemistry on the middle frontal gyrus of cases with a *PSEN1 p.G206A* mutation. We observed a higher burden for coarse-grained plaques and cerebral amyloid angiopathy in cases with a shorter disease duration, whereas we observed a higher burden for classic cored plaques in cases with a longer disease duration.

Table 1. Amyloid-β deposit scores for *PSEN1 p.G206A* mutation carriers

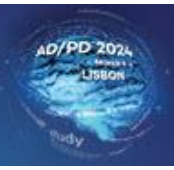
Case	Sex	APOE	Disease duration	CCP	CGP	CAA2	CAA1
1	M	33	17	3	0	0	0
2	F	34	13	3	1	0	0
3	M	33	10	3	1	0	0
4	M	33	11	3	1	1	0
5	F	33	8	2	1	1	0
6	M	34	10	2	3	3	0
7	M	44	14	2	3	2	1
8	F	34	7.9	2	3	3	1

CAA1 cerebral amyloid angiopathy type 1, CAA2 cerebral amyloid angiopathy type 2, CCP classic cored plaque, CGP coarse-grained plaque, F female, M male. Disease duration in years.

Conclusions: The observation that amyloid- β and phosphorylated-tau amount did not correlate with disease duration, but that distinct amyloid-β deposits were associated with disease duration in cases with the same Mendelian cause for AD, strongly suggests a relationship between plaque composition and

disease progression. Transcriptomic analyses will provide new insights into disease mechanisms regarding amyloid-β deposit formation and phenotypic variability.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0540 / #2091

Poster Topic: *Theme A: β-Amyloid Diseases / A05.b. Genetics, Epidemiology: Disease-causing mutations*

ASSESSMENT OF PLASMA APOE AS A SURROGATE MARKER FOR APOE _4 GENOTYPE IN A MILD TO MODERATE ALZHEIMER'S DISEASE COHORT

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

James Rock[1], Han Joo Lee[1], Fred Kim[1], Rosina Degrieck[2], Jia Jun Choung[1], Caroline Dobbels[2], Nathalie Le Bastard[2]
[1]AriBio Co., Ltd, Clinical, San Diego, United States of America, [2]Fujirebio Europe NV, Fujirebio Europe Nv, Ghent, Belgium

Aims: Aim: There are limited genes known to increase the risk of Alzheimer's disease (AD), most well-known is *APOE* e4. It is estimated 25% of people carry one copy and 2-3% carry two copies. The gene encodes the ApoE protein which helps to carry cholesterol and fats in the blood stream and into cells including brain cells, and this may contribute to AD pathology. The Lumipulse ***G*** ApoE4 and Lumipulse ***G*** Pan-ApoE <RUO>, assays to detect the proteins encoded by the *APOE* variants, were used to retrospectively analyze plasma from a phase 2 study.
Methods: Method: Plasma was collected from 181, 133 and 90 subjects at Baseline, Week 26 and Week 52, respectively. Genotyping was not conducted, but plasma was tested retrospectively to determine proteotype status of these subjects. Three different ApoE protein isoforms (ApoE2, ApoE3, and ApoE4) were detected representing 6 phenotypes (3 homozygous types [E2/E2; E3/E3; E4/E4]) and 3 heterozygous types [E2/E3; E3/E4; E2/E4]). When Lumipulse ***G*** ApoE4 is used in conjunction with the Lumipulse ***G*** Pan-ApoE assay to determine the ApoE4/Pan-ApoE ratio meaning absence (null <5%) or presence of ApoE4 only (homozygous ≥75%) or the combination with ApoE2 or E3 (heterozygous ≤5% to <75%).
Results: At Baseline 77 (42.5%), 27 (14.9%), 77 (42.5%) had a ratio consistent with null, homozygous and heterozygous respectively. Subjects with protein levels/ratio consistent with these categories continued to express the same pattern at Week 26 (n=133) and Week 52 (n=90). No subjects expressed a different ratio through Week 52 of testing.
Conclusions: Conclusion: The Lumipulse ***G*** ApoE4 and Lumipulse ***G*** Pan-ApoE assays appear to be highly consistent across multiple timepoints for the detection of both ApoE4 heterozygous, homozygous and those without ApoE4 protein expression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0541 / #2072

Poster Topic: *Theme A: β-Amyloid Diseases / A05.b. Genetics, Epidemiology: Disease-causing mutations*

COMMON STRUCTURAL VARIATIONS CHARACTERIZE GENETIC RISK LOCI IN NEURODEGENERATIVE DISEASES

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Alex Salazar[1], Niccolo Tesi[2], Daniel Alvarez Sirvent[3], Lydian Knoop[2], Yaran Zhang[2], Sven Van Der Lee[2], Sanduni Wijesekera[2], Jana Krizova[2], Wiesje Van Der Flier[4], Yolande Pijnenburg[4], Marcel Reinders[5], Marc Hulsman[2], Henne Holstege[2]
[1]Amsterdam UMC, Department Human Genetics | Genomics Of Neurodegenerative Diseases And Aging, Amsterdam, Netherlands, [2]Vrije Universiteit Amsterdam, Amsterdam UMC, Section Genomics Of Neurodegenerative Diseases And Aging, Department Of Clinical Genetics, Amsterdam, Netherlands, [3]Amsterdam UMC Location VUmc, Department Human Genetics | Genomics Of Neurodegenerative Diseases And Aging, Amsterdam, Netherlands, [4]Amsterdam UMC, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [5]TU Delft, Delft Bioinformatics Lab, CB, Netherlands

Aims: Genome-Wide Association Studies (GWAS) have identified >117 risk loci associated with various neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. However, GWAS-SNPs are generally not causative, implying that other nearby genetic variation in linkage disequilibrium (LD) may drive association signals. Here, we leveraged long-read sequencing data from 214 individuals to genotype large structural variants (SVs) genome-wide and investigated their interplay with GWAS-SNPs.
Methods: We performed long-read whole-genome sequencing of 214 individuals: N=93 AD patients (age 67.2∓8.5), and N=121 cognitively healthy centenarians (age 101.2∓1.8). We identified candidate SVs using sniffles2 genome-wide, and further characterised them through (local) de novo assembly. After quality control, we calculated LD between high quality SVs and imputed genotyped SNPs that were within 1Mb distance from each other. We primarily focused on known GWAS-SNPs associated with neurodegenerative diseases.
Results: In total, we found more than 112,000 unique SVs, of which ~52,000 (46%) were present in at least 5% of individuals. Of these 'common' SVs, 39% were transposable elements (TEs), predominantly from the SINE and LINE groups. Linkage disequilibrium (LD) analysis revealed several TE-related SVs, which were in moderate to strong LD to common SNPs that have been associated with neurodegenerative diseases (R2 = 0.2-1.0) by previous GWAS. These included intronic TEs in TMEM106B, TPCN1, GMNC, CRLS1 and ACE, that were previously associated with neurodegenerative diseases, validating the sensitivity of our approach. The remaining TE-SNP pairs are mostly intronic insertions of TEs that have not been previously reported, and may be candidate drivers of GWAS associations, potentially perturbing gene transcription and/or translation.
Conclusions: This study identifies novel SVs as potential genetic drivers of various previously identified GWAS of neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0542 / #2924

Poster Topic: *Theme A: β-Amyloid Diseases / A05.b. Genetics, Epidemiology: Disease-causing mutations*

PATHOLOGICAL CHARACTERIZATION OF THE NOVEL DE NOVO APP Y681H AROS MUTATION

POSTERS: A05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Silvia Zampar[1,2], Sylwia Libard[3,4], Milena Boczar[5], Wojciech Michno[5], Elena Witzemann[5], Siarhei Hladkou[5], Lena Kilander[5], Ling Wu[1], Sonja Di Gregorio[1,2], Sophia Mastrangelo[1,2], Gustavo Grimmer[1,2], Hansen Wang[1], Stefan Lichtenthaler[6,7,8], Gunnar Schroeder[9,10], Joel Watts[1,11], Gerold Schmitt-Ulms[1,12], Dag Sehlin[5], Paul Fraser[1,13], Niklas Dahl[4], Vilmantas Giedraitis[5], Martin Ingelsson[1,2,5,12]
[1]University of Toronto, Tanz Centre For Research In Neurodegenerative Disease, Toronto, Canada, [2]University Health Network, Krembil Brain Institute, Toronto, Canada, [3]Uppsala University, Department Of Immunology, Genetics And Pathology, Uppsala, Sweden, [4]Uppsala University, Department Of Surgical Pathology, Uppsala, Sweden, [5]Uppsala University, Department Of Public Health And Caring Sciences, Uppsala, Sweden, [6]German Center for Neurodegenerative Diseases, Neuroproteomics, Munich, Germany, [7]Technical University of Munich, Neuroproteomics, School Of Medicine, Klinikum Rechts Der Isar, Munich, Germany, [8]German Center for Neurodegenerative Diseases, Dzne Munich, Munich, Germany, [9]Forschungszentrum Jülich,, Institute Of Biological Information Processing, Structural Biochemistry And Justruct, Jülich Center For Structural Biology, Jülich, Germany, [10]Heinrich-Heine-Universität Düsseldorf, Physics Department, Düsseldorf, Germany, [11]University of Toronto, Department Of Biochemistry, Toronto, Canada, [12]University of Toronto, Department Of Laboratory Medicine And Pathobiology, Toronto, Canada, [13]University of Toronto, Crnd/medical Biophysics, Toronto, Canada

Aims: Mutations in the amyloid precursor protein (APP) gene can cause early onset familial Alzheimer's disease and/or cerebral amyloid angiopathy (CAA). We analysed pathological aspects of the novel *de novo* APP Y681H *Aros* mutation, identified in a Swedish subject who presented with a cerebral hemorrhage at the age of 55. The brain showed prominent amyloid-beta (Abeta) plaque deposition in the cortex and abundant CAA. Because this mutation is located next to the BACE1 beta'-cleavage site on APP and in proximity of neprilysin and insulin degrading enzyme (IDE) Abeta cleavage sites, we analyzed how it affects APP processing, Abeta degradation and aggregation propensities *in vitro*.
Methods: HEK293 cells were transfected with WT or *Aros APP*-containing vectors, and Abeta levels were measured in the supernatants though ELISA assays. Monomers of synthetic Abeta1-42 WT and *Aros* peptides, isolated by size exclusion chromatography, were incubated at 37°C with 20μM ThT to monitor their time-dependent aggregation. *In vitro* digestion of abeta monomers, incubated with recombinant neprilysin and IDE for 2 h at 37°C, was visualized with western blot and quantified with Image Lab software.
Results: Abeta1-40 levels and of Abeta1-40/Abetax-40 ratio was significantly increased in *APP Aros*-transfected cell supernatant compared to *APP* WT. No changes were observed in Abeta1-42 *Aros* aggregation kinetics compared to WT, while Abeta1-42 *Aros* was digested to a lesser extent by neprilysin and IDE *in vitro*.
Conclusions: The *APP Aros* mutation appears thus to influence APP processing and increase Abeta production. Although no changes in aggregation propensities were observed for Abeta1-42 *Aros*, the variants appear to be less degradable, which could also lead to increased Abeta brain levels. We are next assessing the deposit composition, structural features, and toxic properties of the *Aros* Abeta mutant.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0543 / #492

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

THE ROLE OF AUTOSOMES IN ALZHEIMER'S DISEASE GENETICS ACROSS APOE*4 AND SEX

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Michael Belloy[1], Pablo García-González2[2], Atahualpa C. Morales[3], Yann Le Guen[4], Ilaria Stewart[4], Christina Young[4], Elizabeth C Mormino[4], Valerio Napolioni[5], Zihuai He[4], Andre Altmann[6], Michael Greicius[4]
[1]Washington University in Saint Louis, Neurology, Saint Louis, United States of America, [2]Universidad Internacional de Catalunya, Research Center And Memory Clinic, Ace Alzheimer Center Barcelona, Barcelona, Spain, [3]Cardiff University, School Of Medicine, Cardiff, United Kingdom, [4]Stanford University, Department Of Neurology And Neurological Sciences, Stanford, United States of America, [5]University of Camerino, School Of Biosciences And Veterinary Medicine, Camerino, Italy, [6]University College London, Centre For Medical Image Computing (cmic), London, United Kingdom

Aims: We performed a large-scale, stratified genome-wide association study (GWAS) of Alzheimer's disease (AD) to chart the role of autosomal genetic variation in AD sexual dimorphism and heterogeneity of *APOE**4-related AD risk.
Methods: The study overview and GWAS models are shown in **Figure.1A**. SNP-array AD GWAS datasets primarily composing the ADGC, together with whole-genome sequencing (WGS) from ADSP (NG00067.v7), provided case-control diagnoses for phase-1. The UK Biobank provided subjects with ICD codes and family history of AD status for phase-2. Subjects were of European ancestry. Linear mixed model regressions were performed (LMM-BOLT v.2.3.4) on AD outcome measures, adjusting for sex, *APOE**4/*APOE**2 dosage, genetic principal components, and array/batch/center. GWAS hits (P<5e-*8) were evaluated for interactions effects (meta-regression for phase1+2 meta-analyses) and assessed in functional follow-up analyses.
Results: Stratified AD GWAS identified 28 loci/variants, including 5 known lead variants in known AD loci, 6 novel independent variants in known AD loci, and 17 novel loci (**Figure.1B**). 13 out of 17 novel loci showed varying degrees of functional support, with 4 also showing evidence for QTL colocalization (**Figure.2**). Many implicated genes showed prior support or effects relevant to AD (e.g. *MARCHF10* was recently implicated as a risk gene for all-cause dementia) Nonetheless, most novel hits were low/uncommon frequency variants and QTL colocalization evidence was limited. Further, there appeared to be no predictive benefit for stratified GRS analyses (**Figure.3**).

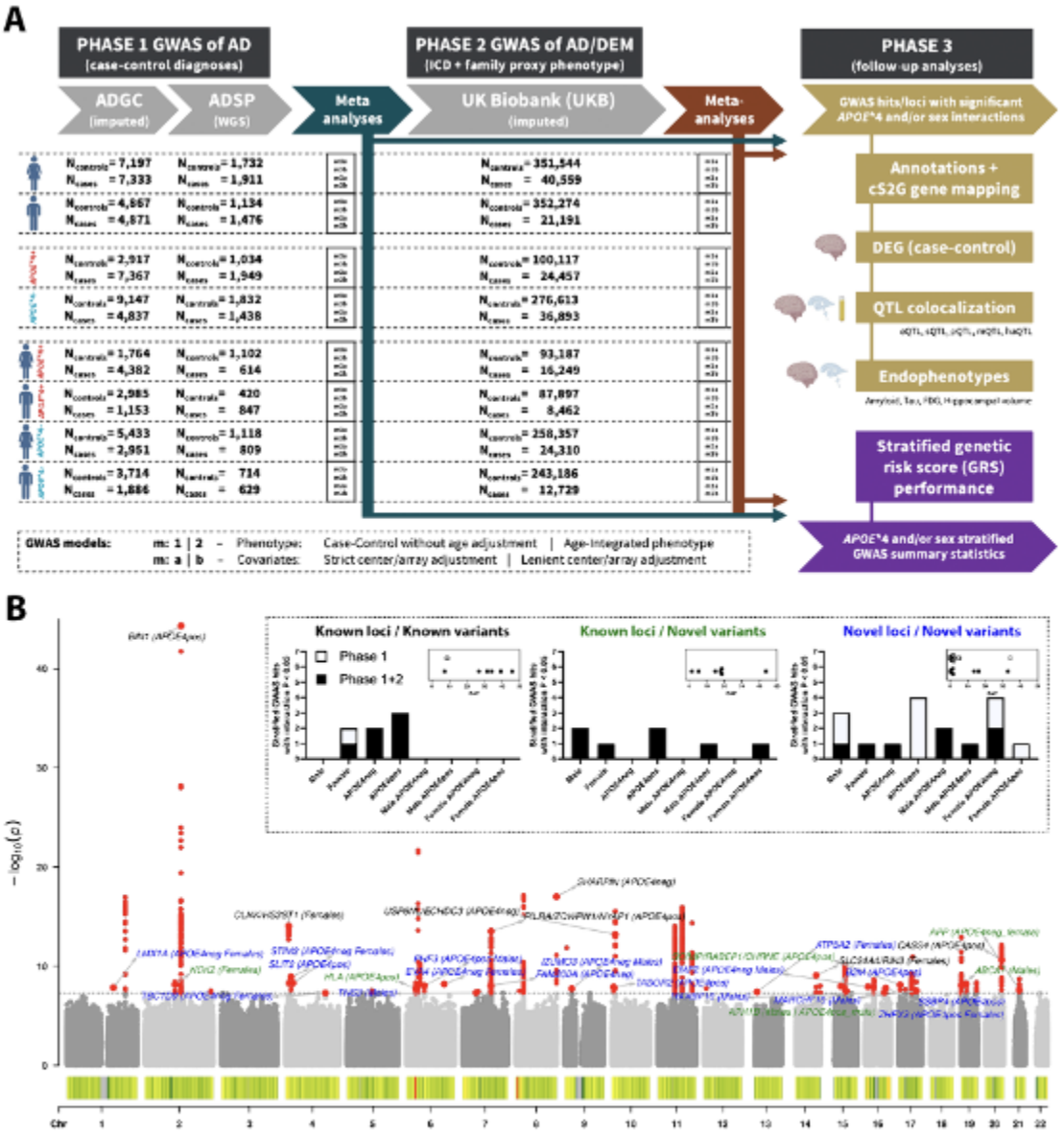


Figure 1. Comprehensive GWAS of AD across *APOE4- and sex strata. A)** Study design illustrating phase 1 and phase 1+2 GWAS meta-analyses with subsequent phase 3 functional mapping and genetic risk score (GRS) follow-up analyses. **B)** GWAS Manhattan plot showing minimum P-value per variant for all GWAS (8 strata * 4 models * 2 designs = 64 GWAS). Variants passing GWAS significance (P<5e-8) in a given stratum and having at least nominal significance for matching variant-by-stratum interaction tests are labelled: Black) known index variants from prior AD GWAS; Green) novel variants in known AD loci independent from known index variants (R2<0.1), and Blue) novel index variants in novel loci (labelled with nearest protein coding gene from GENCODE v42). Inset shows distribution across strata and GWAS designs, together with effect allele frequencies (EAF) for labelled variants.

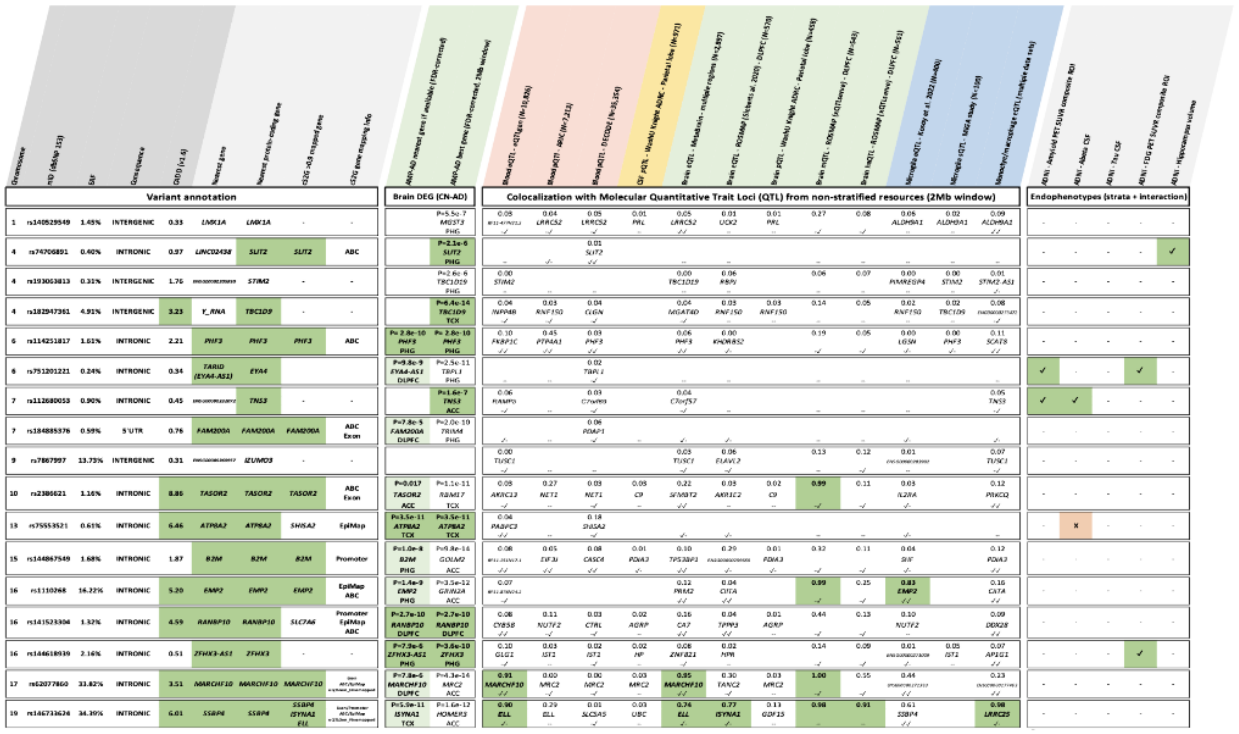


Figure 2. Stratified GWAS functional follow-up analyses of novel loci. Every row represents a novel locus with its index variant. Green shaded cells indicate positive follow-up results, which include: elevated CADD scores, nearest (protein coding) gene matching to cS2G mapped gene and/or differentially expressed gene (DEG) in brain tissues, closest by gene having the most significant DEG in brain tissues (or at least significant DEG = light green), colocalization probability >0.7, and endophenotype effects that match with the stratified GWAS effects.

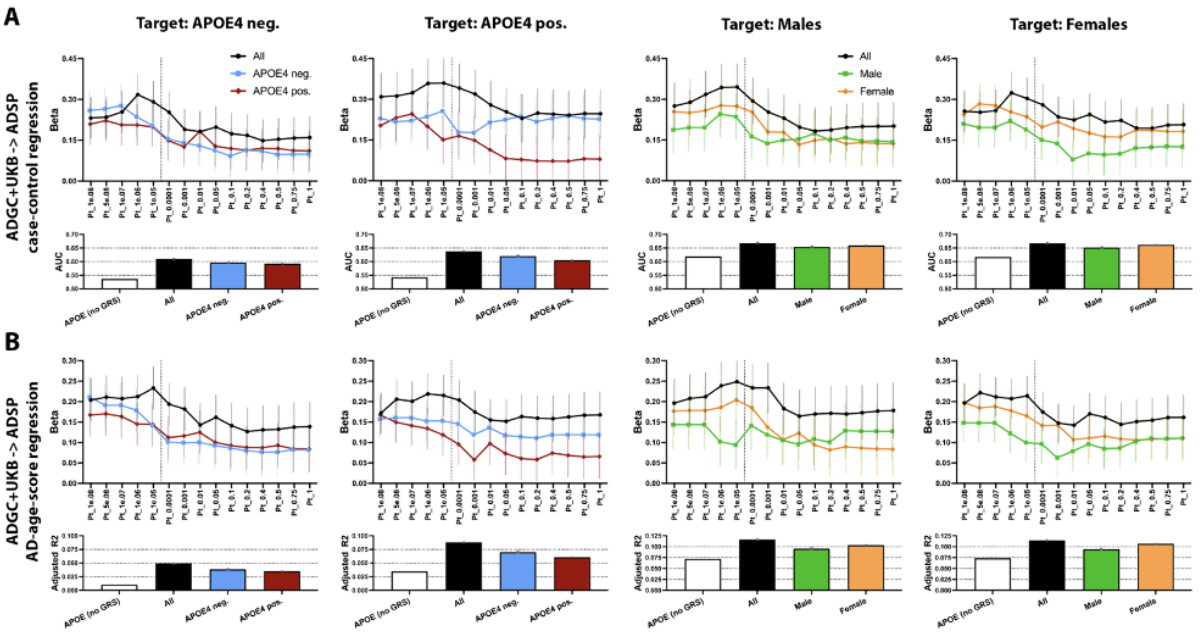


Figure 3. Stratified GWAS genetic risk score (GRS) follow-up analyses. Stratified GRS performance was evaluated using meta-analyzed GWAS summary statistics from ADGC+UKB (base) to construct GRS in independent samples from ADSP (target), using a case-control regression model without age adjustment **(A)** or an age-integrated phenotype model termed "AD-age-score" **(B)** as in Le Guen & Belloy et al., 2021 (similar to cox regression). Columns indicate the target strata in ADSP. Colored traces/bars indicate the base strata from ADGC/UKB. Top panels indicate betas with 95% confidence intervals for GRS derived at different P-value thresholds (Pt), where the vertical dotted lines distinguish oligogenic (left) from polygenic (right) signal. Lower panels show predictive performance. Note that stratified GRS never improved predictive performance and GRS derived from full sample GWAS provided the highest performance (results were consistent when only ADGC was used as the base for GRS).

Conclusions: We identified novel loci/variants differentially associated with AD risk across *APOE*4* and/or sex. Yet, we inferred relatively limited evidence for stratified effects (propensity for low frequency hits and no benefit for stratified GRS). Overall, our findings contribute to our understanding of the genetic etiology of AD, which in turn contributes to advance personalized genetic medicine.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0544 / #876

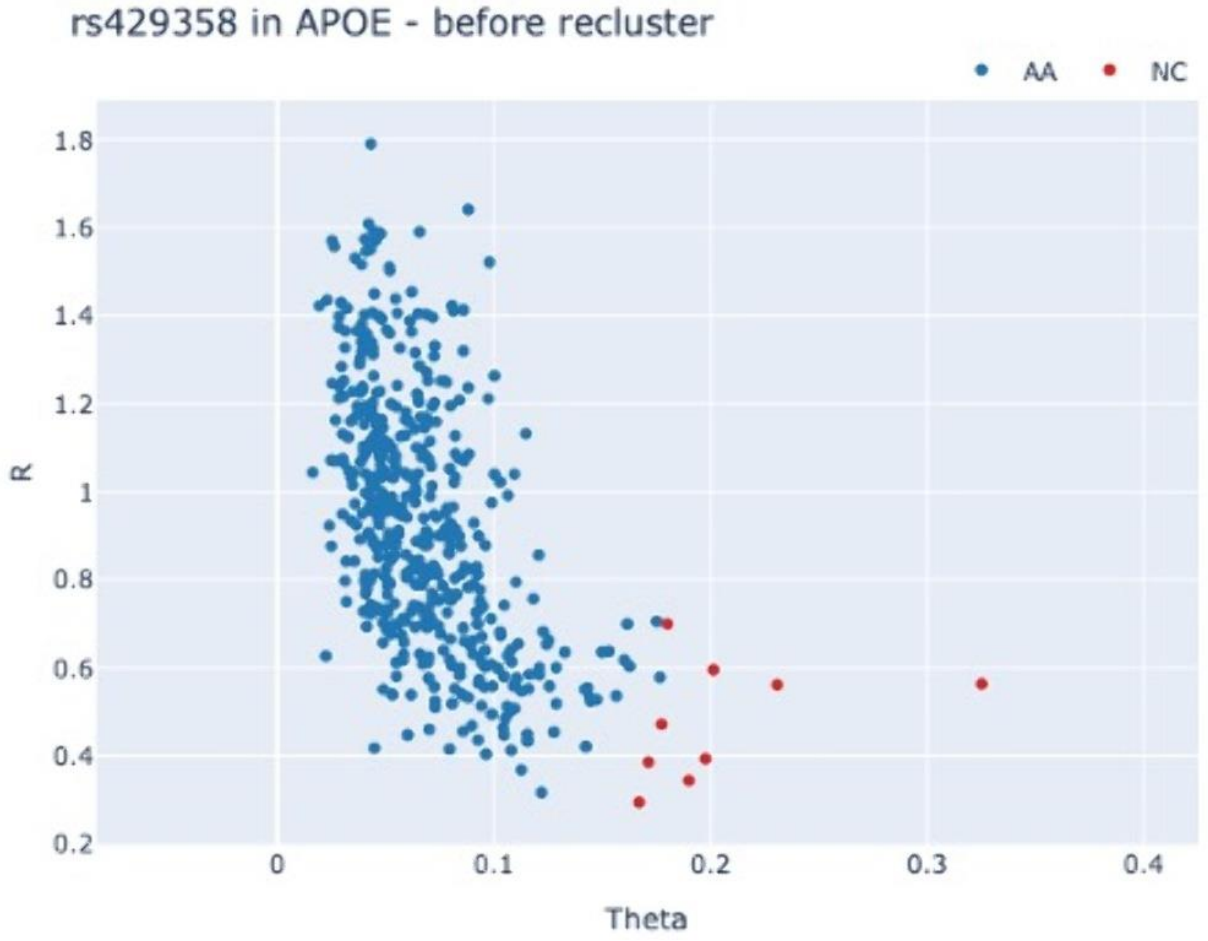
Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

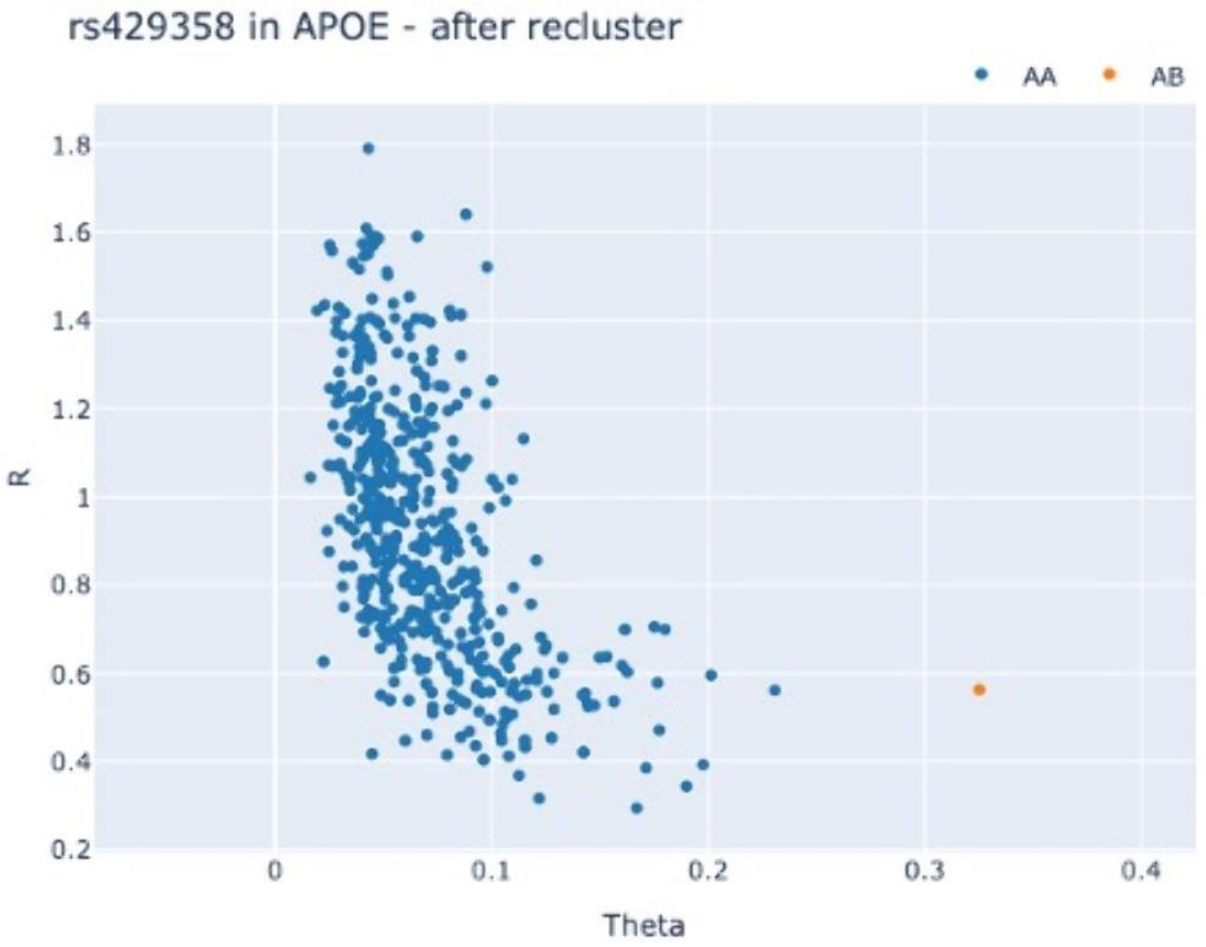
CLUSTER BUSTER: A MACHINE LEARNING APPROACH TO GENOTYPING SNPS FROM RAW DATA

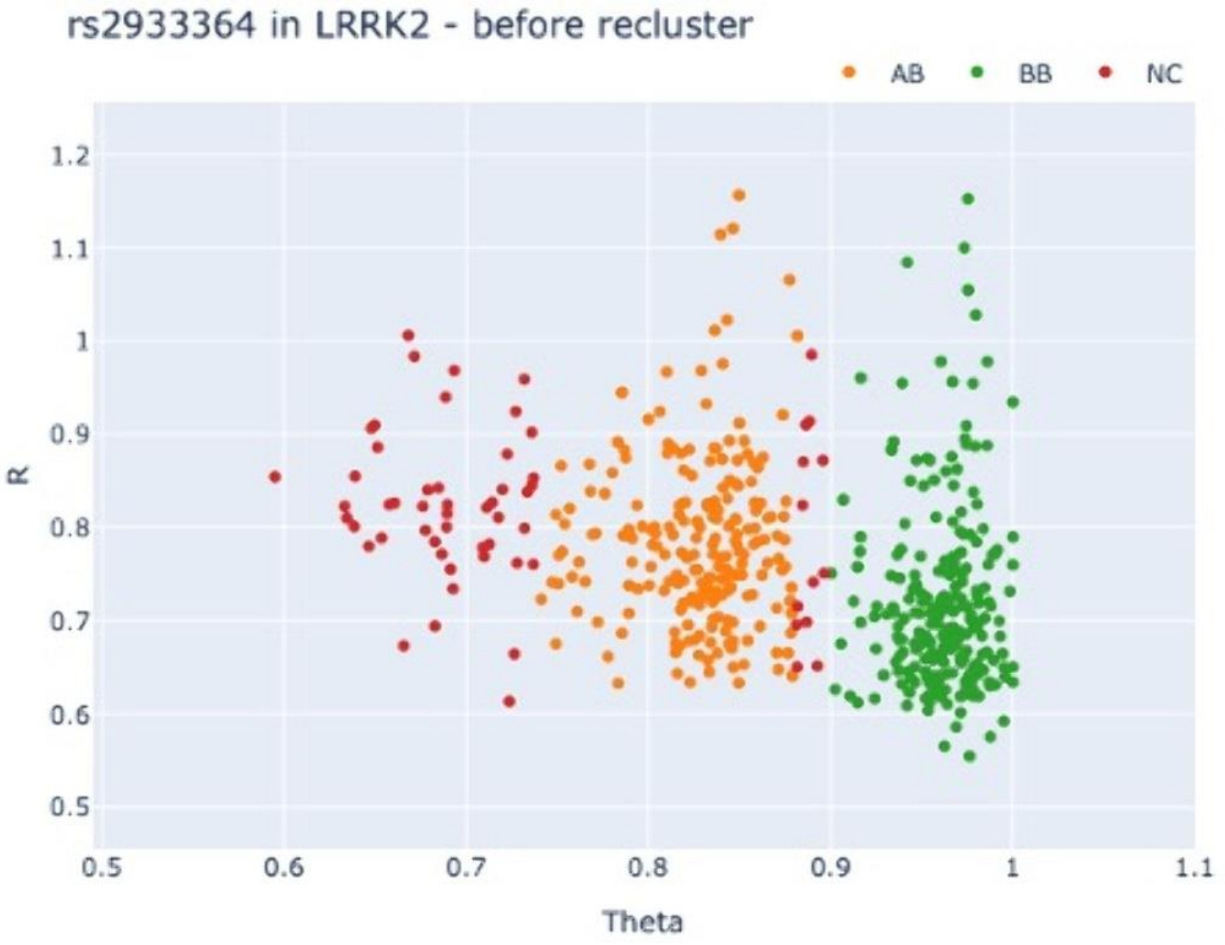
POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Jessica Martin, Nicole Kuznetsov, Mathew Koretsky, Daniel Vitale
National Institutes of Health, Center For Alzheimers And Related Dementia, Rockville, United States of America

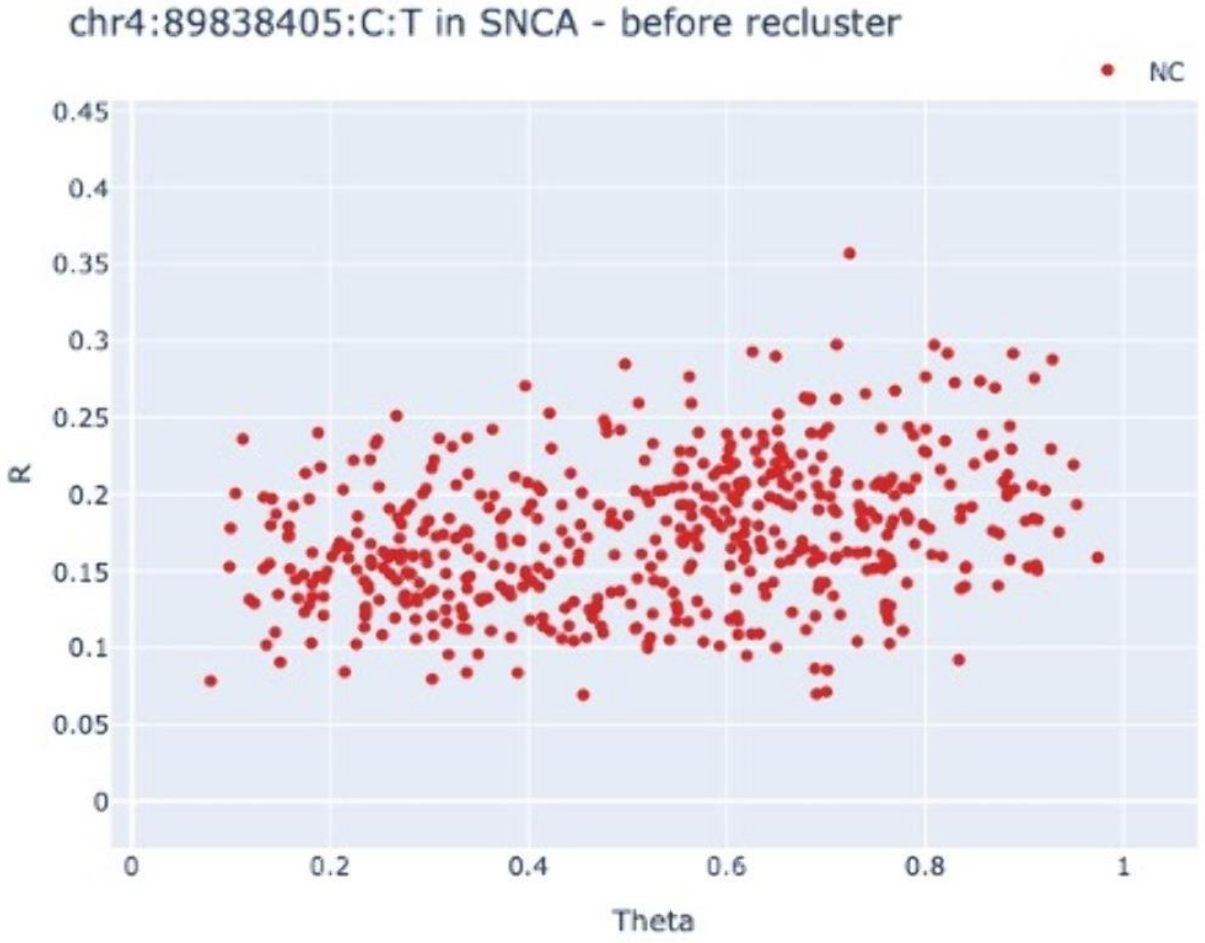
Aims: The Global Parkinson's Genetics Program (GP2) collects information about single nucleotide polymorphisms (SNPs) from individuals with and without Alzheimer's or Parkinson's Disease. Here we develop ClusterBuster, a machine learning method for recovering previously uncalled genotypes from Illumina's GenCall algorithm to refine genotypes for GWAS studies.
Methods: We trained a Support Vector Classifier (SVC) of 3rd degree polynomial kernel on a subsection of 750 genotyped SNPs data from GP2 with an even distribution across minor allele frequency rarities, ancestries and phenotypes represented to ensure generalizability. Using R and Theta values from the Illumina SNP array machine as features, the SVC then predicts the genotype of the SNP.
Results: Our genotype predicting machine learning model reached an accuracy of 99% on a section of training data (80:20) held out for validation purposes. Comparing model genotype predictions with previous genotype calls produced by Illumina revealed a discrepancy in 0.39% of validation SNPS. Using this novel machine learning method, we have recovered 662 unique SNPs in the APOE locus, 421 unique SNPs in the LRKK2 locus, 614 unique SNPs in the GBA1 locus, and 354 SNPs in the SNCA locus.

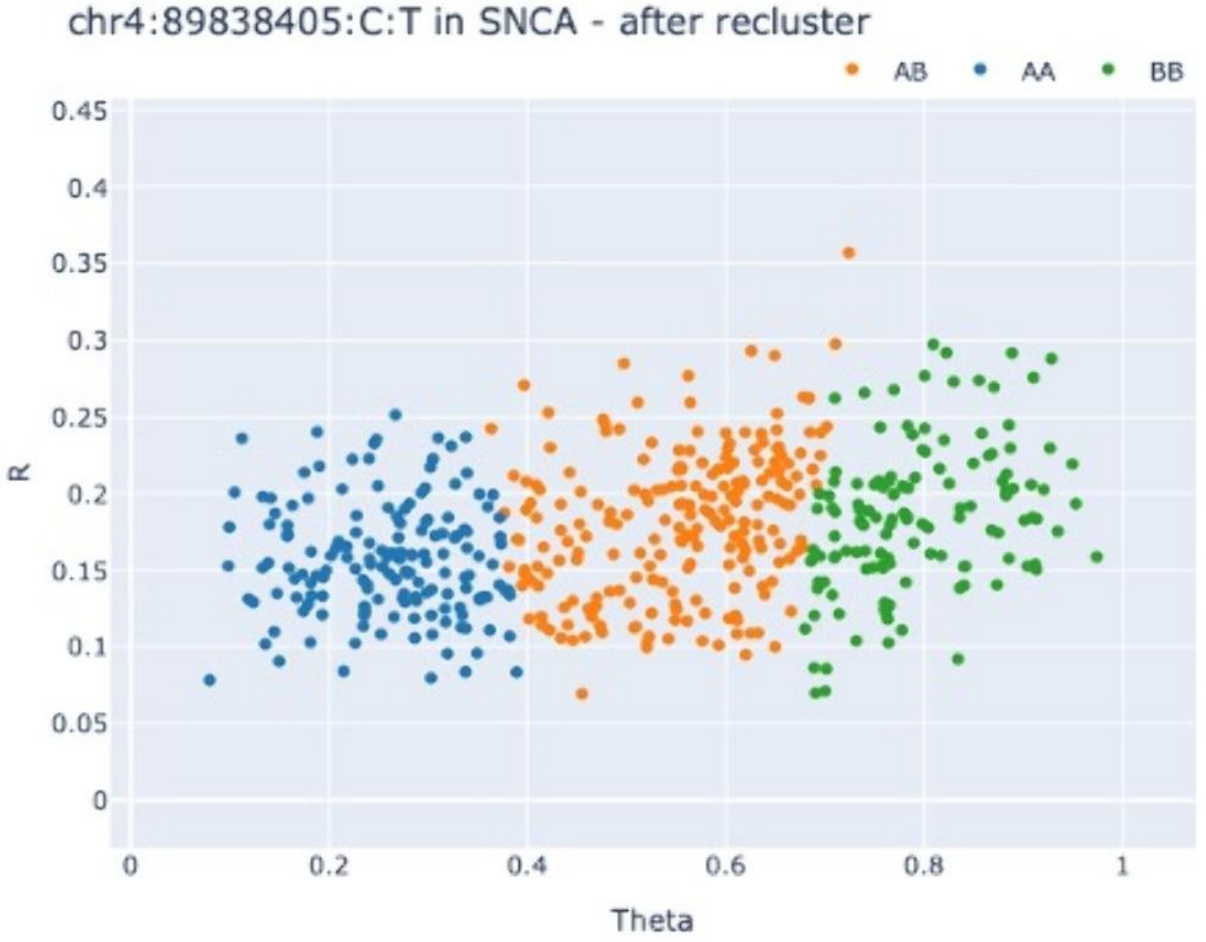

rs429358 in APOE - before recluster
AA
NC
R
Theta
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.1
0.2
0.3
0.4

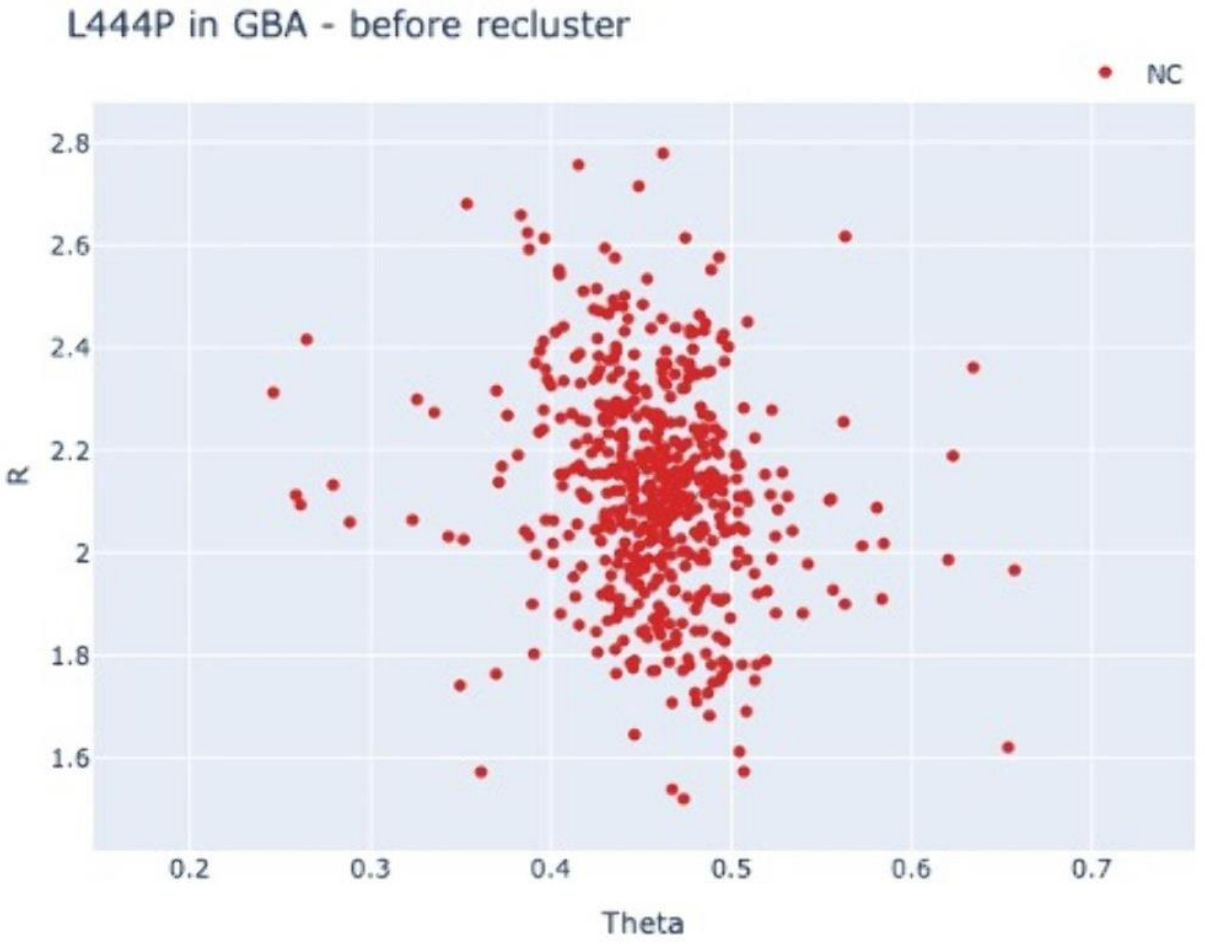

rs429358 in APOE - after recluster
AA
AB
R
Theta
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.1
0.2
0.3
0.4


rs2933364 in LRRK2 - before recluster
AB
BB
NC
R
Theta
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.5
0.6
0.7
0.8
0.9
1
1.1


rs2933364 in LRRK2 - after recluster
AB
BB
R
Theta
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.5
0.6
0.7
0.8
0.9
1
1.1


chr4:89838405:C:T in SNCA - before recluster
NC
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
R
0
0.2
0.4
0.6
0.8
1
Theta


chr4:89838405:C:T in SNCA - after recluster
AB
AA
BB
R
Theta
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
0.2
0.4
0.6
0.8
1


L444P in GBA - before recluster
NC
R
Theta
2.8
2.6
2.4
2.2
2
1.8
1.6
0.2
0.3
0.4
0.5
0.6
0.7

Conclusions: Our novel algorithm allows for previously unusable SNP data to be included in future analyses in the GP2 data. This genotyping algorithm will be added to the GP2 cohort browser and allow for interested parties to view our reclustering efforts on the SNP metrics page for all SNPs on the NeuroBooster array. In the future, we will use this algorithm to validate genotypes for the full release of GP2 data and make this a deployable tool for researchers to apply to their own data.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0545 / #495

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

APOE AND ALZHEIMER DISEASE RISK ACROSS AGE, SEX, RACE AND ETHNICITY, AND ANCESTRY

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Michael Belloy[1], Shea J. Andrews[2], Yann Le Guen[3], Michael Cuccaro[4], Lindsay A Farrer[5], Valerio Napolioni[6], Michael Greicius[3]
[1]Washington University in Saint Louis, Neurology, Saint Louis, United States of America, [2]University of California San Francisco, Department Of Psychiatry And Behavioral Sciences, San Francisco, United States of America, [3]Stanford University, Department Of Neurology And Neurological Sciences, Stanford, United States of America, [4]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [5]Boston University Schools of Medicine and Public Health, Department Of Medicine, Boston, United States of America, [6]University of Camerino, School Of Biosciences And Veterinary Medicine, Camerino, Italy

Aims: *APOE* status is highly relevant towards clinical trial design and AD research broadly. The associations of *APOE* genotypes with AD are modulated by age, sex, race, ethnicity, and ancestry, but these associations remain unclear, particularly in historically understudied non-white samples.
Methods: The study overview is shown in **Figure.1**. Various case-control, family-based, and longitudinal AD genetic cohorts were available through public repositories and underwent extensive genotype and phenotype quality control. These cohorts contributed data for Non-Hispanic Whites (NHW), Non-Hispanic Blacks (NHB), and Hispanics (HISP). Global ancestry was determined using SNPweights v2.1. Case-control logistic regression models evaluated the AD risk associations of *APOE**2 dosage, *APOE**4 dosage, and *APOE* genotype, with regard to *APOE**33 as the reference, while adjusting for sex, array/batch/center, and global European, African, and Amerindian ancestry. *APOE* associations in East-Asians (EAS) were obtained through meta-analyses of published AD genetic studies, given the relative paucity of EAS in publicly available genetic
cohorts.

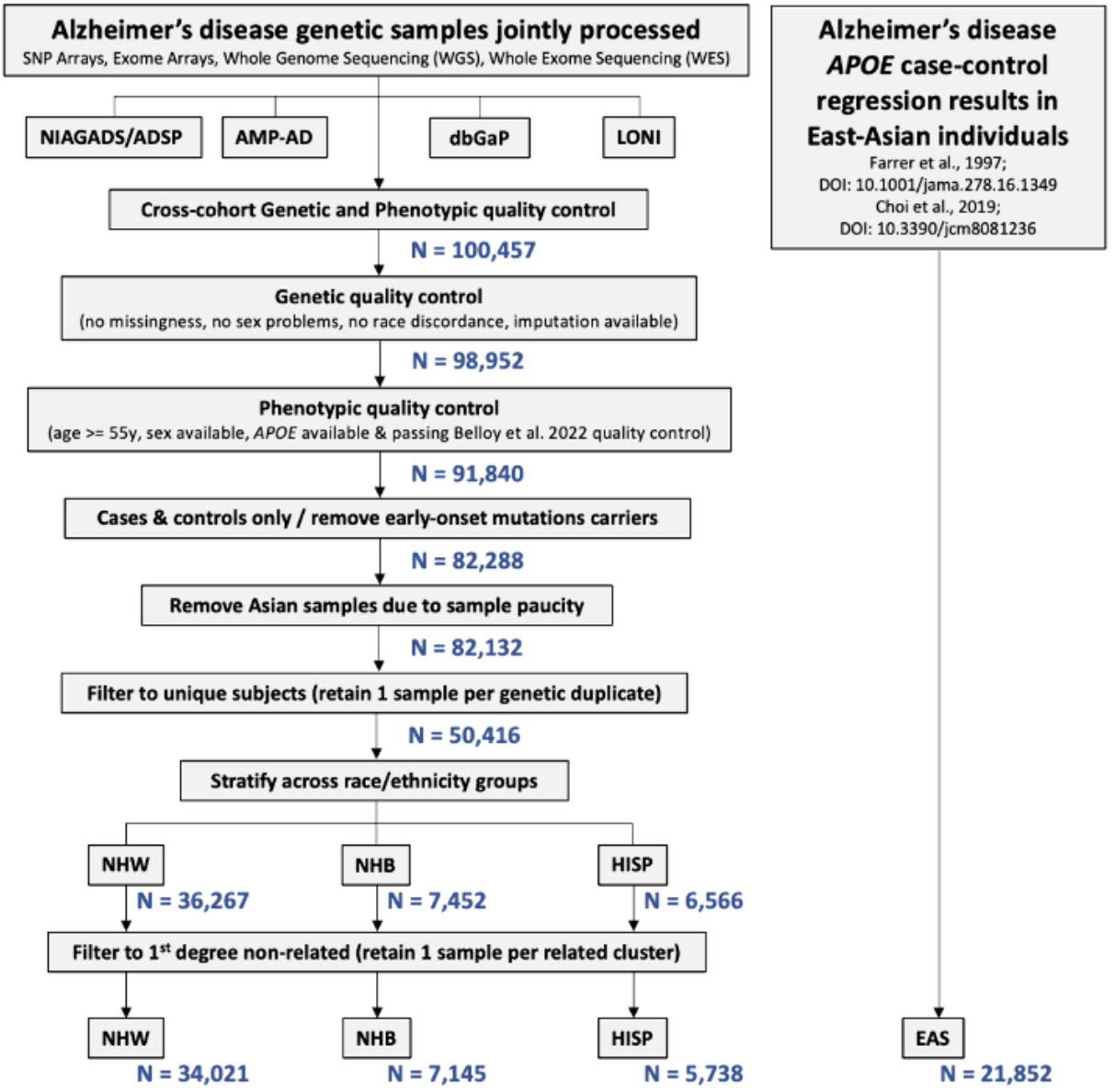


Figure 1. Flow chart of sample/participant filtering for *APOE* association analyses with Alzheimer's disease risk.

Results: We made several novel observations (**Figure.2**). Notably, the associations of *APOE* genotypes with AD risk were least pronounced in HISP, which was not explained by global ancestry. Further, not just *APOE**4, but also *APOE**2 followed a reduced association strength with AD risk according to the pattern of EAS > NHW > NHB > HISP (with the exception of *APOE**2 in EAS, which showed no significant association). The sex-by-age-specific association of *APOE**34 in NHW, which was shown to be stronger in women, was reproduced here at ages 60-70 years, and additionally replicated in NHB and HISP.

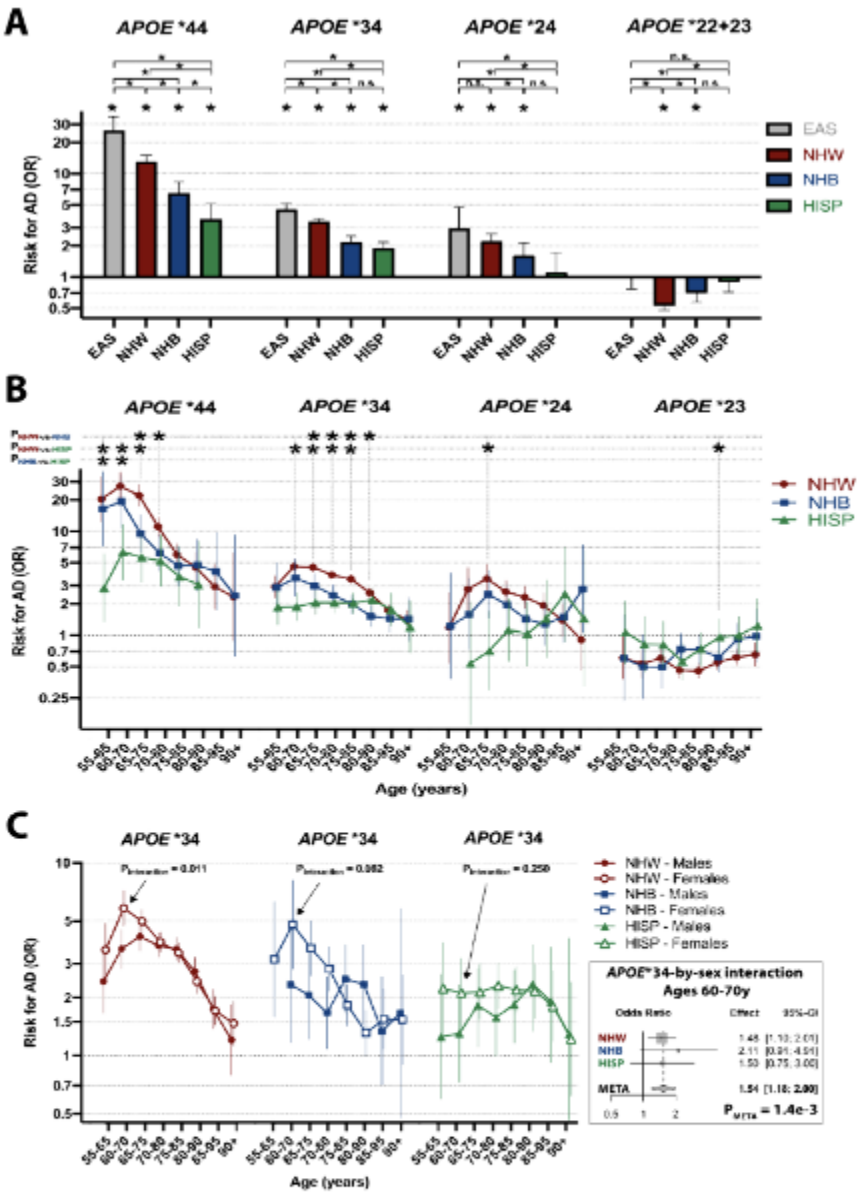


Figure 2. Associations of *APOE* genotypes with AD risk across race/ethnicity, age, and sex. A) Race/Ethnicity stratified and heterogeneity results. Note the stepwise pattern across groups and least pronounced associations of *APOE* genotypes with AD risk in Hispanics. Significance (*) was P<0.05. **B)** Race/Ethnicity stratified and heterogeneity results, further stratified across 10-year age bins using a sliding window approach (5-year overlap). In age-stratified analyses, significant discoveries (*) were considered for Bonferroni correction of the number of non-overlapping age windows (P<0.05/4=0.0125). **C)** *APOE**34-by-sex stratified and interaction results, across age strata. The age bin of 60-70 years indicated a significant *APOE**34-by-sex interaction effect in NHW, which was replicated with nominal significance upon meta-analysis of NHB and HISP (P=0.048). Right inset shows the overall meta-analysis.

Conclusions: We provide the largest-to-date overview of *APOE*'s associations with AD risk across important biological and demographic strata. We expect these insights to be critical to guide AD research and clinical trial design.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0546 / #190

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

GLUTATHIONE PEROXIDASE 4 AS A THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Peta Greer[1], Daniel Maddison[1], Leonardo Amadio[2], Owen Peters[3], Gaynor Smith[1]
[1]Cardiff University/Dementia Research Institute, School Of Medicine, Cardiff, United Kingdom, [2]Cardiff University/Dementia Research Institute, School Of Biosciences/medicine, Cardiff, United Kingdom, [3]Cardiff University/Dementia Research Institute, School Of Biosciences, Cardiff, United Kingdom

Aims: Increased oxidative stress and mitochondrial dysfunction are known features of Alzheimer's disease (AD) pathomechanism. The pathological protein amyloid-beta (Aß) drives oxidative stress in AD. These effects are largely counteracted by the glutathione (GSH) system within our cells. Glutathione peroxidase 4 (fly homologue PHGPx) is a critical brain antioxidant within the GSH system. Reduced expression is evident in AD patient brain regions affected by Ferroptosis; a cell death mechanism associated with increased lipid peroxidation and mitochondrial alterations. These observations point towards potential therapeutic value in overexpressing PHGPx to rescue oxidative stress and neurodegeneration. We aimed to discover how levels of PHGPx affect phenotypes within a *Drosophila* model of AD, including survival, Aß accumulation and neurodegenerative phenotypes.
Methods: Levels of PHGPx were altered specifically in fly neurons via the UAS-GAL4 system, using either RNAi for knockdown or cDNA for overexpression. To measure longevity the percentage survival state of flies was recorded over the lifespan compared to control. Locomotor function, used as a readout for overall CNS function, was assessed using a negative geotaxis assay. Analysis of mitochondrial morphology was then achieved using genetically encoded GFP and imaged by confocal microscopy. Mitochondrial dynamic changes that occur during oxidative stress were quantified using ImageJ.
Results: We found overexpression of PHGPx ameliorates Aß toxicity through extension of survival in *Drosophila* and protects against progressive climbing deficits observed in adult *Drosophila.* Conversely, knockdown of PHGPx was shown to cause significantly more round mitochondria and to enhance oxidised glutathione levels in mitochondria.
Conclusions: This suggests overexpression of PHGPx may act as a protective mechanism in context of neurodegenerative diseases involving the pathological hallmark amyloid including AD. Identifying the mechanisms underlying these phenotypes may lead to new therapeutic interventions for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0547 / #1128

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

CONTRIBUTION OF GENETIC POLYMORPHISMS TO VARIABLE SLEEP DISTURBANCES IN ALZHEIMER'S DISEASE

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Alesha Heath[1], M Windy Mcnerney[2], Jerome Yesavage[1]
[1]Stanford University, Psychiatry And Behavioral Sciences, Stanford, United States of America, [2]VA Palto Alto, Mirecc, Palo Alto, United States of America

Aims: Alzheimer's disease (AD) presents itself as a highly heterogeneous disorder. Many diagnosed express variable symptom base which may further contribute to cognitive decline or be protective against the neurodegeneration caused by this disorder. One such factor is sleep. Aspects of sleep architecture are known to be heritable and influenced by genetic polymorphisms. Therefore, we hypothesized that genetic differences which underlie sleep disturbances influence the progression of AD.
Methods: This study used existing data collected through the Alzheimer's Disease Sequencing Project and National Alzheimer's Coordinating Center's Uniform Data Set (NACC). In order to determine whether genetic differences underlie these sleep effects, we used VNTRseek to genotype over 200,000 tandem repeats of interest in sequencing data from non Hispanic White population (n=5116).
Results: Using a logistic regression model controlling for sex and AD status we did not find any association of VNTRs with sleep disturbances in this dataset after correction for multiple testing. As it is well known that having sleep disturbances increases the chance of developing AD, we wanted to see if any genetic polymorphisms mediated this effect. Using a cox regression model controlling for sex and APOE4 status we found one tandem repeat, upstream from the carbohydrate sulfotransferase 3 gene, was associated with faster time to diagnosis of AD in those with sleep disturbances.
Conclusions: We plan to extend these findings to include SNPs to evaluate multiple types of polymorphic contributions. As sleep remains one of the only modifiable factors that could easily influence the progression of AD, by identifying genetic associations which could allow us to predict factors which may accelerate the progression of this disorder we will open up avenues to apply early interventions and monitor the progression of this symptom closely.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0548 / #1067

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

CONFIRMING DIFFERENTIATED RELATEDNESS IN FAMILY-BASED STUDIES FOR ALZHEIMER'S DISEASE AND RELATED DEMENTIAS IN REDLAT

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Samantha Hong[1], Mathew Koretsky[1], Daniel Vitale[1,2]
[1]National Institutes of Health, Center For Alzheimers And Related Dementias, Bethesda, United States of America, [2]DataTecnica LLC, Datatecnica, Washington, United States of America

Aims: Family-based Genome-Wide Association Studies (GWAS) serve as a powerful analysis for the identification and investigation of rare genes associated with heightened risk while avoiding issues with population stratification in population-based GWAS. To effectively conduct family-based GWAS, the familial relationships among the study participants must be validated. We present a tool that will be implemented within an automated quality-control tool for pre-GWAS workflows to do thorough relatedness profiling for whole-genome sequencing for RedLat, an initiative studying Alzheimer's disease and related dementias in Latin America.
Methods: We built a Python pipeline for family-based GWAS that leverages the RedLat genomic data, accurately determining and verifying familial relationships among individuals. The tool utilizes PLINK2 and KING to infer pairwise kinship coefficients, labeling the relationships as either full siblings, parent-offspring, 2nd-degree, or 3rd-degree relatives. We also compare the reported familial relations with the genomically determined relatedness using identity-by-descent (IBD) values.
Results: This method will label all of the samples within the RedLat dataset based on kinship clusters and the familial relationships that exist within the clusters. The kinship coefficients are used to flag and remove samples with cryptic relatedness (individuals found to be related to more than two families) and ignore background relatedness as noise. We also confirm that the disclosed relatedness matches the genomic relatedness using IBD cutoffs to differentiate the relationships. We have verified that the results generated from our automated pipeline align with results produced manually.
Conclusions: Our pipeline will confirm relatedness within RedLat so that family-based studies can be performed confidently on the data, increasing the accessibility and power of familial GWAS. In the future, this pipeline can be applied to any disease dataset once hereditary information is available.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0549 / #1948

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

PLASMA NEUROFILAMENT LIGHT CHAIN CORRELATES WITH POLYGENIC RISK BEFORE CLINICAL MANIFESTATION OF ALZHEIMER'S DISEASE.

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Sonja Kagerer[1], Swapnil Awasthi[2], Stephan Ripke[2], Aleksandra Maleska[3], Pascal Benkert[4], Aida Fall[5], Peter Riederer[6], Peter Riederer[7], Susanne Walitza[8], Edna Grünblatt[8], Jens Kuhle[3], Paul Unschuld[5]
[1]University of Zurich, Institute For Regenerative Medinice, Schlieren, Switzerland, [2]Charite Berlin, Department Of Psychiatry And Neurosciences, Berlin, Germany, [3]University Hospital and University of Basel,, Department Of Neurology, Basel, Switzerland, [4]University Hospital and University of Basel, Department Of Neurology, Basel, Switzerland, [5]University of Geneva (UniGE), Department Of Psychiatry, Geneva, Switzerland, [6]University Hospital of Würzburg, Center Of Mental Health, Clinic And Policlinic Of Psychiatry, Psychosomatics And Psychotherapy, Würzburg, Germany, [7]Social Medicine Center East-Donauspital, Department Of Psychiatry, Wien, Austria, [8]Psychiatric University Hospital Zurich, University of Zurich, Department Of Child And Adolescent Psychiatry And Psychotherapy, Zurich, Switzerland

Aims: Objectives: Efforts to establish valid blood-based diagnostic approaches for individual susceptibility to Alzheimer's Disease (AD) play a pivotal role in advancing strategies aimed at AD prevention and early therapeutic interventions. Two emerging indicators, Neurofilament light chain (NfL) and polygenetic risk scores (PRS) for AD, show promise in this context. The present study evaluated the correlation of both markers and their combined predictive value in cognitively healthy persons prior to clinical AD onset.
Methods: We conducted data analysis using a cohort of 144 75-year-old participants drawn from the Vienna Transdanube Aging (VITA) longitudinal study. Participants were categorized based on development of AD over a 90-month study period. Plasma NfL was assessed using single molecular array technology (Simoa) at baseline, 30-, 60-, and 90-months. For validity control, NfL z-scores were computed accounting for the influence of age and BMI. Furthermore, genotype data from participants were collected and used to calculate individual late-onset AD continuous shrinkage polygenetic risk scores (PRS) based on the largest available AD genome-wide association study (GWAS).
Results: 19 participants developed AD after a median time to diagnosis of 60 months (IQR 30). Plasma NfL levels increased significantly in both groups over 90 months (AD: $p=1.2x10^{-4}$, controls: $p=6.0x10^{-18}$). In the AD group baseline NfL plasma levels correlated with PRS (r=0.75, p<0.001). This relationship was not observable in the control group (r=-0.06, p=0.49; Fisher's r-to-z: z=3.89, p<0.001). PRS-CS combined with baseline plasma NfL predicted development of AD (p<0.01).
Conclusions: Our data suggest that polygenic risk for AD and plasma NfL closely interact years before onset of clinical symptoms. Our findings support the notion that peripheral NfL may serve as a diagnostic measure supporting early therapeutic intervention and secondary prevention in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0550 / #2443

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

CELL-TYPE-SPECIFIC ISOFORM CALLING USING LONG-READ SINGLE-NUCLEI SEQUENCING

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Tijs Watzeels, Lara De Deyn, Lena Duchateau, Jasper Van Dongen, Peter De Rijk, Wouter De Coster, Fahri Küçükali, Renzo Mancuso, Kristel Sleegers
VIB Center for Molecular Neurology, Complex Genetics Of Alzheimer's Disease Group, Antwerpen, Belgium

Aims: Alternative splicing as well as distinct cell types have been gaining in interest regarding their role in complex human diseases, as advances in technologies have made studying their respective impact on disease risk increasingly feasible. We attempt to combine both long-read and single-cell sequencing to investigate the effect of alternative splicing in a cell-type specific context in the etiology of Alzheimer's disease (AD).
Methods: We sequenced a cohort of n = 15 AD patients and n = 8 controls using 10X single-nuclei Oxford Nanopore Technologies (ONT) long-read sequencing. Nuclei isolation was performed using a density gradient protocol optimized for human fresh frozen brain. For comparison, we performed Illumina short-read sequencing on the same 10X libraries. We compared short-read-free classification of barcodes, gene calling and cell typing results to short-read Cell Ranger-based analysis, which is the current "gold standard".
Results: Using our ONT-single-nuclei-based generated data we obtain highly similar results to the standard short-read workflow. Identification of non-empty droplets and percentage of cell type distributions show very high overlap, and we find a strong correlation in per-cell UMI count, with correlation coefficients ranging between 0.92 and 0.85. Importantly, we also obtain isoform counts, which are unreliable when relying on short reads.
Conclusions: We show that short-read sequencing is not required for either barcode assignment, clustering, or cell-type characterization, which evidently comes with a great reduction in experiment cost. Furthermore, without significant loss of information we generate transcript isoform information, which is unreliable in short-read based experiments, which we will use next to investigate alternative splicing in human disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0551 / #1330

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

NOVEL LOCI IDENTIFIED FOR ALZHEIMER'S DISEASE VIA ENDOPHENOTYPE GENOME-WIDE ASSOCIATION STUDY IN KOREAN POPULATION

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Sarang Kang[1], Junwoo Park[2], Jang Jae Lee[2], Jung-Min Ha[3], Ari Chong[3], Kyu Yeong Choi[2], Kun Ho Lee[4]
[1]Chosun University, Department Of Integrative Biological Sciences And Bk21 Four Educational Research Group For Age-associated Disorder Control Technology, Gwangju, Korea, Republic of, [2]Chosun University, Asian Dementia Research Initiative, Gwangju, Korea, Republic of, [3]Chosun University Hospital, Department Of Nuclear Medicine, Gwangju, Korea, Republic of, [4]Chosun University, Department Of Integrative Biological Sciences, Gwangju, Korea, Republic of

Aims: The Seoul Neuropsychological Screening battery (SNSB) is a widely used cognitive test battery for Korean speakers. However, the effects of genetic variation on the SNSB are not well understood, despite the fact that it is widely used in Korea. We conducted a genome-wide association study (GWAS) using genotype data to investigate associations with neuropsychological tests in order to address these research concerns.
Methods: Over 10,000 subjects enrolled in Gwangju Alzheimer's and Related Dementia cohort undergo cognitive assessment with SNSB with follow-up diagnosis. SNSB contains five cognitive domains; attention, language, visuospatial functions, memory, and executive functioning. We used the latest SNSB screening results from 2,055 subjects. Subject genotype data were acquired using Affymetrix® Axiom KORV1.0 and imputed with HRC panel V.1.1. SNPs with minor allele frequency<1%, call rates<95%, HWE p-value $<1\times10^{-6}$ were excluded from analysis. We performed linear regression with raw test scores and 10 million imputed genotype variants with PLINK software. Age, sex, education level, and the first four PCs were adjusted as covariates.
Results: The missense variant of the genome-wide significant (GWS) loci on chromosome 14 showed substantial associations in RCFT delayed recall (1.71×10^{-11}) and K-MMSE total score (4.14×10^{-9}).
Conclusions: The missense variant on chromosome 14 may effectively predict overall cognitive dysfunction and long-term visuospatial memory loss, which are the testing domains of MMSE and RCFT. Additional analyses on protein structure and in-vivo studies are required to thoroughly investigate the functional effects of the missense mutation. Since RCFT delayed recall also showed significant associations with CSF phospo-Tau level (Seo et al., 2021), the identified GWS variant may indicate neurodegeneration in Tauopathy and AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0552 / #1620

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

MULTI-TRAIT GENOME-WIDE ASSOCIATION STUDY DISCOVERS GENES WITH PLEIOTROPIC EFFECT ON ALZHEIMER'S DISEASE AND INFLAMMATION

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Fotios Koskeridis, Abbas Dehghan, Ioanna Tzoulaki
Imperial College London, Epidemiology And Biostatistics, London, United Kingdom

Aims: Inflammation is involved in a plethora of pathophysiological conditions including brain dementia. Several genes of Alzheimer's disease (AD) have also been associated with inflammation biomarkers including C-reactive protein (CRP). Here, we aim to investigate further the common genetic architecture between AD and inflammatory biomarkers and identify pleiotropic loci. We perform a large-scale multi-trait GWAS analysis on AD and CRP followed by genetic colocalization analysis to highlight candidate pleiotropic genes and their tissue sites of action.
Methods: We performed a multi-trait analysis on AD and CRP using MTAG followed by colocalisation analysis on the top signals indicated from MTAG. A trait-expression quantitative trait loci (eQTL) colocalisation using AD, CRP and eQTL from 48 tissues to detect possible shared genes between the traits and investigate the tissues they are expressed.
Results: We highlight 13 possibly shared genes between AD and CRP located in 4 loci and additionally, we prioritise 4 candidate causal variants. The variant rs11136254 colocalises via EEF1D in brain hypothalamus, while rs1582763 via RP11-1036E20.9 in whole blood and via TMEM132A in muscle skeletal. The variant rs34173062 colocalises in 6 different tissues via 4 distinct genes including CPSF1 in lung, artery coronary, muscle skeletal and adipose subcutaneous, PARP10 in artery tibial, ZNF251 in lung and SLC52A2 in adipose visceral omentum. Finally, rs62090056 colocalises via SERPINF2 in testis.
Conclusions: Our findings provide insights into shared mechanisms underlying inflammation and neurodegeneration, representing potential preventive and therapeutic targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0553 / #2336

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

IMPACT OF SEX, AGE, AND ANCESTRY ON APOLIPOPROTEIN E (APOE) RISK FOR ALZHEIMER'S DISEASE

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Brian Kunkle[1], Omar Rodriguez[1], Lily Wang[2], Juan Young[1], Alzheimer'S Disease Genetics Consortium Adgc[3], Margaret Pericak-Vance[1], Eden Martin[1]
[1]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [2]University of Miami, Human Genetics, Miami, United States of America, [3]University of Pennsylvania, Perelman School Of Medicine, Philadelphia, United States of America

Aims: Studies have shown non-Hispanic white (NHW) females carrying the *APOEε*2 or ε4 allele differ in risk of developing Alzheimer's disease (AD) compared to men, though this difference may be age-dependent. Here we comprehensively evaluate the association between sex, age, ancestry, and *APOE* with AD in cohorts from the Alzheimer's Disease Genetics Consortium (ADGC).
Methods: A case-control study was conducted in 50 datasets (n=42,295). Logistic, linear, and Cox regression models were used to evaluate associations between disease status and age, sex, race/ethnicity (as proxy of ancestry), and *APOE*.
Results: Men and women with *APOE*ε3/ε4 showed no significant difference in risk of AD after accounting for age. Ancestry-specific analyses showed when comparing subjects with *APOE*ε3/ε4 (vs. ε3/ε3), East-Asian (EA) females (*OR,* 5.00) and males (*OR,* 4.20) had strongest risk; whilst the weakest risk was for South-Asian (SA) men (*OR,* 1.23). Age and ancestry-specific analyses found NHW females (*OR,* 4.66 vs. males: *OR,* 3.99) and African American (AA) females (*OR,* 4.27 vs. AA men: *OR,* 1.98) with *APOE* ε3/ε4 presented higher risk between ages 66-75; whereas EA and SA exhibited this pattern at 55-64. In Hispanics, the relationship was reversed, with males aged 55-65 years carrying *APOE*ε3/ε4 (*OR,* 3.42 vs. females: *OR,* 2.30) having stronger risk than females. Nonetheless, these differences were not statistically significant. Case-only and survival analyses also established that NHW, AA, and EA female APOEε3/ε4 carriers had earlier age-at-onset than their male counterparts. When comparing *APOE*ε2 carriers vs. ε3/ε3 carriers, NHW women (*OR*, 0.64) and men (*OR*, 0.50) presented the lowest *OR*s among ancestries.
Conclusions: Our findings suggest ancestry and age-specific sex differences in AD risk in *APOE*ε2 and ε4 carriers. However, local ancestry analyses for *APOE* are warranted to confirm these findings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0554 / #1834

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

INTERACTION ANALYSIS OF GWAS SIGNIFICANT VARIANTS IN ALZHEIMER'S DISEASE

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Gonzalo Leguia Fauro[1,2], Tijs Watzeels[1,2], Fahri Küçükali[3], Kristel Sleegers[2], Renzo Mancuso[1]
[1]VIB Center for Molecular Neurology, Microglia And Inflammation In Neurological Disorders (mind) Lab, Antwerpen, Belgium, [2]VIB Center for Molecular Neurology, Complex Genetics Of Alzheimer's Disease Group, Antwerpen, Belgium, [3]University of Antwerp, Department Of Biomedical Sciences, Wilrijk, Belgium

Aims: *APOEε4* is the major genetic risk factor for sporadic Alzheimer's Disease (sAD). Despite its strong effect in disease development, there is a huge variability in the age of onset of *APOEε4* carriers. We aim to detect synergistic combinations of low-risk variants that dramatically modify *APOE* influence in sporadic Alzheimer's Disease (sAD).
Methods: We accessed the European AD Biobank (EADB) dataset with >42.000 individuals. We conducted multifactor dimensionality reduction and multiplicative logistic regression on 85 GWAS index variants over the EADB data stratified by the number of *APOEε4* alleles, to study the synergistic effect of all possible trios of variants. We combined the effect deviated from the additive weight of those combinations and compared the performance of both standard GRS and epistatic GRS models in >4.200 independent samples.
Results: We identified >400 novel combinations of genetic variants that significantly deviate from their predicted additive effect and drastically associate AD. The epistatic GRS model outperform significantly standard GRS, identifying >80% of the individuals' status correctly. When stratifying by the number of apoe4 alleles, epistatic GRS also significantly improves AD prediction when compared to standard GRS. The improvement is remarkable in *APOEε44* carriers, where standard GRS have an AUC of 78% and the epistatic GRS of >88%.
Conclusions: We described numerous *APOE* interactors that dramatically influence the disease development, many of them interacting synergistically to promote sAD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0555 / #1762

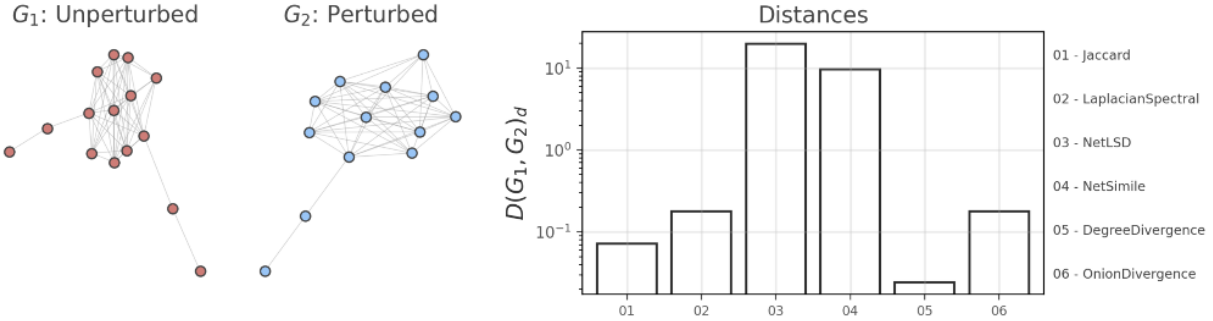
Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

SYNTHETIC PERTURBATION INTERACTIONS IN NETWORKS (SPINN): APPLYING GRAPH THEORY FOR THE ANALYSIS OF TRANSCRIPTOMICS ACROSS NEURODEGENERATIVE DISEASES

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Mary Makarious[1,2], Chelsea Alvarado[3], Cory Weller[3,4], Mathew Koretsky[3], Faraz Faghri[4], Hampton Leonard[1,5,6], Andrew Singleton[1], Michael Nalls[4]
[1]National Institute on Aging, Laboratory Of Neurogenetics, Bethesda, United States of America, [2]UCL Movement Disorders Centre, University College London, London, United Kingdom, [3]National Institutes of Health, Center For Alzheimers And Related Dementias, Bethesda, United States of America, [4]Data Tecnica, Data Tecnica, Glen Echo, United States of America, [5]DataTecnica LLC, Datatecnica Llc, Washington, United States of America, [6]Center for Alzheimer's and Related Dementias, National Institutes Of Health, Bethesda, United States of America

Aims: The rapid evolution of transcriptomics is highlighting the importance of understanding the complex gene networks within the human brain, especially across neurodegenerative diseases such as Alzheimer's. Here we provide a community resource, termed "Synthetic Perturbation INteractions in Networks (SPINN)", an in silico method that leverages machine learning to decipher, query, and visualize these networks and provide researchers with a method to prioritize gene knock-out experiments in vivo or in vitro.
Methods: Key genes in this pilot research include *APOE*, *GRN*, *KANSL1*, and *NOTCH4*. The OpenTargets API was queried to extract associated genes from databases like IntAct, Signor, and Reactome, to construct preliminary networks. A distinct matrix reflecting gene expression across multiple cell types in the adult human brain, focused on the profiles from blood, serum, and cerebrospinal fluid, by Linnarsson and colleagues was used. Employing community clustering and graph network analyses, gene networks were formed. Distance metrics to compare the similarities in the network dynamics pre- and post-synthetic perturbations are calculated.
Results: Our pilot research to assess *APOE* gene networks in microglia indicates that the overall structure of the network is maintained, while the way the genes connect and interact has changed considerably following perturbation (NetLSD distance metric = 1; **Supplementary Figure**). The analysis emphasizes understanding expression shifts based on their regulatory roles. To ensure robustness, the methodology will be applied to a mouse-derived expression matrix, where *APOE* was knocked out.
Conclusions: SPINN presents a framework for decoding the gene expression networks present in neurodegenerative diseases to aid in nominating knockout experiments, directly inform CRISPR studies, and provide an accessible platform to assess the impact of drugs on gene networks.



SPINN prototype: Assessing connectivity of *APOE* in microglia pre- and post-synthetic perturbation with distance metrics

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0556 / #2333

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

SPECIFICITY OF VARIANTS IN ALZHEIMER'S DISEASE POLYGENIC RISK SCORE IN HIPPOCAMPAL SCLEROSIS MRI SURROGATES

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Clàudia Olivé[1], Itziar De Rojas[1,2], Linda Zhang[3], Oscar Sotolongo-Grau[1], Inés Quintela[4], Pablo Garcia-Gonzalez[1,2], Ainhoa Garcia-Sanchez[1], Raquel Puerta[1], Fernando García Gutiérrez[1], Laura Montrreal-Navarro[1], María Capdevila-Bayo[1], Amanda Cano[1,2], Miguel Calero[2,5], Alberto Rábano[2,5], Ana Belén Pastor[5], Teodoro Del Ser[5], Miguel Medina[2,5], Ángel Carracedo[4,6], María Eugenia Sáez[7], Lluís Tárraga Mestre[1,2], Sergi Valero[1,2], Marta Marquié[1,2], Maria Victoria Fernández[1], Pascual Sanchez-Juan[2,5], Merce Boada Rovira[1,2], Bryan Strange[3,5], Agustín Ruiz Laza[1,2]
[1]Ace Alzheimer Center Barcelona, Research Center And Memory Clinic, Barcelona, Spain, [2]CIBERNED Network Center for Biomedical Research in Neurodegenerative Diseases, National Institute Of Health Carlos Iii, Madrid, Spain, [3]Laboratory for Clinical Neuroscience, Centre for Biomedical Technology, Universidad Politécnica De Madrid, Idissc, Madrid, Spain, [4]Grupo de Medicina Xenómica,Centro Nacional de Genotipado (CEGEN-PRB3-ISCIII), Universidad De Santiago De Compostela, Santiago de Compostela, Spain, [5]CIENFoundation, Queen Sofia Foundation Alzheimer Centre, Madrid, Spain, [6]Fundación Pública Galega de Medicina Xenómica, Ciberer-idis, Santiago de Compostela, Spain, [7]CAEBI, Centro Andaluz De Estudios Bioinformáticos, Sevilla, Spain

Aims: Hippocampal sclerosis of aging (HS-aging) is a cause of dementia in older adults which is often misdiagnosed as Alzheimer's disease (AD). HS-aging hippocampal atrophy pattern might help differentiate it from AD. We aim to find risk SNPs previously associated with AD that might be more related to HS-aging.
Methods: We calculated a polygenic risk score (PRS) combining 83 SNPs associated with AD by the European Alzheimer and Dementia consortium (EADB; Bellenguez et al. 2022) and assessed their relation with an HS-by-proxy based on magnetic resonance imaging (MRI) data of hippocampal subfield volumes from 1,130 individuals without dementia syndrome from Fundacio ACE (FACE) and ADNI. We used data from 322 cases and 1,386 controls from EADB–FACE/BBB to associate the EADB AD-PRS (83 variants) with AD in the presence of concomitant brain pathologies, as previously done by de Rojas et al. (2021) using their AD-PRS (39 variants).
Results: From the 14 subfields analyzed, fimbria and hippocampal body and head (HBH) showed a significant association with AD-PRS. Association with these hippocampal subfields was also observed in *SHARPIN* rs34173062 (OR_{HBH}=0.85[0.77-0.93]; $p\text{-value}_{HBH}=2.63\times10^{-04}$;$OR_{fimbria}$=0.83[0.75-0.91]; $p\text{-value}_{fimbria}=2.09\times10^{-04}$) and *TNIP1* rs871269 ($OR_{HBH}$=0.90[0.85-0.95]; $p\text{-value}_{HBH}=1.71\times10^{-04}$). These loci remained consistently associated to HS-aging after analyzing an independent cohort of cognitively healthy individuals (N = 729) from Fundacion CIEN. We replicated the stronger association of AD-PRS with AD in the presence of HS-aging than with AD pathology alone.
Conclusions: The results presented in this study suggest that some SNPs that have recently been identified as AD risk variants might be more closely related to atrophy in hippocampal subfields instead of AD. Hence, these results could be instrumental to refine genuine AD and HS-aging pathways, their interrelationships, and to identify specific therapeutic targets for each condition.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0557 / #1068

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

IDENTIFICATION OF NEW ENHANCER AND PROTECTIVE GENES ON THE TOXIC EFFECTS OF AMYLOID BETA-PEPTIDE

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Cristina Plata[1], Pol Picón-Pagès[1], Mònica Bosch-Morató[1], Laia Subirana[1], Francisca Rubio-Moscardó[1], Biuse Guivernau[1], Hugo Fanlo-Ucar[1], Melisa Ece Zeylan[2], Simge Senyuz[2], Víctor Herrera-Fernández[1], Rubén Vicente[1], José Manuel Fernández-Fernández[1], Jordi García-Ojalvo[1], Attila Gursoy[3], Ozlem Keskin[3], Baldomero Oliva[1], Francesc Posas[1,4], Eulalia De Nadal[1,4], Francisco J. Muñoz[1]
[1]Universitat Pompeu Fabra, Department Of Medicine And Life Sciences, Barcelona, Spain, [2]Koc University, Computational Science And Engineering, Istanbul, Turkey, [3]Koc University, College Of Engineering, Istanbul, Turkey, [4]The Barcelona Institute of Science and Technology, Institute For Research In Biomedicine, Barcelona, Spain

Aims: The misfolding of amyloid β-peptide (Aβ) into β-sheets caused Alzheimer's disease (AD) but this knowledge has not yet led to treatments to prevent AD. To identify novel molecular players in Aβ toxicity, we carried out a genome-wide screen in *Saccharomyces cerevisiae*, using a library of gene knock-out strains expressing $A\beta_{1-42}$.
Methods: i) Cell viability assay of 5,154 knock-out strains of *Saccharomyces cerevisiae* that overexpress $A\beta_{1-42}$ and identification of the enhancer and protective genes regarding amyloid toxicity; ii) *In silico* analysis of genes to perform text-mining and interactome studies; iii) Molecular and cellular studies of the role of SURF4 in $A\beta_{1-42}$ toxicity in human neuroblastoma cells (SH-SY5Y cells).
Results: We identified 81 mammalian orthologue enhancers and 157 protectives genes regarding $A\beta_{1-42}$ toxicity. Text mining and interactome studies showed that the most relevant cellular functions implied in $A\beta_{1-42}$ toxicity/protection are calcium regulation, protein translation and mitochondrial activity. SURF4, a major regulator of store operated calcium entry (SOCE), arose as an enhancer of amyloid toxicity. We demonstrated that its overexpression in SH-SY5Y cells enhanced amyloid toxicity, while its silencing protects cells, by decreasing basal intracellular calcium.
Conclusions: Our data suggest that there are more genes involved in the regulation of amyloid toxicity than those proposed in human GWAS and SURF4 is one of them contributing to amyloid neurotoxicity by decreasing SOCE activity. This work was supported by Spanish Ministry of Science and Innovation and Agencia Estatal de Investigación through grants PID2020-117691RB-I00/AEI/10.13039/501100011033, PID2020-113203RB-I00, PID2021-127311NB-I00, RTI2018-094809-B-I00 and PID2019-106755RB-I00, PID2021-124723NB-C21/C22 plus FEDER Funds. Government of Catalonia (2017 SGR 799). Spanish Institute of Health Carlos III by project AC20/00009 -FEDER/UE and European Research Area Net (ERANET) ERA-CVD_JTC2020-015 & TÜBİTAK UPAG ERA-CVD 220N252.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0558 / #758

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

IDENTIFYING DRUG TARGETS FOR ALZHEIMER'S DISEASE USING MULTIOMICS DATA

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Chenxi Qin, Ida Karlsson, Thais De Oliveira, Nancy Pedersen, Sara Hägg
Karolinska Institutet, Department Of Medical Epidemiology And Biostatistics, Stockholm, Sweden

Aims: To identify potential drug targets for Alzheimer's disease and related dementia (ADRD) by integrating multi-omics data.
Methods: Genetic and observational study approaches were combined to identify drug targets for ADRD (Figure 1). We integrated summary statistics of genetic associations from ADRD GWAS and *cis*-pQTL data, and then performed colocalization analysis to identify the candidate causal variant between two traits within the target gene region. Leveraging the candidate causal variant as the instrument, *cis*-Mendelian Randomization (MR) can estimate the effect of target proteins on ADRD risk. SATSA is a longitudinal study with genotypes and DNA methylation in 468 twins whose dementia status was followed through December 31, 2016. A HyPr-genetic risk score (GRS) was constructed using aforementioned candidate causal variants weighted by coefficients in ADRD GWAS. The HyPr-GRS effect on dementia risk in SATSA was estimated by Cox models. The association between the causal variant and dementia was estimated in subgroups with different CpG methylation levels to evaluate CpG island modulation of causal variants on
dementia.

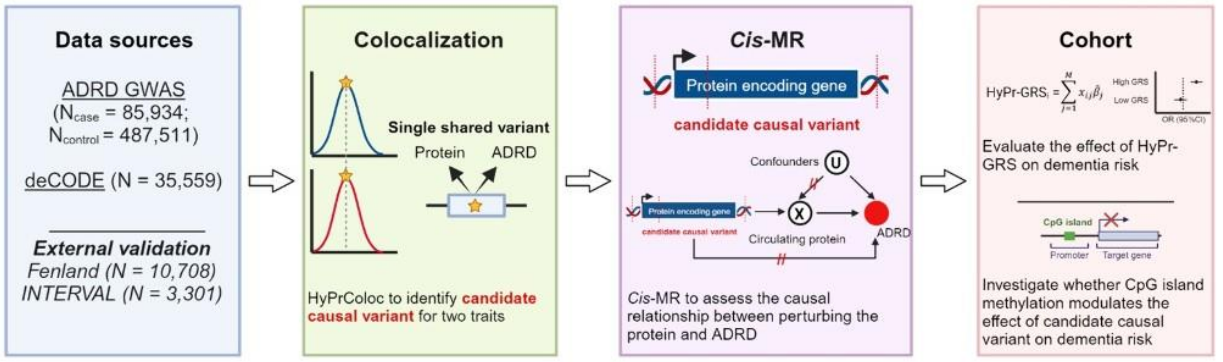


Figure 1. The study design flowchart

ADRD, Alzheimer's disease and related dementia; MR, Mendelian randomization; GRS, genetic risk score.

This study integrates summary statistics of genetic associations from ADRD GWAS and *cis*-pQTL data, and then performs colocalization analysis to identify the candidate causal variant between two traits within the target gene region. Leveraging the causal variant as the genetic instrument, *cis*-MR is used to estimate the causal effect of the target gene of interest on the risk of ADRD. Based on these candidate causal variants, a HyPr-genetic risk score (GRS) is calculated and its effect on dementia risk is evaluated in Swedish Adoption/Twin Study of Aging. And the candidate causal variant effect on dementia risk is further estimated in subgroups with different methylation levels in the CpG island of the target gene of interest.

Results: Seven loci were identified by colocalization. Genetic variation in CR1, SIGLEC9, *CTSH* and *C1S* exhibited an increased ADRD risk, while genetic variation in *PILRA*, *PLOD2* and *GRN* had a lower ADRD risk (Figure 2). The highest tertile of HyPr-GRS was associated with a higher all-cause dementia risk compared with the lowest tertile (HR 1.82, 95%CI 1.00-3.32) (Table 1). The causal variant of *CR1* had a stronger effect on dementia risk among individuals with

the lowest CpG island methylation level (Figure 3).

Target gene	Instrument	OR (95%CI)	*P* value
PILRA	rs1859788	0.94 (0.93-0.96)	1.16×10^{-17}
C1S	rs12146727	1.07 (1.04-1.10)	6.41×10^{-06}
SIGLEC9	rs2075803	1.03 (1.02-1.04)	4.30×10^{-05}
CR1	rs679515	1.28 (1.23-1.33)	5.65×10^{-33}
PLOD2	rs148118826	0.59 (0.46-0.76)	6.18×10^{-05}
CTSH	rs2289702	1.04 (1.03-1.06)	3.10×10^{-06}
GRN	rs5848	0.74 (0.68-0.81)	2.19×10^{-12}

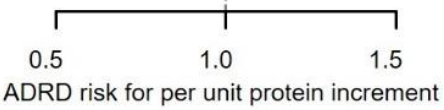


Figure 2. The effect of genetic variation in target genes on ADRD risk using the *cis*-MR analysis

OR, odds ratio; ADRD, Alzheimer's disease and related dementia; MR, Mendelian randomization.

The candidate causal variant identified through colocalization analysis is leveraged as the genetic instrument to proxy the perturbation of the target protein. Combining genetic associations of the instrument with the protein and ADRD, the Wald ratio test is used to estimate the effect of genetic variation in the target gene on ADRD risk. MR estimates are scaled to ORs of ADRD per unit increment of the protein encoded by the target gene.

Table 1. The effect of HyPr-GRS on the risk of incident dementia and main subtypes

Endpoint	Low HyPr-GRS	Medium HyPr-GRS	High HyPr-GRS
All-cause dementia			
Case/participants	23/158	23/155	36/155
HR(95%CI)	1.00 (Ref.)	1.09 (0.57-2.10)	1.82 (1.00-3.32)
ADRD			
Case/participants	12/147	12/144	16/135
HR(95%CI)	1.00 (Ref.)	0.82 (0.30-2.22)	1.45 (0.55-3.80)
Vascular dementia			
Case/participants	5/140	8/140	17/136
HR(95%CI)	1.00 (Ref.)	1.67 (0.53-5.28)	4.45 (1.59-12.50)

ADRD, Alzheimer's disease and related dementia; GRS, genetic risk score.
The effect of HyPr-genetic risk score on the risk of dementia and subtypes are estimated by Cox proportional hazard model. The model adjusts for age, sex, APOE genotypes, educational level and smoking status, and uses twin pair as the random effect.

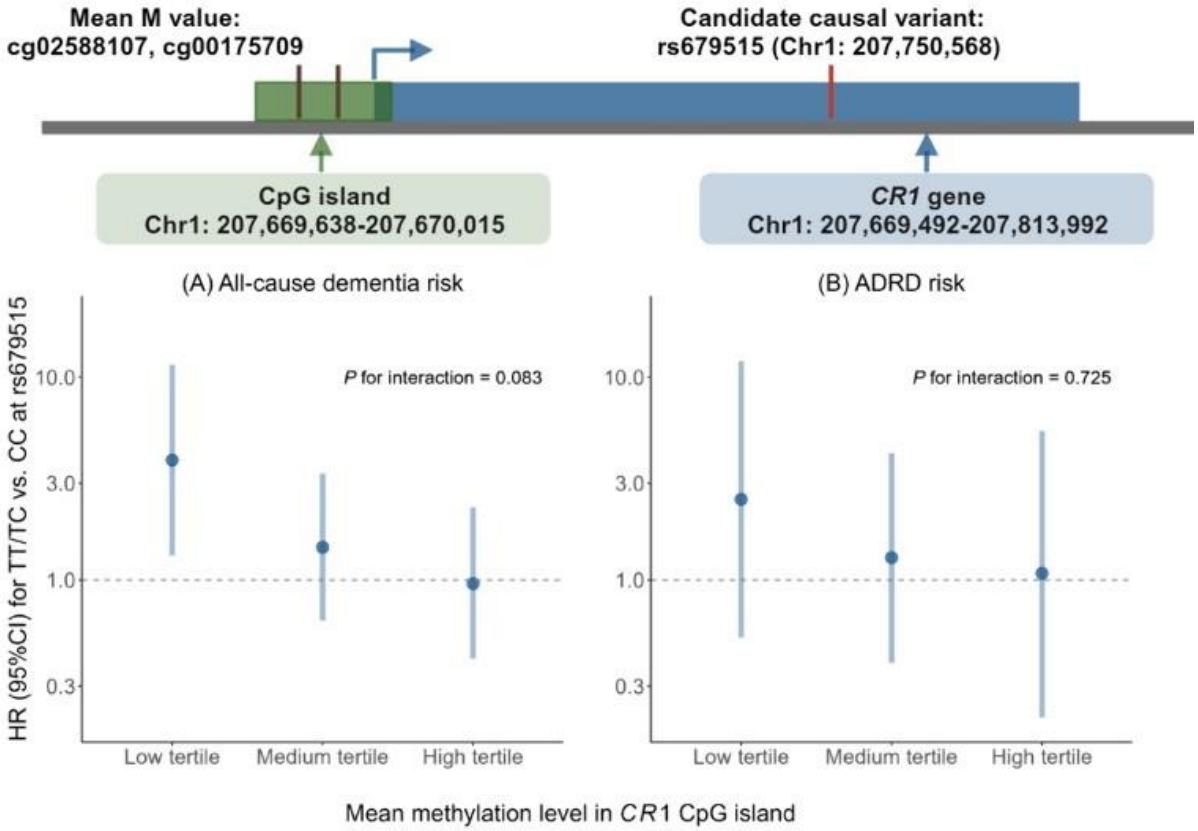


Figure 3. The effect of the candidate causal variant in *CR1* gene on dementia risk in groups with different methylation levels of *CR1* CpG island

ADRD, Alzheimer's disease; HR, hazard ratio; CI, confidence interval.

The upper panel illustrates positions of CpG island and the candidate causal variant in the *CR1* gene region. The lower panel shows the candidate causal variant on dementia risk in three methylation levels of the CpG island of the *CR1* gene. The Cox proportional hazard model uses twin pair as the random effect and adjusts for age, sex, APOE genotypes, educational level, smoking status, and HyPr-genetic risk score excluding the candidate causal variant of the *CR1* gene. The *P* value indicates the significant level of the interaction between the candidate causal variant and CpG island methylation tertiles.

Conclusions: Seven potential targets for ADRD were found. Individuals with lower DNA methylation in the *CR1* CpG island may have greater ADRD risk reduction through inhibiting plasma CR1 protein.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0559 / #1696

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

A RISK LOCUS ON CHROMOSOME 12 IS SUGGESTED BY GENOME-WIDE ASSOCIATION STUDY IN PUERTO RICANS FOR ALZHEIMER DISEASE.

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Farid Rajabli[1], Briseida Feliciano-Astacio[2], Bilcag Akgun[1], Joe Rivero[1], Kara Hamilton-Nelson[1], Larry Adams[1], Vanessa Rodriguez[1], Pedro Mena[1], Jose Sanchez[1], Patrice Whitehead[1], Katrina Celis[1], Parker Bussies[1], Michael Prough[1], Heriberto Acosta[3], Anthony Griswold[1], Clifton Dalgard[4], Gary Beecham[1], Katalina Mcinerney[5], Jeffery Vance[1], Michael Cuccaro[1], Margaret Pericak-Vance[1]
[1]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [2]Universidad Central del Caribe, -, Bayamón, Puerto Rico, [3]Clinica de la Memoria, -, San Juan, Puerto Rico, [4]Uniformed Services University of the Health Sciences, Department Of Anatomy, Physiology, And Genetics, Bethesda, United States of America, [5]University of Miami Miller School of Medicine, Department Of Neurology, Miami, United States of America

Aims: Puerto Ricans (PR), the second-largest Hispanic group in the mainland US, remain underrepresented in Alzheimer disease (AD) genetic studies. Including diverse ancestral populations is important for understanding the genetic underpinnings of AD. To bridge this gap, we conducted a genome-wide association study (GWAS) in the PR population to identify novel AD susceptibility loci and characterize known AD genetic risk loci.
Methods: The PR dataset includes Whole Genome Sequencing (WGS) and phenotype data from 639 individuals (334 cases; 305 cognitively unimpaired (CU)). We employed a generalized linear mixed model using SAIGE software. Two separate models were analyzed; the first model accounted for sex, age, population substructure and relatedness, and the second model also included the dosage of *APOEe4*. We assessed the polygenic risk scores (PRS) using non-Hispanic White (NHW) GWAS summary statistics results.
Results: We identified a promising signal on chromosome 12q13.13 with suggestive significance (rs10783462 OR=1.9, CI(1.7-2.3); $8.6x10^{-7}$) localized on the *SCN8A* gene in both models. Additionally, we replicated four known AD-associated loci (Kunkle et al. 2019, same reported markers), at the *APOE*, *TREM2*, *CLU*, and *FERMT2* genes. The PRS showed a good predictive power with the area under the curve of 0.62.
Conclusions: PR GWAS identified a potential risk locus in the *SCN8A* gene, which was previously identified as having a significant linkage with AD in NHW family studies and was associated with decreased AD pathogenesis in mouse models. The good predictive capacity of PRS might be attributed to the high European ancestral background in PRs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0560 / #2229

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

AN INTEGRATED TOOLKIT FOR MICROGLIAL FUNCTIONAL GENOMICS REVEALS DIVERGENT ROLES OF AD-ASSOCIATED GENE SORL1 IN NEURODEGENERATION

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Falak Sher
Columbia University, Neurology, New York City, United States of America

Aims: Microglia, the central nervous system's resident immune cells, play pivotal roles in brain functions and diseases like Alzheimer's (AD). However, a robust human microglia in vitro model is lacking, hampering our understanding of genes linked to neurodegeneration. Aims: 1. Streamline microglia functional genomics by improving differentiation protocols. 2. Validate the model through extensive genomics studies and functional assays. 3. Investigate the role of AD-associated gene, SORL1, in microglia.
Methods: 1. We developed an efficient two-step protocol to differentiate human induced pluripotent stem cells into microglia (iMG). 2. The iMGs were validated using single-cell RNA-sequencing, proteomics, and functional assays. 3. An integrated toolkit, including a drug-inducible CRISPR system, was also introduced. 4. Data is available on an online platform.
Results: Leveraging our state-of-the-art integrated microglia functional genomics toolkit, in tandem with primary human microglia samples, we delved deeply into understanding the role of the AD-associated gene, SORL1, in microglial cells. Our comprehensive approach, which combined cutting-edge genomics techniques with conventional methods, revealed the intricate ways SORL1 influences disease associated microglial phenotypes. A salient finding was that SORL1-deficient microglia exhibited defective phagocytosis of brain-associated substrates. Moreover, these deficient cells showed impaired immune responses. Significantly, the role of SORL1 in microglia was distinct from its function in neurons, highlighting the cell-specific effects of this gene in the neural milieu
Conclusions: Our innovative toolkit highlights the distinct role of the AD-associated gene, SORL1, in microglia. SORL1-deficient microglia present with impaired phagocytosis and altered immune responses. Crucially, SORL1 functions differently in microglia compared to neurons, emphasizing the value of cell-type specific AD research. Our toolkit facilitates translating genetic insights into molecular mechanisms, and the newfound role of SORL1 in microglia paves the way for tailored neurodegenerative disease therapies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0561 / #2344

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

IMPROVING POLYGENIC RISK SCORES FOR ALZHEIMER'S DISEASE

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Peyton Smith[1], Christoph Lange[1], Sanghun Lee[2], Rudolph Tanzi[3,4,5]
[1]Harvard T.H. Chan School of Public Health, Department Of Biostatistics, Boston, United States of America, [2]Massachusetts General Hospital, Neurology, Boston, United States of America, [3]Massachusetts General Hospital, Henry And Allison Mccance Center For Brain Health, Boston, United States of America, [4]Genetics and Aging Research Unit, Massachusetts General Hospital, Neurology, Charlestown, United States of America, [5]Massachusetts General Hospital/Harvard U, Genetics And Aging Research Unit, Neurology, Charlestown, United States of America

Aims: A polygenic risk score (PRS) is a metric which captures an individual's genetic susceptibility to a particular trait, condition, or disease based on multiple genetic variants or single nucleotide polymorphisms (SNPs) across their genome. PRS is a concept primarily used in the field of genomics and genetics, and it has gained significant attention in recent years due to advances in genetic research and the availability of large-scale genome-wide association studies (GWAS). To date, it is being used to predict an individual's risk of developing Alzheimer's disease or the individual Alzheimer-free survival.
Methods: Here, we will evaluate several machine learning approaches to incorporate ancestry information and several genomic platforms, developing ancestry-specific predictions for both overall disease risk and disease-free survival. We will compare the approaches in simulation studies and by application to the NIAGEDS data set.
Results: We developed an improved PRS with respect to predicting the development of Alzheimer's disease and an individual's Alzheimer-free survival.
Conclusions: These improvements have applications in calculating PRSs to predict the onset of diseases other than Alzheimer's, including cardiovascular disease and type 1 diabetes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0562 / #824

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

REVISITING THE ABCA7 EXON 18 VNTR IN ALZHEIMER'S DISEASE USING LONG-READ SEQUENCING

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Ilaria Stewart[1], Lia Talozzi[1], Yann Le Guen[2], John Gorzynski[3], Michael Greicius[1]
[1]Stanford Univeristy, Department Of Neurology And Neurological Sciences, Stanford, United States of America, [2]Stanford Univeristy, Stanford Medicine Quantitative Sciences Unit, Stanford, United States of America, [3]Stanford Univeristy, Department Of Genetics, Stanford, United States of America

Aims: The *ABCA7* (ATP binding cassette subfamily A member 7) gene has been previously associated with Alzheimer's disease (AD) (Bellenguez et al.2022). However, the genetic causes driving this association remain unclear. A variable number tandem repeat (VNTR) expansion flanking exon18 may play a driving role (as the top single nucleotide polymorphism (SNP) in Bellenguez is in intron18). The VNTR's expansion has been shown to be enriched in AD cases OR=4.5 (De Roeck et al.2018). The risk-increasing SNPs in De Roeck were also significantly associated with AD risk in Bellenguez. Here, we leveraged long-read sequencing (LRS) to further elucidate this locus, focusing on VNTR size and heterogeneity.
Methods: All participants underwent whole-genome LRS (~15x coverage) and a subgroup (82%) short-read sequencing (SRS). Among 571 participants, 114 were diagnosed with AD or mild cognitive impairment, 97 a synucleinopathy (either Parkinson's or Lewy Body disease), and 358 were controls. VNTRs were called with Vamos which provides quantification of length and polymorphic motifs. Motif composition was modeled using dimensionality reduction and hierarchical clustering.
Results: Using all Bellenguez SNPs within the *ABCA7* gene, we calculated associations with VNTR length, which are reported in Fig.1-2. Notably, we find no correlation between the top Bellenguez SNP and VNTR length and the strongest correlation with intronic SNP rs4807499. VNTR length and motif composition are reported in Fig.2-3. VNTR length did not differ between cases and controls. However, we identified five VNTR clusters, one of which appeared to be enriched in AD cases (Fig.4). This may implicate motif heterogeneity in increased AD
risk.

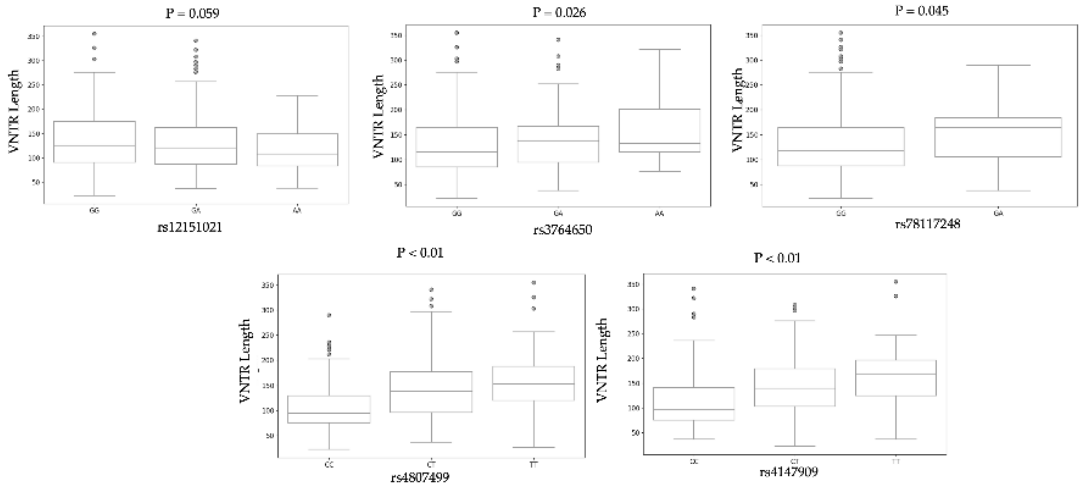


Figure 1. Correlating Bellenguez and De Roeck SNPs with VNTR length. Using Spearman's rank correlation coefficient, we report the associations (p-val) between SNP dosage and VNTR length. The top Bellenguez SNP (rs12151021) does not significantly correlate with VNTR length. The two intronic risk-increasing SNPs (rs3764650 and rs78117248) in De Roeck were significantly correlated with VNTR length, but not as strongly as rs4807499 (p−1.08E-16) and rs4147909 (p−3.28E-16), which are intronic variants on introns 44 and 10, respectively.

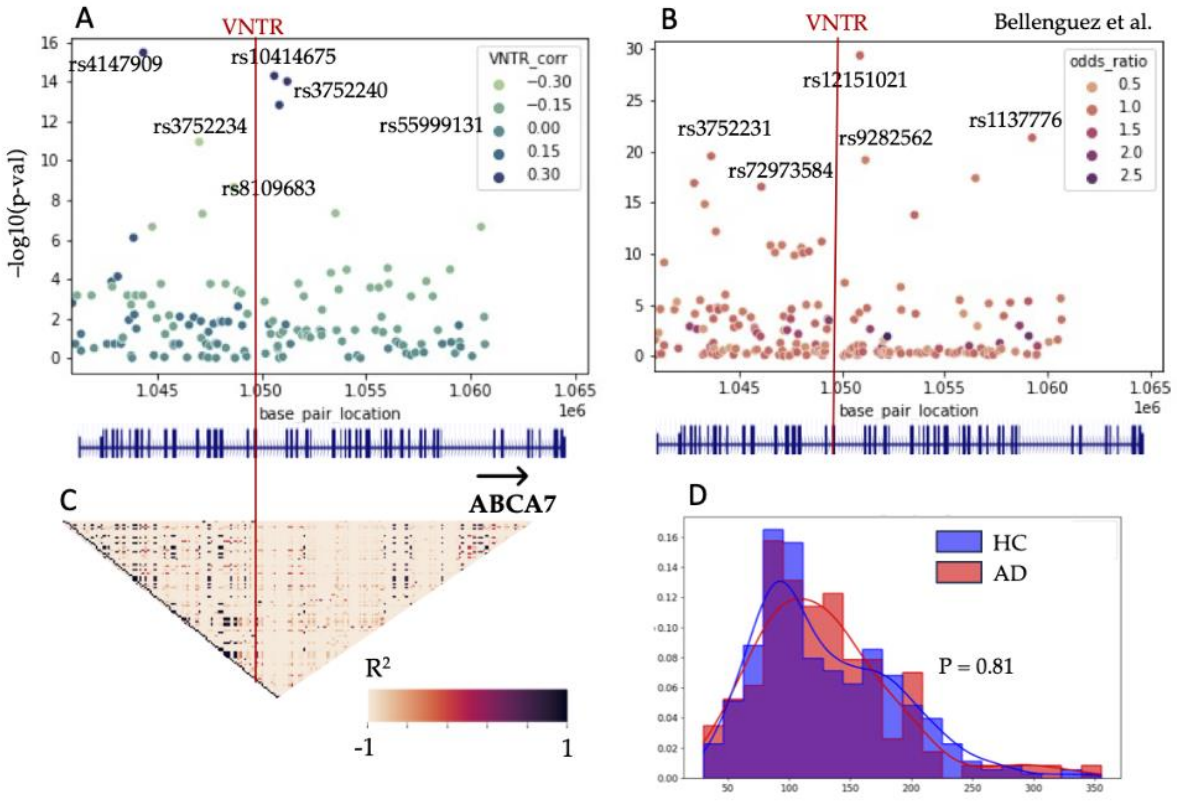


Figure 2. Variable Number Tandem Repeat (VNTR) length correlation with SNPs and diagnosis. A) Plot showing Spearman's correlations between *ABCA7* SNPs and VNTR length. **B)** Locus Zoom from Bellenguez et al. showing p-vals and odd ratios associated with AD. In A and B, the SNPs previously reported in Figure 1 are colored in blue. **C)** Linkage disequilibrium matrix showing R^2 correlations across the *ABCA7* locus. The blue colored SNPs rs4147909 and rs4807499 had an $R^2 = 0.591$. **D)** Histogram depicting VNTR length in base pairs in Alzheimer's disease (AD) cases and controls (HC). There is no significant difference in length between AD cases and controls (T-statistic = 0.24).

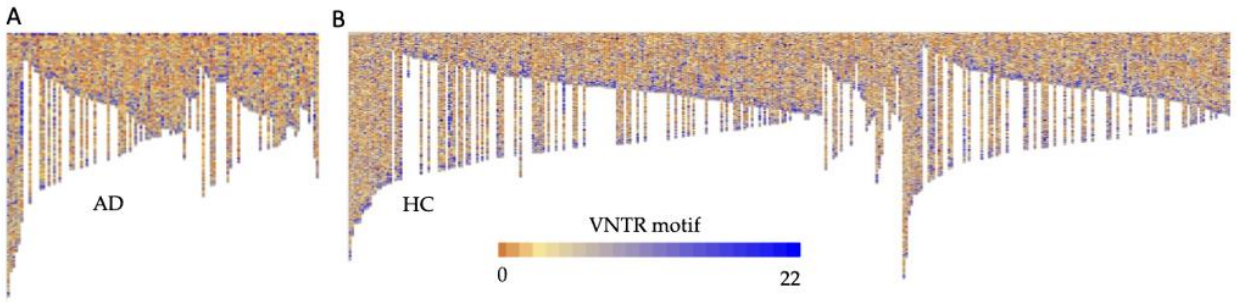
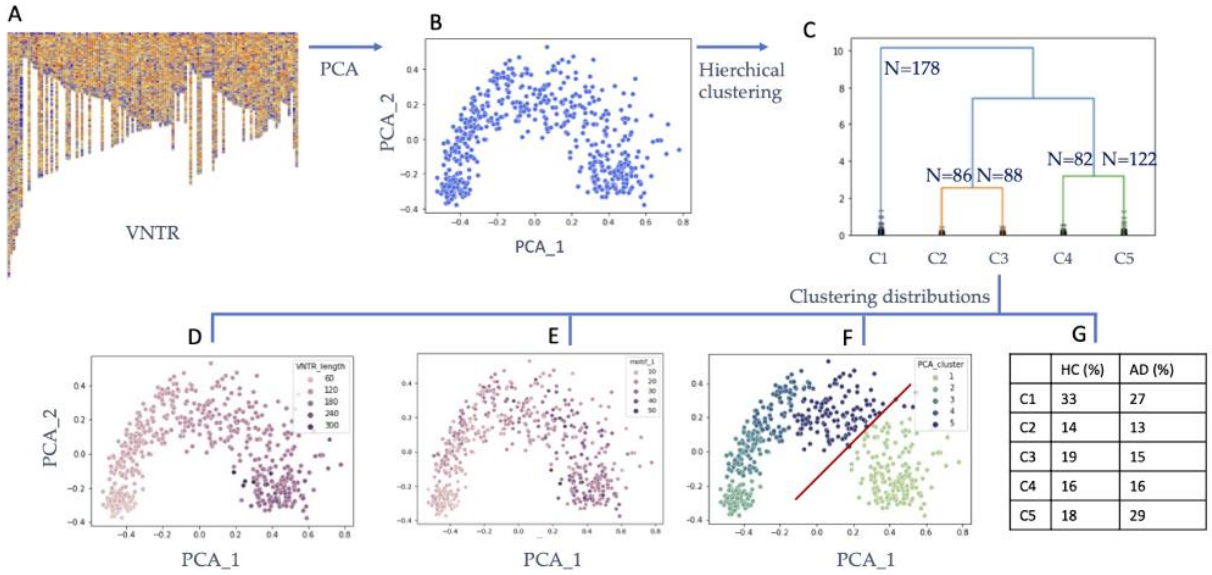


Figure 3. Visualizing *ABCA7* Variable Number Tandem Repeat (VNTR) Motif Polymorphisms in Alzheimer's disease (AD) and healthy controls (HC). Each column in the table is a participant and each cell is a particular motif. The motif frequency classification heat map is included on the right, where the most common motifs are orange, and the least are blue.



	HC (%)	AD (%)
C1	33	27
C2	14	13
C3	19	15
C4	16	16
C5	18	29

Figure 4. Dimensionality Reduction and Clustering. A) The Variable Number Tandem Repeat (VNTR) input. **B)** Principal Component Analysis (PCA) plot of the first two components. **C)** Hierarchical clustering dendrogram illustrating 5 distinct clusters (C1-5). **D)** PCA plot colored by VNTR length. **E)** PCA plot colored by the number of repeats with motif 1 normalized by the VNTR length. **F)** PCA plot colored by the dendrogram clusters. The red line divides the two main ramifications. **G)** Table depicting the percentage of participants that fall into each cluster separated by diagnosis HC and AD.

Conclusions: Our study highlights the potential importance of VNTR motif characterization. We utilized the increased read length of LRS to identify specific motifs enriched in AD cases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0563 / #1686

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

SEX-SPECIFIC GENETIC REGULATION OF PROTEOMICS IN CEREBROSPINAL FLUID UNCOVERS GENETIC CAUSES FOR SEX DIFFERENCES IN NEURODEGENERATION

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Lihua Wang[1], Daniel Western[1], Jigyasha Timsina[1], Priyanka Gorijala[1], Ruiz Agustin[2], Pau Pastor[3], Hen Chen[4], Carlos Cruchaga[1], Yun Ju Sung[1]
[1]Washington University School of Medicine in Saint Louis, Psychiatry, Saint Louis, MO, USA, United States of America, [2]Universitat Internacional de Catalunya, Ace Alzheimer Center Barcelona, Barcelo, Spain, [3]Germans Trias i Pujol Research Institute, Neurogenerative Diseases, Badalona, Spain, [4]UTHealth, School Of Public Health, Houston, Spain

Aims: Clear sex differences exist in Alzheimer's and Parkinson's diseases. While sex-stratified eQTLs by GTEx show genetic differences between males and females, they primarily focus on cis regions. Therefore, the molecular mechanisms that underlie sex differences remain elusive. This study aims to investigate sex-specific genetic regulation of proteomics in neurologically relevant cerebrospinal fluid (CSF).
Methods: We recently identified 3,373 pQTL for 1,961 proteins of which 1,131 were unique to CSF, demonstrating genetic regulation specific to CSF. For 7,028 aptamers (SOMAscan), we performed sex-stratified pQTLs (in 1,640 males and 1,713 females). We examined pQTL in either males or females for both cis (at $P < 5\times10^{-8}$) and trans regions (at $P < 3.45\times10^{-11}$).
Results: We identified 1,702 significant pQTLs (1,065 cis; 637 trans) in either males or females. There were 393 (23.1%) sex-biased pQTLs (sb-pQTLs), showing association in females only (173), or in males only (220), but not in both. Among them, 141 showed effect differences between males and females ($P < 0.05$). We identified a pleotropic region chr19q13.32 near *APOE* that were enriched for neuron-specificity and neurological development. This *APOE* region regulated several AD genes (including APOE, NEFL, NECTIN2, APOC2, NRXN2) with stronger associations in males, as well as several AD proteins (SMOC1, YWHAB, YWHAZ, PPP3R1, VSNL1) with stronger associations in females. In addition, we found the *LRRK2* region chr12q12 regulated several PD genes (GRN, GPNMB, ITGB2) with stronger associations in males.
Conclusions: This large sex-stratified CSF protein QTL study uncovered distinctive sex-specific genetic regulation of CSF proteome. Our findings identified novel pQTL in both cis and trans, providing insights on dissecting the underlying biological causes and mechanisms contributing to sex differences in neurodegenerative disorders. More detailed characterizations is underway.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0564 / #2102

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

UNCOVERING ALZHEIMER'S DISEASE GENETIC RISK PROFILES IN THE ALZHEIMER'S CONTINUUM

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Natalia Vilor-Tejedor[1], Patricia Genius[1], Blanca Rodríguez-Fernández[1], Carolina Minguillón[1], Iman Sadeghi[1], Armand González Escalante[1], Marta Crous-Bou[1], Marc Suarez-Calvet[1], Oriol Grau-Rivera[1], Anna Brugulat-Serrat[1], Gonzalo Sánchez Benavides[1], Manel Esteller[2], Karine Fauria[1], José Molinuevo[3], Arcadi Navarro[1], Juan Gispert[1]
[1]BarcelonaBeta Brain Research Center, Pasqual Maragall Foundation, Barcelona, Spain, [2]Josep Carreras Leukaemia Research Institute, (ijc), Badalona, Barecelona, Spain, [3]H. Lundbeck A/S, H. Lundbeck A/s, Valby, Denmark

Aims: To characterize the Alzheimer's disease (AD) genetic risk at preclinical stages to understand the underlying biological mechanisms.
Methods: We included 2,527 cognitively unimpaired (CU) individuals from the ALFA study and 1,333 participants from ADNI (Controls=530, MCI=598, AD=205). In all participants, A+ was based on CSF Aβ42 levels and cohort-specific pre-established cut-off values. We characterized the genetic risk to AD and other neurological/age-related conditions using various polygenic risk scores (PRSs). We compared AD predisposition in ALFA with the entire ADNI disease spectrum using median tests, stratifying by Aβ status.
Results: The ALFA study exhibited a high prevalence of *APOE-ε4* carriers compared with the general European population (35.6% vs. 14%; $p < 0.001$) [Figure 1]. PRS-AD showed the highest variability in the sample (IQR=0.25) [Figure 2]. The median value of the PRS-AD increased along the AD continuum ($p_{corrected}<0.05$) [Figure 3]. Genetic predisposition to AD in ALFA was higher than in ADNI CN ($p<0.001$). ALFA A+ CU showed a higher genetic predisposition than MCI A+ in ADNI. When removing the *APOE* region, genetic predisposition was significantly lower in CN compared to AD. Also, we consistently observed a higher median score between CN, ALFA A+, MCI and AD. Furthermore, ADNI groups had a higher genetic predisposition to frontotemporal dementia than ALFA, with no significant differences for life expectancy [Figure 4].

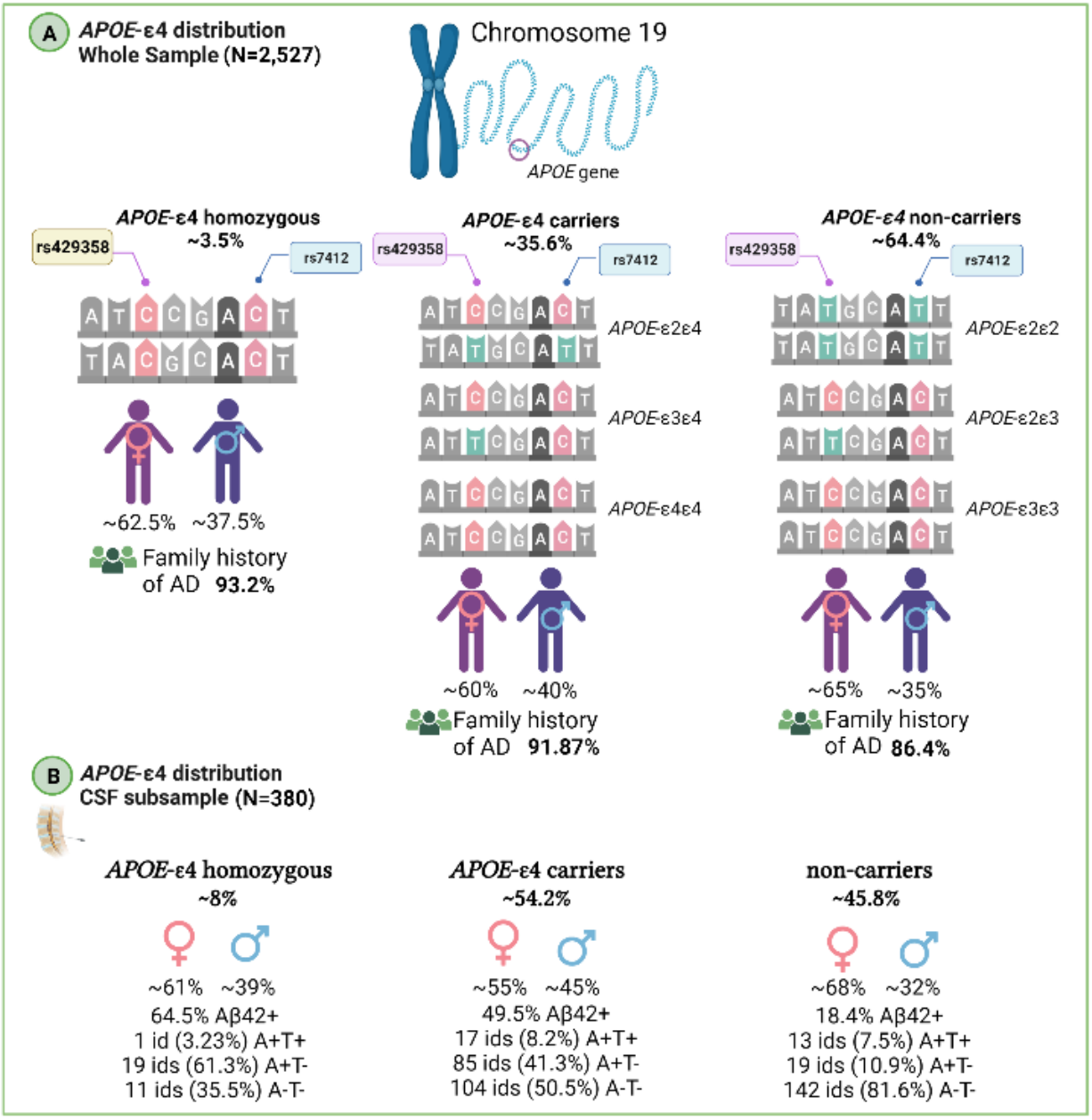


Figure 1. Distribution of *APOE*-ε4 carriership in the ALFA and ALFA+ samples.

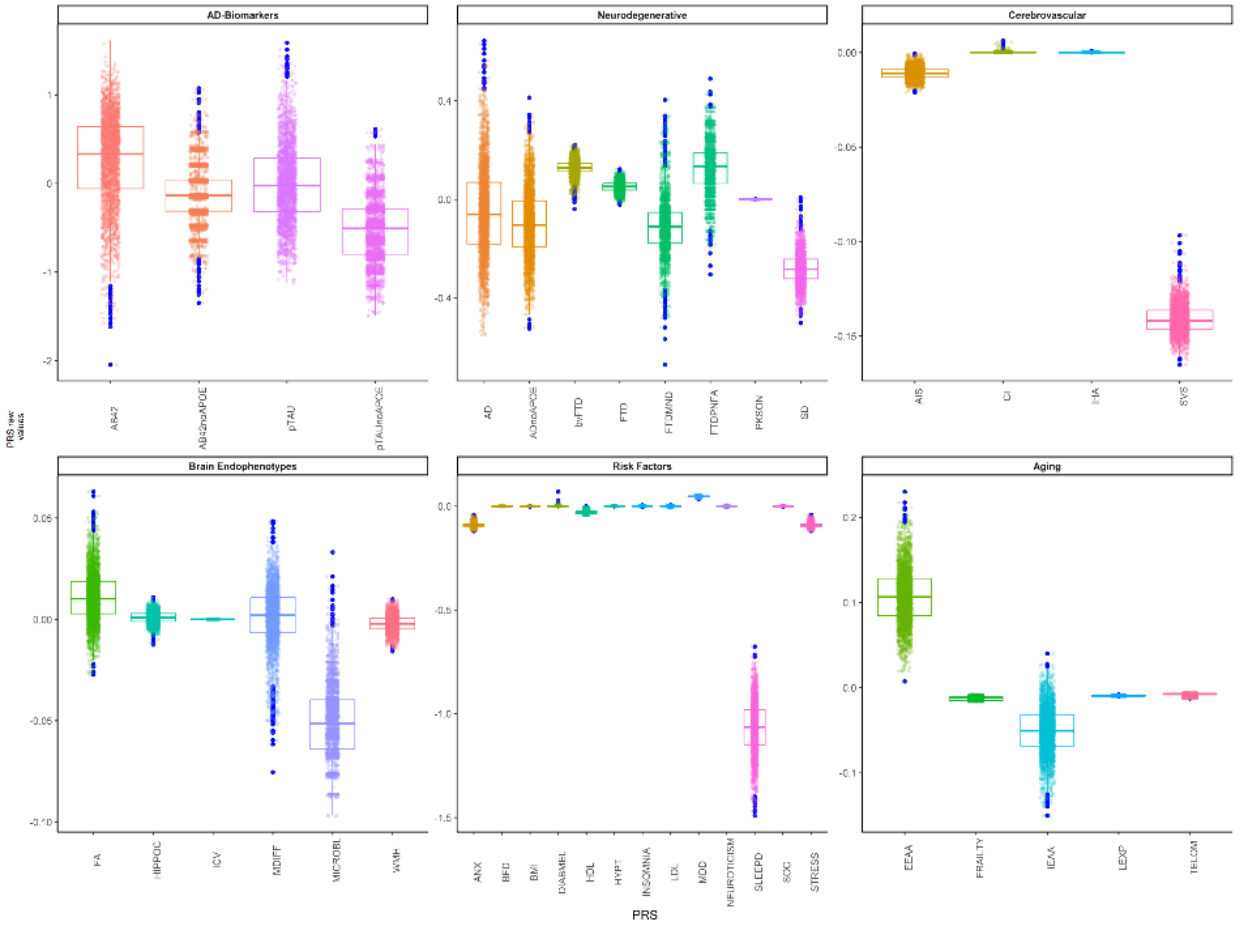


Figure 2. Distribution of genetic scores in the ALFA parent cohort.

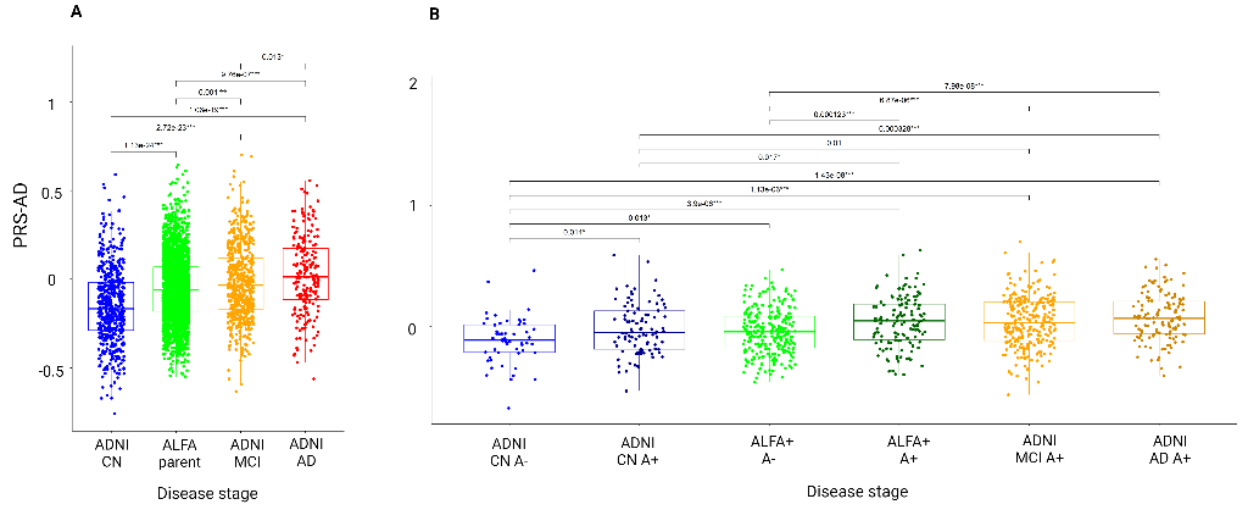


Figure 3. Distribution of genetic scores of Alzheimer's disease along the AD continuum. A) Subgroups from ALFA and ADNI within the AD continuum. B) Subgroups within the AD continuum stratifying ALFA participants by amyloid status. Pairwise comparisons are assessed to compare the median PRS-AD (Wilcoxon test) among groups. Significant results at nominal p-value are displayed (p-value <0.05 *; p-value <0.01 **, p-value <0.001 ***).

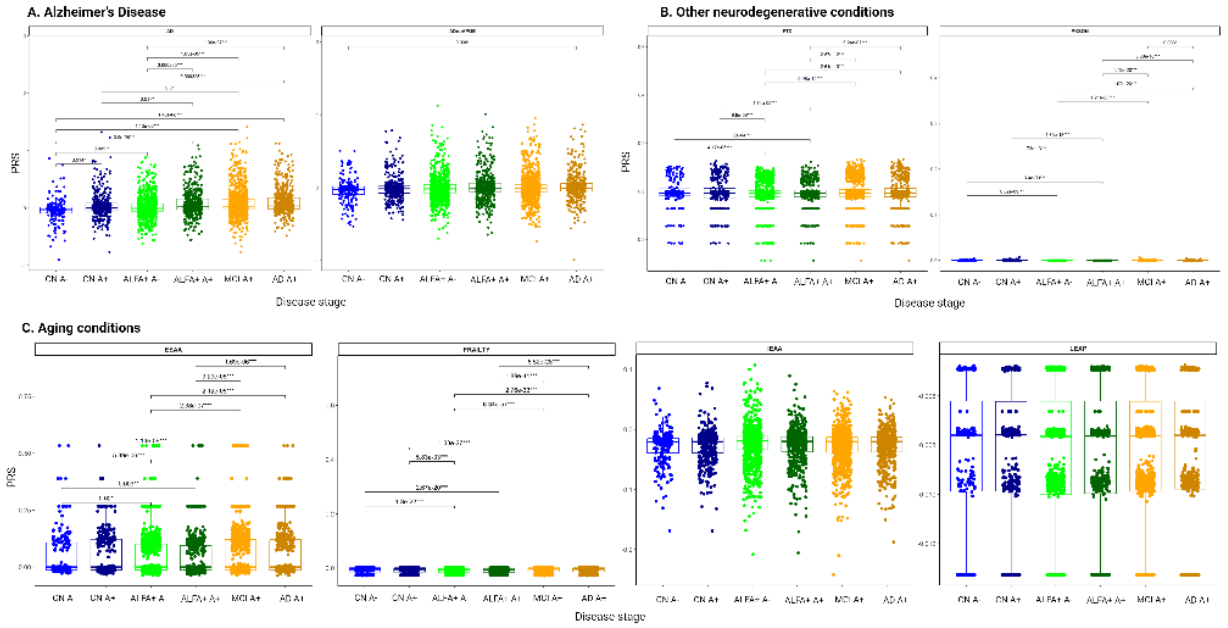


Figure 4. Distribution of genetic scores of Alzheimer's disease (A) and other neurodegenerative (B) and aging (C) conditions along the disease continuum stratifying by amyloid status. Pairwise comparisons are assessed to compare the median (Wilcoxon test) of the PRS among groups. Significant results at nominal p-value are displayed (p-value <0.05*; p-value <0.01**; p-value <0.001***).

Conclusions: The ALFA project successfully established a cohort of CU individuals with a high genetic risk for AD, ideal for studying early pathophysiological changes in preclinical AD. These results emphasize *APOE*'s pivotal role in early AD pathogenesis and imply the involvement of other genetic variants in the overall genetic risk profile.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0565 / #1960

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

3D GENOME STRUCTURE PROVIDES INSIGHT ON ANCESTRY-SPECIFIC GENETIC RISK

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Liyong Wang[1], Wanying Xu[2], Xiaoxiao Liu[2], Farid Rajabli[3], Katrina Celis[1], Leina Lu[2], Marla Gearing[4], David Bennett[5], Margaret Flanagan[6], Sandra Weintraub[7], Changiz Geula[7], Theresa Schuck[8], William Scott[1], Derek Dykxhoorn[1], Anthony Griswold[1], Margaret Pericak-Vance[1,3], Juan Young[1], Fulai Jin[2], Jeffery Vance[9]
[1]University of Miami Miller School of Medicine, John P. Hussman Institute For Human Genomics, Miami, United States of America, [2]Case Western Reserve University, Department Of Genetics And Genome Sciences, Cleveland, United States of America, [3]University of Miami Miller School of Medicine, Dr. John T Macdonald Foundation Department Of Human Genetics, Miami, United States of America, [4]Emory University School of Medicine, Dpt. Of Pathology And Laboratory Medicine And Dpt. Of Neurology, Atlanta, United States of America, [5]Rush University Medical Center, Rush Alzheimer's Disease Center, Chicago, United States of America, [6]University of Texas Health San Antonio, Pathology And Bigg's Institute, San Antonio, United States of America, [7]Northwestern University, Adc Pathology Core, Chicago, United States of America, [8]University of Pennsylvania, Pathology, Philadelphia, United States of America, [9]University of Miami Miller School of Medicine, Department Of Neurology, Miami, United States of America

Aims: Genetic risk for Alzheimer Disease (AD) varies across populations with different ancestry. 3D genome architecture regulates gene transcription. African American (AA) individuals are admixed with European (EU) and African (AF) ancestry, thus it is important to include local ancestry (LA) in their analyses. We hypothesize that variations of 3D genome features on different ancestry background could offer novel epigenetic understanding of ancestry-specific AD risk.
Methods: Hi-C was done in frontal cortex from *APOEε4* homozygotes (4 AA/ 4 Non-Hispanic White (NHW)). LA was calculated using RFMix. Compartmentalization was measured by the first principal component (PC1) of Hi-C contact matrices and compared at a 500kb-resolution. *DeepLoop* was used to call chromatin loops. Population-enriched loops were identified using pairwise T-test (P value<0.05, with an absolute fold change >2).
Results: 2~3% of compartments were switched between AF and EU. *APOE* confers higher risk in NHW than AA and the PC1 value over *APOE* is higher on the EU than the AF genome, suggesting it is more active on the EU genome. In contrast, the PC1 value over *RBFOX1(*AA susceptibility locus) is higher on the AF than the EU genome. 12,082 loops are enriched in NHW and 2885 loops are enriched in AA. NHW-enriched loops are larger than the AA-enriched loops (median size= 496 kb and158 kb, respectively). AA-loops were enriched for co-localization with H3K27ac and H3K4me3 (score=1.2~1.53). Many of the NHW-enriched long-range interactions are mediated by CTCF, 30 of them are absent in AA due to AA specific SNPs in the CTCF motif.
Conclusions: 3D genome regulatory maps could explain the known ancestral differences in AD risk and will be essential to identifying causal genes in GWAS in both NHW and AA populations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0566 / #2019

Poster Topic: *Theme A: β-Amyloid Diseases / A05.d. Genetics, Epidemiology: Aging*

VALIDITY AND CORRELATION OF THE ELECTRONIC FRAILTY INDEX AGAINST SEVERITY ASSESSMENT OF VETERANS WITH ALZHEIMER'S DISEASE

POSTERS: A05.D. GENETICS, EPIDEMIOLOGY: AGING

Joel Reisman[1], Byron J Aguilar[2], Qinqing Li[3], Megan Cheslock[1], Maureen O'Connor[2], Peter Morin[4], Dan Berlowitz[5], Raymond Zhang[6], Amir Tahami Monfared[7], Quanwu Zhang[8], Weiming Xia[2,9,10]
[1]VA Bedford Healthcare System, Geriatric Research and Clinical Center, Center For Healthcare Organization & Implementation, Bedford, United States of America, [2]VA Bedford Healthcare System, Geriatric Research Education And Clinical Center, Bedford, United States of America, [3]Univ. of Edinburgh, Mathematics, Edinburgh, United Kingdom, [4]Boston University Chobanian & Avedisian School of Medicine, Department Of Neurology, Boston, United States of America, [5]University of Massachusetts, Department Of Public Health, Lowell, MA, United States of America, [6]Eisai, Inc., Alzheimer's Disease And Brain Healthe, Nutley, United States of America, [7]McGill Univ., Epidemiology, Biostatistics And Occupational Health, Montreal, Canada, [8]Eisai, Inc., Alzheimer's Disease And Brain Healthe, Nutley, NJ, United States of America, [9]University of Massachusetts, Department Of Biological Sciences, Lowell, MA, United States of America, [10]Boston University Chobanian & Avedisian School of Medicine, Department Of Pharmacology, Physiology & Biophysics, Boston, United States of America

Aims: Electronic frailty indices expand measurement of frailty in clinical assessment of patients with Alzheimer's disease (AD). We aim to determine its correlation with AD severity and define its predictive validity in associations with clinical outcomes.
Methods: Veterans who underwent Mini-Mental State Examination (MMSE) and/or Montreal Cognitive Assessment (MoCA) between fiscal year (FY) 2017-2019 within the Department of Veterans Affairs Healthcare System were identified and their corresponding testing results were extracted in addition to clinicians' judgment on disease severity. The test scores were extracted using a rule-based natural language processing (NLP) system to support and define patients with mild, moderate and severe AD. Harvard claims-based frailty index was calculated based on the structured data of these Veterans.
Results: There were 223,420 Veterans without a record of MMSE or MoCA scores ("untested"). A total of 14,940 Veterans had MMSE or MoCA scores within "normal" range, and the numbers of Veterans with "mild", "moderate" and "severe" AD were 17,747, 12,596, and 9,981, respectively. Age-dependent increases of frailty indices were found among male (0.156-0.167) and female (0.151-0.175) Veterans, and there was no statistically significant difference between male and female subjects, adjusted by age. Every unit increase in frailty indices was associated with an increase in the AD severity from untested, normal, mild, moderate to severe subjects.
Conclusions: Veterans not suspected of AD ("untested" group, i.e., absence of MMSE/MoCA scores) have the best frailty index. Performance on MMSE and MoCA tests correlates with frailty indices, suggesting a predictive value in associations with clinical outcomes from future disease modifying therapy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0567 / #1718

Poster Topic: *Theme A: β-Amyloid Diseases / A05.d. Genetics, Epidemiology: Aging*

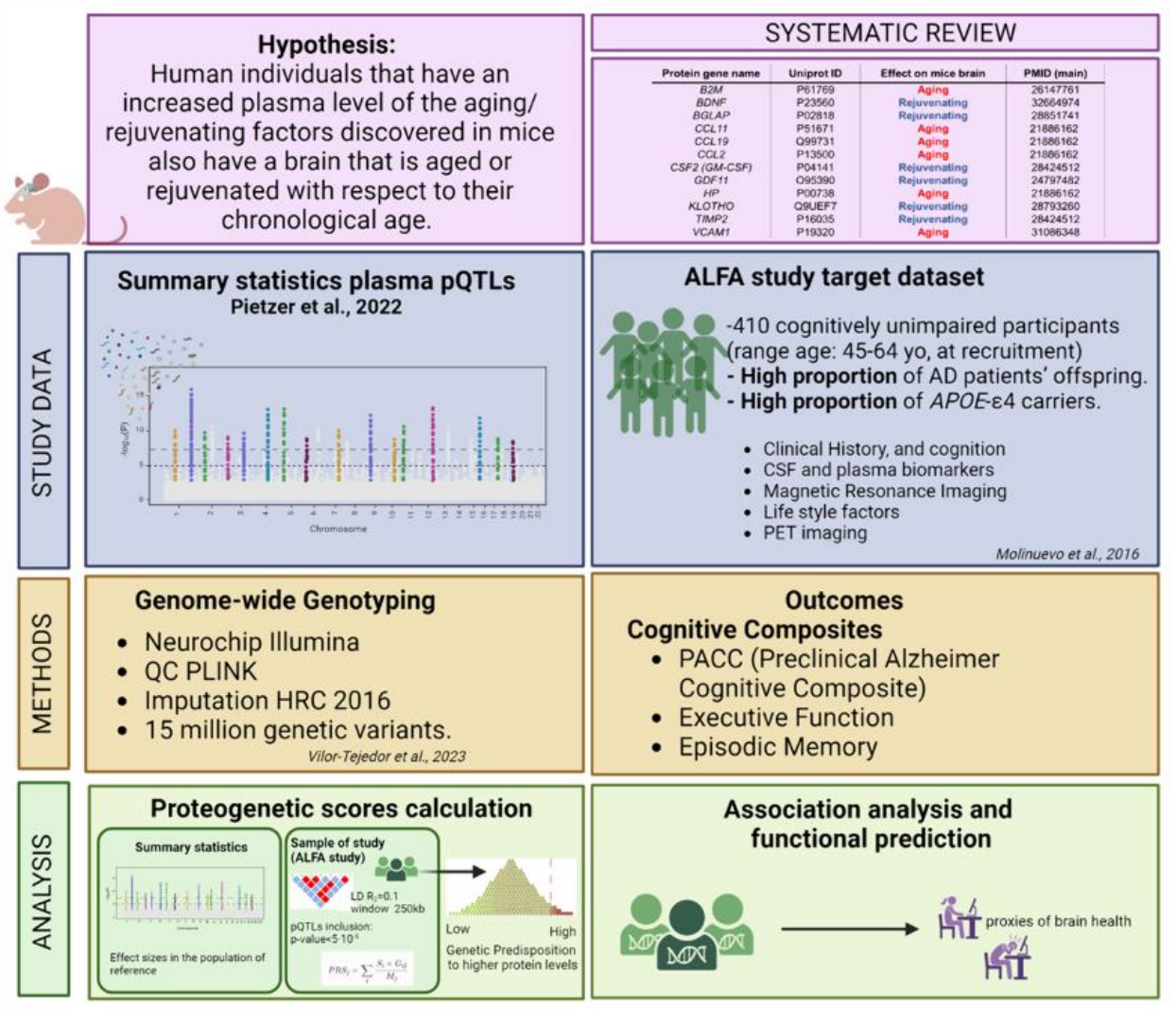
HIGHER GENETICALLY PREDICTED TIMP2 PLASMA LEVELS ARE ASSOCIATED WITH BETTER COGNITIVE PERFORMANCE IN INDIVIDUALS AT RISK OF ALZHEIMER'S DISEASE

POSTERS: A05.D. GENETICS, EPIDEMIOLOGY: AGING

Federica Anastasi[1], Patricia Genius[1], Blanca Rodríguez-Fernández[1], Armand González Escalante[1], Luigi Lorenzini[2], Iman Sadeghi[1], Marta Del Campo Milán[1], Gonzalo Sánchez Benavides[1], Carolina Minguillón[1], Manel Esteller[3], Arcadi Navarro[1], Juan Gispert[1], Marc Suárez[1], Natalia Vilor-Tejedor[1]
[1]Barcelonabeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain, [2]Amsterdam UMC, location VUmc, Radiology & Nuclear Medicine, Amsterdam, Netherlands, [3]Josep Carreras Leukaemia Research Institute, (ijc), Badalona, Barecelona, Spain

Aims: Mice studies have identified blood proteins that influence brain aging, but translating these findings to humans remains a challenge. Here, we report an innovative approach that leverages genetic data to predict the plasma levels of these proteins in humans and assess their association with cognitive performance (Fig1).

Figure 1. Summary of project workflow.



Methods: Through a systematic review, we identified 13 circulating proteins with an aging/rejuvenating effect on the mouse brain. We retrieved data on summary statistics of protein quantitative trait loci (pQTLs) associated with these proteins in human plasma (Pietzner et al.,2021). We used these DNA variants to compute protein-based genetic scores (PRS) of each protein for 410 cognitively unimpaired individuals at risk of Alzheimer's disease of the ALFA cohort (60% women; 55% *APOE*-ε4 carriers, Fig2). We assessed the associations between each PRS and cognitive performance through general linear models stratified by sex, amyloid-β (Aβ) status (based on CSF Aβ42/40 ratio) and *APOE*-ε4 carriership.

Figure 2. Participants characteristics of the ALFA+ study cohort.
*Aβ positivity (A+) is defined by CSF Aβ42/40 < 0.071.

Variable	**N** [410]
Age (years), Median (IQR)	61.64 (58, 64.8)
Sex, n(%)	
Men	163 (39.8%)
Women	247 (60.2%)
Education Years, Median (IQR)	12 (11, 17)
CSF Aβ42/40 status*, n(%)	388
Aβ-negative (A-)	255 (65.7%)
Aβ-positive (A+)	133 (34.3%)
APOE-ε4, n (%)	
non-carriers	179 (44.8%)
carriers	221 (55.2%)
PACC, Median (IQR)	0.055 (-0.44, 0.46)
Episodic Memory, Median (IQR)	0.063 (-0.42, 0.47)
Executive Function, Median (IQR)	-0.043 (-0.52, 0.50)

Results: Our main results revealed that genetic predisposition to elevated plasma levels of TIMP2 (Metalloproteinase inhibitor 2), a protein with a rejuvenating effect on mice brain, is associated with better cognitive performance as measured by the preclinical Alzheimer cognitive composite (PACC) and episodic memory composite scores. TIMP2-PRS association with PACC was also significant in the stratified models. Only the Aβ-positive group did not survive FDR correction (Fig3). In addition, the TIMP2-PRS significantly predicted the actual levels of TIMP2 protein in plasma (Fig4).

Figure 3. Results of the association analysis of the computed PRS with cognitive composites PACC and EM. Colors represent the direction of the association effect, where blue, refers to a rejuvenating effect and red to an aging effect. Significance is reported at group-correction (two experimental aging groups) and cluster-correction levels (** p<0.025, ***p<0.0125 respectively).

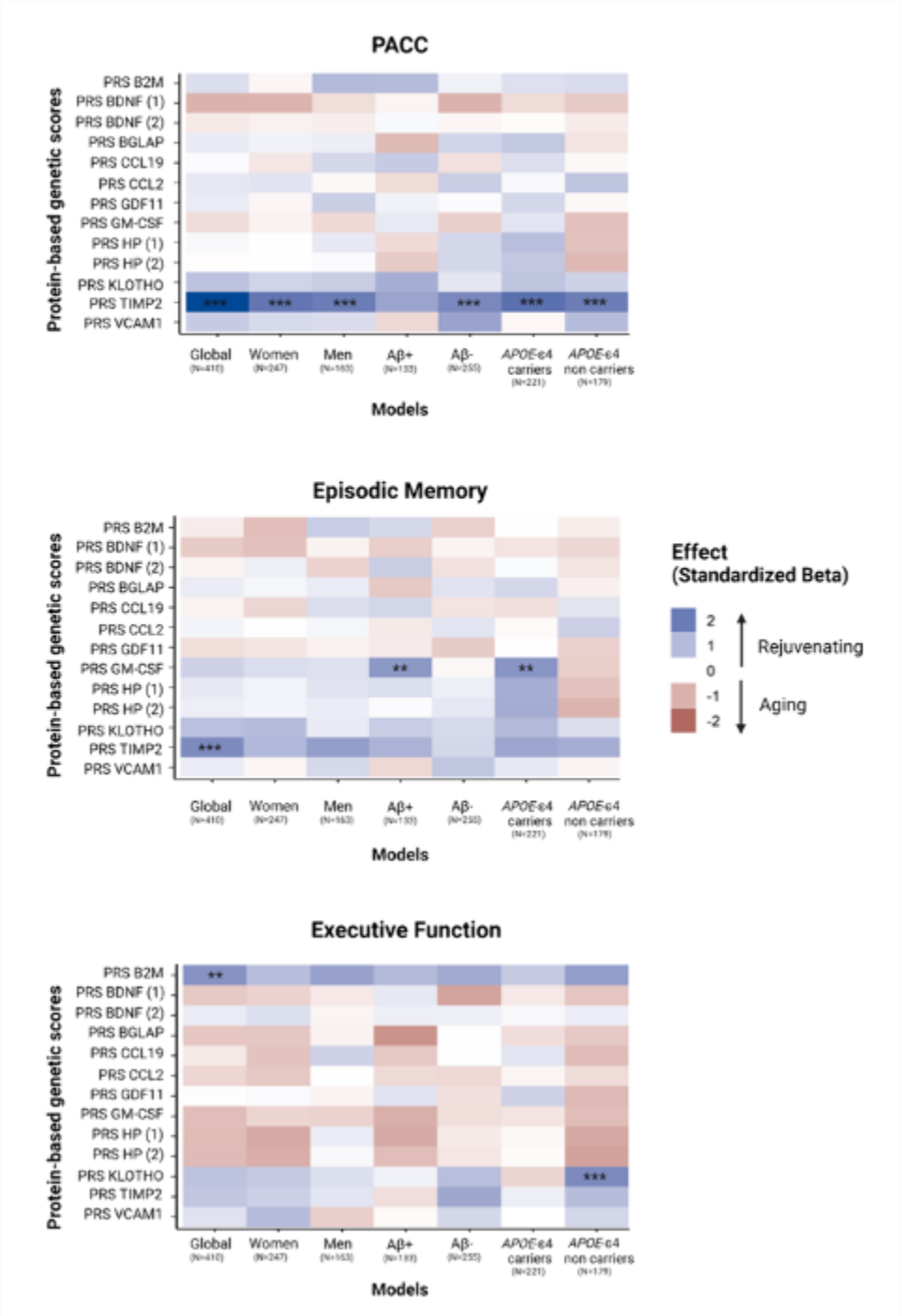
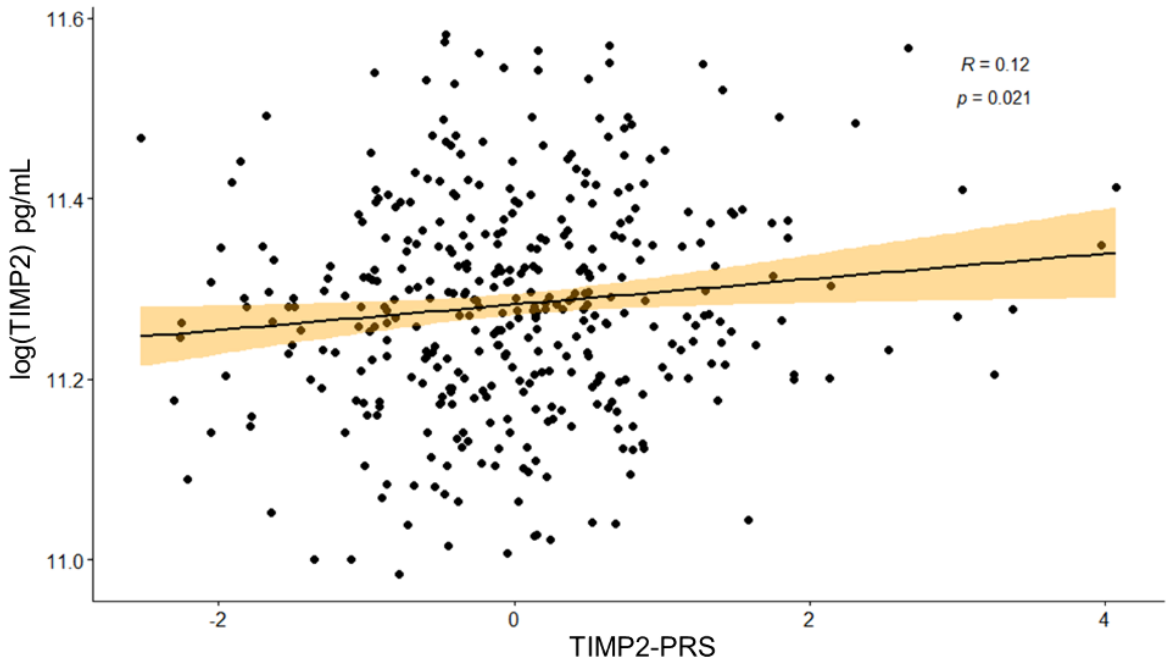


Figure 4. Associations between genetically predicted plasma levels of TIMP2 and TIMP2 actual protein levels as measured by R&D DuoSet® commercial Elisa assay.



Conclusions: This innovative use of protein-based PRS computation may overcome translational challenges encountered in animal studies. Specifically, our study provides a complementary means to investigate the association of TIMP2 with brain performance in humans, suggesting TIMP2 as a potential therapeutic target in brain aging and cognitive function.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0568 / #377

Poster Topic: *Theme A: β-Amyloid Diseases / A05.d. Genetics, Epidemiology: Aging*

GENETIC BIOMARKERS AND BIOLOGICAL AGING PREDICT THE RISK OF DEMENTIA IN THE UK BIOBANK

POSTERS: A05.D. GENETICS, EPIDEMIOLOGY: AGING

Shayan Mostafaei, Jonathan Mak, Chenxi Qin, Sara Hägg
Karolinska Institutet, Department Of Medical Epidemiology And Biostatistics, Stockholm, Sweden

Aims: This study aims to explore the links between genetic biomarkers, their combinations, biological aging markers (BA), and their potential in predicting dementia risk among UK Biobank (UKB) participants.
Methods: In this study, we analyzed 328,047 dementia-free UK Biobank participants. We calculated an individual's polygenic risk score (PRS) based on 75 dementia-related risk loci. Additionally, we employed three biological aging measures (KDM, PhenoAge, HD) and the frailty index (FI) for dementia risk prediction. To make these predictions, we used a support-vector-machines (SVM) algorithm with a sigmoid kernel. The model's performance was assessed using the area-under-ROC curve (AUROC) through holdout validation (2/3 training and 1/3 testing samples). All models were adjusted for age, sex, ethnicity, smoking, alcohol consumption, and the top 10 genetic principal components.
Results: We studied 328,047 dementia-free participants at baseline (mean age: 56.4 [SD=8.1] years, 54.1% female). They were followed for a median of 6.9 (SD=2.0) years, with 1,617 individuals (0.49%) eventually developing dementia. In univariate analysis, the predictors ranked in importance as follows: PhenoAge, KDM, HD, PRS, and FI. The PRS model's predictive accuracy on the testing set, both with and without the APOE region, was AUROC=0.759 (95% CI: 0.749, 0.769) and 0.721 (95% CI: 0.710, 0.731), respectively. Combining PRS and BA predictors raised the AUROC to 0.793 (95% CI: 0.783, 0.803). Including the frailty index in the model increased the AUROC to 0.80 (95% CI: 0.791, 0.810). Statistically, the AUROCs of the PRS+BA+FI model and PRS+BA model significantly outperformed the PRS model (both P-values<0.01).
Conclusions: Our findings highlight the value of combining genetic and biological aging markers, along with assessing frailty, to improve dementia risk prediction accuracy. These insights hold significant promise for early detection and preventive measures in dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0569 / #2796

Poster Topic: *Theme A: β-Amyloid Diseases / A05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

GENOME WIDE ASSOCIATION STUDY OF CHRONIC TRAUMATIC ENCEPHALOPATHY ENDOPHENOTYPES IMPLICATES THE MAJOR HISTOCOMPATIBILITY COMPLEX CLASS 1 REGION OF CHROMOSOME 6.

POSTERS: A05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Niki Konstantinides[1,2,3], Xudong Han[4], Jillian Petroskly[4], Sarah Bald[4], Yichi Zhang[4], Richard Sherva[5], Jaeyoon Chung[5], Bobak Abdolmohammadi[6], Shruti Durape[1,6], Brett Martin[2,7], Joseph Palmisano[2,7], Kurt Farrell[8,9], John Farrell[5], John Cherry[2], Victor Alvarez[2,6], Betrand Huber[2,10,11], Kathryn Lunetta[12], Gyungah Jun[5], Adam Labadorf[2,4,6,11], Michael Alosco[2,13], Yorghos Tripodis[2], Robert Stern[1], Thor Stein[2], Lindsay A Farrer[12], John Crary[9,14], Ann Mckee[2], Jesse Mez[2,6,15]
[1]Boston University Chobanian & Avedisian School of Medicine, Neurology, Boston, United States of America, [2]Boston University Chobanian & Avedisian School of Medicine,, Boston University Alzheimer's Disease Research Center, Boston, United States of America, [3]Boston University Medical Center, Cte Center, Boston, United States of America, [4]Boston University, Bioinformatics Graduate Program, Boston, United States of America, [5]Boston University Chobanian & Avedisian School of Medicine, Section Of Biomedical Genetics Department Of Medicine, Boston, United States of America, [6]Boston University Chobanian & Avedisian School of Medicine, Boston University Chronic Traumatic Encephalopathy Center, Boston, United States of America, [7]Boston University School of Public Health, Biostatistics And Epidemiology Data Analytics Center, Boston, United States of America, [8]Icahn School of Medicine at Mount Sinai, Fishberg Department Of Neuroscience, New York, United States of America, [9]Icahn School of Medicine at Mount Sinai, Department Of Pathology, Friedman Brain Institute, Ronald M. Loeb Center For Alzheimer's Disease, New York, United States of America, [10]Boston VA Healthcare System, Boston Va, Boston, United States of America, [11]Department of Veterans Affairs, Medical Center, Bedford, United States of America, [12]Boston University School of Public Health, Department Of Biostatistics, Boston, United States of America, [13]Boston University, Pathology, Boston, United States of America, [14]Icahn School of Medicine at Mount Sinai, Neuropathology Brain Bank & Research Core, Department Of Pathology, New York, United States of America, [15]Boston University Schools of Medicine and Public Health, Department Of Medicine, Boston, United States of America

Aims: Chronic traumatic encephalopathy (CTE) is a neurodegenerative tauopathy associated with repetitive head impact (RHI) exposure. We conducted a genome-wide association study (GWAS) of CTE neuropathological endophenotypes in individuals with RHI exposure.
Methods: 458 brain donors [mean age: 68.3 (16.1 SD); 313 (68.3%) with CTE] from the UNITE Brain Bank were included. All donors had exposure to RHI from contact sports or military service. Neuropathologists conducted semiquantitative assessments of CTE stage (0-IV, IV most severe) and phosphorylated tau (ptau) burden (0-3, 3 most severe) across 11 brain regions commonly affected in CTE. We tested the association of genome-wide genotyped and imputed single nucleotide polymorphisms with CTE stage and ptau burden in each region using ordinal logistic regression models adjusted for age at death and 10 principal components of population substructure.
Results: One locus (top hit: rs6910517; MAF=0.12) achieved genome-wide significance for ptau burden in the CA2 region of the hippocampus (OR=5.4; p=4.84E-13). Located within the major histocompatibility complex (MHC) class 1 region of chromosome 6, rs6910517 is intergenic, ~50KB downstream of HLA-A and ~70KB downstream of RNF39. In the hippocampus, rs6910517 is a cis eQTL for RNF39, which has been associated with early phase synaptic plasticity and prolonged long term-potentiation maintenance. The hippocampus CA2 region is preferentially affected in high stage CTE, differing from CA1 and the subiculum, which are preferentially affected in Alzheimer's disease.

Conclusions: In the first GWAS of CTE endophenotypes, one locus in the MHC class I region of chromosome 6 achieved genome wide significance with ptau pathology in the CA2 region of the hippocampus, implicating immune pathophysiology and neuronal function. In addition to RHI exposure, genetic architecture may alter an individual's risk profile for CTE-related outcomes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0570 / #2247

Poster Topic: *Theme A: β-Amyloid Diseases / A05.d. Genetics, Epidemiology: Aging*

PHYSICAL EXERCISE MODULATES ADAM10 METHYLATION IN ACUTELY HOSPITALIZED ELDERLY PATIENTS

POSTERS: A05.D. GENETICS, EPIDEMIOLOGY: AGING

Amaya Urdánoz-Casado[1], Fabricio Zambom-Ferraresi[2,3], Mónica Macías[1], Idoia Blanco-Luquin[1], Miren Roldan[1], Eneko Cabezon-Arteta[1], Nicolás Martínez-Velilla[2,3], Maite Mendioroz[1,4]
[1]Navarrabiomed, Hospital Universitario de Navarra-IdiSNA (Navarra Institute for Health Research), Universidad Pública de Navarra (UPNA), Neuroepigenetics Laboratory, Pamplona, Spain, [2]Navarrabiomed, Hospital Universitario de Navarra, Universidad Pública de Navarra (UPNA), IdiSNA, Department Of Geriatric Medicine, Pamplona, Spain, [3]Instituto de Salud Carlos III, Ciber Of Frailty And Healthy Aging (ciberfes),, Madrid, Spain, [4]Hospital Universitario de Navarra-IdiSNA (Navarra Institute for Health Research), Neurology, Pamplona, Spain

Aims: Acute hospitalization of elderly patients leads to bed rest, which in 20-50% of patients triggers an accelerated ageing process, manifested as rapid functional and cognitive decline. Physical exercise (PE) during hospitalization can prevent it. The expression of ADAM10, a protein involved in the non-amyloidogenic pathway of amyloid precursor protein (APP), increases with PE. In this study we wanted to explore potential dynamic changes in *ADAM10* gene methylation after 3 days of PE in hospitalized patients.
Methods: A randomized clinical trial of 37 controls (no PE) and 36 subjects undergoing PE intervention was established. Blood samples were obtained before and 3 days after PE program or without. Genomic DNA isolated from PBMCs was bisulfite converted. Three CpG methylation levels of the *ADAM10* promoter were analyzed by pyrosequencing. For each study group the % methylation median changes due to intervention (or control) were calculated as follows: % methylation post-intervention - % methylation pre-intervention. Mann-Whitney U tests were performed with IBM SPSS v20.
Results: After PE, the changes observed in methylation levels at the *ADAM10* CpG_1 and 2 positions were greater in the intervention group than in the control group. However, there were no differences in the CpG_3 position or in the average for the 3 CpGs.

***ADAM10* methylation Median changes % (IQR)**	**Intervention**	**Controls**	**P-value**
CpG1	0.52 (-0.12–1.43)	-0.05 (-0.36–0.34)	0.041
CpG2	0.00 (-3.17–1.63)	0.00 (-0.02–2.78)	0.028
CpG3	0.00 (-1.36 - 1.62)	0.00 (-0.25–1.07)	0.946
Average	-0.20 (-1.1–1.08)	0.14 (-0.29–0.93)	0.356

Conclusions: Three days of PE is sufficient to induce changes in DNA methylation levels in *ADAM10* gene. Furthermore, *ADAM10* methylation levels could be postulated as a biomarker to quantify the response to PE intervention in hospitalized elders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0571 / #1420

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

ROLE OF DEPRESSION AS A RISK FACTOR CONCERNING AMYLOID AND P-TAU STATUS

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Gábor Csukly, Zsolt Huszár
Semmelweis University, Department Of Psychiatry And Psychotherapy, Budapest, Hungary

Aims: Preventing dementia involves taking early action to address modifiable risk factors like depression. However, the extent of the significance of risk factors such as depression when beta-amyloid or phosphorylated-tau (p-tau) changes are present remains uncertain. In this current investigation, our objective was to investigate the potential impact of depression as a modifiable risk factor on conversion separately among individuals who are either Amyloid and Tau positive or negative.
Methods: Utilizing the ADNI database, we examined how depression influenced the progression to dementia in two distinct cognitive groups: cognitively unimpaired (CU) and mild cognitively impaired (MCI) individuals, with beta-amyloid negative (A-) and positive (A+), as well as beta-amyloid and p-tau negative (A-T-) and positive (A+T+) protein status. This investigation involved a total of 367 CU subjects and 619 MCI subjects. The Cox proportional hazard model was applied for the survival analyses.
Results: Among MCI subjects, there was a significant increase in conversion for subjects with depressive symptoms at baseline compared to those without (HR= 1.4 (CI 1.2; 1.6) in the A- group, HR= 1.7 (CI 1.2; 2.5) in the A+ group). In the A+T+ group, subjects with depressive symptoms at baseline showed a significantly higher conversion: HR=1.4 (CI 1.2; 1.6), whereas, in the A-T- group, depressive symptomatology did not affect conversion, HR=1.1 (CI 0.6; 1.9). Among CU individuals, a history of depression was associated with a significantly increased conversion to MCI or dementia compared to those without depression (HR= 1.6 (CI 1.1, 2.3) in the A- group and HR= 1.6 (CI 1.1, 2.5) in the A+ group.
Conclusions: Our research reinforces the importance of addressing modifiable risk factors, even in cases where amyloid or p-tau pathology has already manifested.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0572 / #1634

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

MEDICATION EXPOSURE AND NEURODEGENERATIVE DISEASE RISK ACROSS NATIONAL BIOBANKS

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Gracelyn Hill, Hampton Leonard, Kristin Levine, Michael Nalls, Hirotaka Iwaki, Andrew Singleton
Center for Alzheimer's and Related Dementias, National Institute On Aging, Bethesda, United States of America

Aims: We examined potential links between medication exposures and neurodegenerative disease risk In order to determine possible risk associations between medications and neurodegenerative diseases, and to identify medications with a possible protective effect.
Methods: Using time series data from the UK Biobank (UKB), we used the Cox proportional hazards model to test the association between medication exposure and NDD diagnosis during the study period, adjusting for age, sex, Townsend deprivation index, and number of times prescribed. We additionally compared PRS scores for Alzheimer's and Parkinson's between those who took medications of interest, and the average PRS scores in UKB.
Results: After conducting multiple test corrections, we found 81 medications with protective associations and 162 associated with increased risk across 6 neurodegenerative diseases: Alzheimer's, Parkinson's, motor neuron disease (ALS), multiple sclerosis, general dementia and vascular dementia. Association between Donepezil and Alzheimer's was confirmed (p=4.28E-52) as a positive control. Drugs with psychotropic and anticholinergic properties with established associated risk for Alzheimer's disease were found across multiple other neurodegenerative diseases. Prescriptions of these drugs were associated with significant shifts in PRS score distribution in Alzheimer's and Parkinson's patients; cases with lower PRS had higher attributable risk due to non-genetic factors.
Conclusions: Our observations support the evidence for high risk groups of medications known to interact with NDD phenotypes and provide new findings for drug interactions across several neurodegenerative disorders. Multiple common vaccines for viruses were found to be protective against neurodegenerative diseases, further underscoring the importance of vaccination and the risk that viral infections may impose for dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0573 / #2191

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

SEX-SPECIFIC EFFECTS OF MIND DIET ON DEMENTIA RISK: INSIGHTS FROM UK BIOBANK DATA WITH USUAL INTAKE ESTIMATION

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Jiyun Hwang[1], Young Ho Park[2], Joohon Sung[3], Dong Woo Kim[4]
[1]Seoul National University, Public Health Science, Seoul, Korea, Republic of, [2]Seoul National University Bundang Hospital, Neurology, Seongnam, Korea, Republic of, [3]Seoul National University, Department Of Public Health Science, Seoul, Korea, Republic of, [4]Korea National Open University, Division Of Human Ecology, Seoul, Korea, Republic of

Aims: The relationship between the Mediterranean-Dietary Approach to Systolic Hypertension (DASH) diet Intervention for Neurodegenerative Delay Diet (MIND diet) with cognitive function and dementia has been inconclusive. In previous studies, there often was a failure to consider the shortcomings of the 24-hour recall method, particularly in regard to non-consumption days and day-to-day variability. This study aimed to investigate the relationship between the MIND diet and dementia using usual intake estimations and a sex-specific analysis within the UK Biobank Study.
Methods: We excluded wine, olive oil, and butter/margarine-ingredients that are subjects of going health debates or ambiguously defined in the UK Biobank-from the evaluation of the remaining 12 MIND diet components. Usual food group intakes were estimated by Multiple Source Method (MSM program). Each diet component received 0, 0.5 or 1 based on the original MIND criteria. Dementia diagnosis was ascertained from hospital and death register data recorded by ICD coding system, and self-reported data. We used Cox proportional-hazards regressions adjusted for age, sex, socioeconomic status, education, smoking status, sleep duration, physical activity, and MIND*sex interaction, to explore the associations between the MIND diet and dementia.
Results: Among 68,963 participants aged 60 or older, 1,620 individuals (2.35%) developed dementia during an average follow-up of 10.7 years. Overall, MIND diet was not significantly associated with reduced dementia risk (HR=0.9507, 95% CI: 0.9032-1.0006). However, lower risk was observed in females (HR=0.9475, 95% CI: 0.8997-0.9978), but not in males (HR=0.9998, 95% CI: 0.9564-1.045).
Conclusions: Our study suggests that the effectiveness of MIND diet in reducing dementia risk differs by sex. This finding was made possible through a refined analytical approach that factored in usual dietary intakes and sex differences. Further investigation with advanced modeling could elaborate on these associations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0574 / #1886

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

CONSEQUENCES OF NEUROTOXIANT EXPOSURE IN MOUSE MODELS OF LATE-ONSET ALZHEIMER'S DISEASE

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Kevin Kotredes[1], Olga Minaeva[2], Ravi Shanker Pandey[3], Alaina Reagan[1], Juliet Moncaster[2], Gregory Carter[1], Bruce Lamb[4], Lee Goldstein[2], Gareth Howell[1]
[1]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America, [2]Boston University School of Medicine, Bu Alzheimer's Disease & Cte Center, Boston, United States of America, [3]THE JACKSON LABORATORY, For Genomics Medicine, FARMINGTON, United States of America, [4]Indiana University School of Medicine, Stark Neuroscience Research Institute, Indianapolis, United States of America

Aims: Recent human datasets have revealed LOAD (late-onset Alzheimer's disease) genetic risk factors that are correlated to the degree of AD burden. These risk factors are modulated by exposure to environmental toxicants such as lead (Pb), cadmium (Cd), and arsenic (As). While the toxicants-LOAD association is known, the molecular mechanisms that underpin gene-environmental interactions are unknown. Examination of these risk factors in animal models provides essential insight into the heterogeneity observed in human disease and may reveal more appropriate targets for therapy development.
Methods: Mouse models of LOAD were exposed to Pb, Cd, As, or a mixture in drinking water. Toxicants and endogenous biometals were assayed by ICP-mass spectrometry in the brain, blood, and urine. Spatial profiling by high-resolution metallomic imaging mass spectrometry (MIMS) confirmed brain mapping of toxicants. Transcriptional profiling of brains revealed specific changes in LOAD-related gene expression indicating mechanisms of LOAD progression. Transcriptional and proteomic profiling was used to identify human-aligned genes and protein networks predicted to drive LOAD risk.
Results: Neurotoxicants were detected in all tissue samples collected. Pb, Cd, and As accumulated in the brain and altered expression of LOAD-relevant genes in a toxicant-specific manner. We detected changes in LOAD-relevant gene expression, including a decrease in *Vgf* and an increase in *App*. Reduced *VGF* expression has been observed and reported in all four independent AMP-AD studies and nominated as a key therapeutic target in each and *APP* encodes amyloid precursor protein (APP) from which the Aβ peptides are generated.
Conclusions: These experiments provide critical feedback related to exposures of specific toxicants as environmental factors in novel LOAD models. Collectively these data suggest a direct effect of neurotoxicant exposure related to LOAD progression in patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0575 / #1937

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

TITLE: ASSOCIATION BETWEEN AIR POLLUTION AND LEWY-BODY PATHOLOGY – A LARGE AUTOPSY STUDY

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Ge Li[1,2], Karl Brown[3], C.Dirk Keene[4], Caitlin Latimer[4], Paul Crane[5], Eric Larson[5], Joel Kaufman[6,7], Debby Tsuang[1], Lianne Sheppard[6,8]
[1]VA Puget Sound Health Care System, Geriatric Research Education And Clinical Center, SEATTLE, United States of America, [2]University of Washington, Psychiatry And Behavioral Sciences, SEATTLE, United States of America, [3]Seattle Institute of Biomedical and Clinical Research, Va Puget Sound, Seattle, United States of America, [4]University of Washington, Department Of Laboratory Medicine And Pathology, SEATTLE, United States of America, [5]University of Washington, Department Of Medicine, SEATTLE, United States of America, [6]University of Washington, Department Of Environmental And Occupational Health Sciences, SEATTLE, United States of America, [7]University of Washington, Department Of Medicine And Epidemiology, SEATTLE, United States of America, [8]University of Washington, Department Of Biostatistics, SEATTLE, United States of America

Aims: We examined the association between long-term exposure to $PM_{2.5}$ and NO_2 with neuropathologic changes of Lewy-body related pathology (LRP) in a large autopsy sample.
Methods: 843 participants from the Adult Change in Thought study, a community-based cohort study, underwent autopsies. LRP was assessed in multiple brain regions. A spatiotemporal model was used to generate 10-year average air pollution (AP) exposure values prior to the date of death, linked to participants' residential addresses. Inverse probability weighted multiple logistic regression was used to evaluate the association between exposure to $PM_{2.5}$ or NO_2 and LRP. Additional analyses examined if the association between AP exposure and LRP differed significantly across the levels of sex, smoking history, or age-at-death (< 90 vs 90+ years).
Results: The average age at death in the sample was 89.2 years. Of the 843 individuals autopsied, a majority were female (57.3 %), White (94.1%), and had a history of smoking (55.0%). LRP was identified in 21.4% of the sample and there were no differences in LRP across sex or smoking history.
$PM_{2.5}$ exposure was not associated with the presence of LRP (OR = 1.03, 95% confidence interval 0.90-1.19) after adjusting for study cohort, age-at-death, sex, race, education, neighborhood deprivation index, year of death, smoking history, and APOE genotype. Similarly, NO_2 exposure was not associated with LRP (OR=1.01, 0.91-1.12). There was no evidence for any modification of the association between either pollutant and LRP based on age-at-death, sex, or smoking history.
Conclusions: We did not find any significant associations between long-term exposure to $PM_{2.5}$ or NO_2 and increased risk of Lewy-body pathologies in the brain.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0576 / #2324

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

BLOOD-BASED MULTIVARIATE METHYLATION RISK SCORE FOR COGNITIVE IMPAIRMENT AND DEMENTIA

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

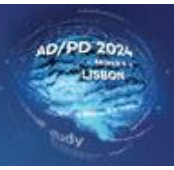
Jarno Koetsier[1], Rachel Cavill[2], Rick Reijnders[1], Joshua Harvey[3], Kay Dekkers[1], Sebastian Köhler[1], Lars Eijssen[1], Adam Smith[4], Gemma Shireby[5], Emma Walker[4], Eilis Hannon[5], Emma Dempster[4], Tim Frayling[5], Jonathan Mill[6], Valerija Dobricic[7], Yasmine Sommerer[7], Andre Franke[8], Rik Vandenberghe[9], Jolien Schaeverbeke[9], Yvonne Freund-Levi[10], Lutz Froelich[11], Philip Scheltens[12], Charlotte Teunissen[13], Giovanni Frisoni[14], Oliver Blin[15], Jill Anderson[16], Régis Bordet[17], Sebastiaan Engelborghs[18], Ellen De Roeck[19], Pablo Martinez-Lage[20], Alberto Lleó[21], Mikel Tainta[20], Isabel Sala[22], Julius Popp[23], Gwendoline Peyratout[23], Frans Verhey[1], Magda Tsolaki[24], Ulf Andreasson[25], Kaj Blennow[26], Henrik Zetterberg[26], Johannes Streffer[19], Stephanie Vos[1], Simon Lovestone[27], Pieter Jelle Visser[28], Lars Bertram[7], Katie Lunnon[4], Ehsan Pishva[1]
[1]University of Maastricht, Department Of Psychiatry & Neurophysiology, Maastricht, Netherlands, [2]University of Maastricht, Department Of Advanced Comutational Sciences, Maastricht, Netherlands, [3]University of Exeter, Department Of Clinical & Biomedical Sciences, Exeter, United Kingdom, [4]University of Exeter, Department Of Biomedical And Clinical Sciences, Exeter, United Kingdom, [5]University of Exeter, Clinical And Biomedical Sciences, Exeter, United Kingdom, [6]University of Exeter Medical School, Department For Clinical And Biomedical Sciences, Exeter, United Kingdom, [7]University of Lübeck, Lübeck Interdisciplinary Platform For Genome Analytics (liga), Lübeck, Germany, [8]Christian-Albrechts-University of Kiel, Institute Of Clinical Molecular Biology, Kiel, Germany, [9]KU Leuven, Experimentele Neurologie, Leuven, Belgium, [10]Karolinska Institutet, Clinical Sciences, Stockholm, Sweden, [11]Department of Psychiatry, Charité-universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, [12]Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [13]Amsterdam UMC, Neurochemistry Lab, Amsterdam, Netherlands, [14]University of Geneva (UNIGE and Geneva University Hospital (HUG), Department Of Rehabilitation And Geriatrics, Geneva, Switzerland, [15]Aix-Marseille University-CNRS, Neurology, Marseille, France, [16]GlaxoSmithKline R&D, Neuroscience Therapeutic Area,, Stevenage, United Kingdom, [17]Université de Lille, Neurology, Lille, France, [18]Universitair Ziekenhuis Brussel (UZ Brussel), Department Of Neurology, Brussels, Belgium, [19]University of Antwerp, Department Of Biomedical Sciences, Antwerp, Belgium, [20]CITA-Alzheimer Foundation, Area Of Neurology, Donostia-San Sebastian, Spain, [21]Hospital of Sant Pau, Neurology, Barcelona, Spain, [22]Sant Pau Biomedical Research Institute, Universitat Autònoma de Barcelona, Sant Pau Memory Unit, Department Of Neurology, Barcelona, Spain, [23]University of Zurich, Department For Psychiatry, Psychotherapy And Psychosomatics, Zurich, Switzerland, [24]ITI, Center For Research And Technology Hellas, Thessaloniki, Greece, [25]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [26]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [27]Johnson & Johnson, Research & Development, New Brunswick, United States of America, [28]Maastricht University, Department Of Psychiatry, Maastricht, Netherlands

Aims: Given the established association between DNA methylation and the pathophysiology of dementia and its plausible role as a molecular mediator of lifestyle and environment, blood-derived DNA methylation data could enable early detection of dementia risk. in this study we aimed to establish a blood-derived DNA methylation-based model to predict prospective onset of cognitive decline and dementia.
Methods: In conjunction with an extensive array of machine learning techniques, we employed whole blood genome-wide DNA methylation data as surrogate for 14 modifiable and non-modifiable factors in the assessment of dementia risk.
Results: Using methylation profile scores (MPS) generetd for 14 known modifible and unmodifiable risk

facors for dementia, we established a multivariate methylation risk score (MMRS) to identify the status of mild cognitive impairment (MCI) cross-sectionally, independent of age and sex (AUROC = 0.68). Polygenic scores (PGSs) for the corresponding risk factors exhibited limited predictive power, and their addition to MPSs did not significantly enhance MCI prediction. The incorporation of cerebrospinal fluid (CSF) biomarkers significantly improved MCI prediction (AUROC = 0.88). We further demonstrated significant predictive capability of this score for the prospective onset of cognitive decline in two independent cohorts of Alzheimer's disease (AD) and Parkinson's disease (PD). The top-performing MMRS modle relied on 10 of the 14 MPSs, with depression, HDL cholesterol, physical inactivity, and low education MPSs playing pivotal roles.

Conclusions: Our work shows the potential of employing blood-derived DNA methylation data in the assessment of dementia risk. Our established MMRS model may act as a starting point for future studies, aiming at further improving the model's predictive performance by testing novel feature selection and machine learning methods, incorporating more omics layers, as well as performing model training on larger datasets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0577 / #612

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

IMPACTS OF EDUCATION ON RATES OF COGNITIVE DECLINE IN ALZHEIMER'S DISEASE PATIENTS: RESULTS FROM A MULTINATIONAL EUROPEAN OBSERVATIONAL STUDY

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Zachary Popp[1], Ting Fang Alvin Ang[1,2,3], Rhoda Au[1,2,3,4,5,6], Jinying Chen[7,8]
[1]Boston University Chobanian & Avedisian School of Medicine, Department Of Anatomy And Neurobiology, Boston, United States of America, [2]Boston University Chobanian & Avedisian School of Medicine, Framingham Heart Study, Boston, United States of America, [3]Boston University Chobanian & Avedisian School of Medicine, Slone Epidemiology Center, Boston, United States of America, [4]Boston University Chobanian & Avedisian School of Medicine, Department Of Neurology, Boston, United States of America, [5]Boston University School of Public Health, Department Of Epidemiology, Boston, United States of America, [6]Boston University Chobanian & Avedisian School of Medicine, Department Of Medicine, Boston, United States of America, [7]Boston University Chobanian & Avedisian School of Medicine, Data Science Core, Boston, United States of America, [8]Boston University Chobanian & Avedisian School of Medicine, Department Of Medicine/section Of Preventive Medicine And Epidemiology, Boston, United States of America

Aims: The cognitive reserve hypothesis presumes higher tolerance of Alzheimer's disease (AD)-related pathology without functional decline for those with higher education. However, some studies found the reverse: more rapid decline after AD onset in this population. Evidence accounting for these contradictory results remained limited. Thus, we assessed the relationship between education and cognitive decline in a multi-national cohort of AD patients.
Methods: We analyzed data from patients recruited into the GERAS-EU cohort study from AD clinics in the United Kingdom, Germany, and France. Generalized linear mixed models were employed to assess the effects of education on rate of cognitive decline, i.e., change in Mini-Mental State Examination (MMSE) scores (range: 0-30 points) per 6-month period, over 1.5 to 3 years of follow-up. Education was dichotomized using a 12-year cutoff (approximately U.S. secondary school equivalent); age at diagnosis, gender, disease duration, country, and baseline comorbidities were included as covariates.
Results: A total of 1,330 AD patients were analyzed, with mean age of 77.3 years (SD=7.6), 726 (54.6%) females, 10.4 (SD=3.2) years of education, and 28.6% having lower education (<12 years). Higher education (≥12 years) was associated with 0.19 more points in MMSE decline per 6-month period than lower education ($p<0.001$). Stratified analyses by AD severity at baseline showed that higher education was associated with 0.26 ($p<0.001$) and 0.31 ($p=0.005$) points more decline in MMSE score in mild and severe AD groups.
Conclusions: Our results contribute to evidence contradicting the cognitive reserve hypothesis. One factor that warrants further exploration is whether ceiling effects for cognitive measures (e.g., MMSE) in those with higher education result in delayed AD detection. If so, more sensitive assessment methods are needed to detect early-stage AD in this population.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0578 / #703

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

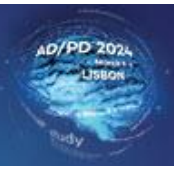
THE CHEMICAL EXPOSOME OF NEURODEGENERATIVE DISEASES

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Cécilia Samieri[1], Sophie Lefèvre-Arbogast[1], Jade Chaker[2], Robert Barouki[3], Xavier Coumoul[3], Gary Miller[4], Arthur David[2]
[1]INSERM, Bordeaux Population Health Research Center, Université Bordeaux Segalen, Bordeaux, France, [2]EHESP, Irset (institut De Recherche En Santé, Environnement Et Travail), Rennes, France, [3]Université Paris Cité, T3s, Inserm Umr-s 1124, Paris, France, [4]Columbia University Mailman School of Public Health, Department Of Environmental Health Sciences, New York, United States of America

Aims: A specific vulnerability of the brain throughout the life-course to environmental chemical stressors has been established. Yet, only a tiny fraction of the tens of thousands of chemicals present on the market has been investigated in neurology research. We provide here a critical review of epidemiological and experimental evidence relating the so-called chemical exposome to neurodegenerative diseases, and we present all the promises that omics-based methodologies could provide to uncover unknown chemical signatures associated with neurodegenerative diseases.
Methods: In total, >150 epidemiological studies investigating chemical exposures and the risk of AD/cognitive impairment and PD, and >270 experimental studies assessing their impact on neurodegeneration-related pathways were considered. We focused on pollutants mostly resulting from anthropic activities including pesticides, volatile organic solvents, metal trace elements, combustion air pollutants, dioxins, flame retardants, fluorosurfactants, plastic components and food and cosmetic additives. We identify gaps and pitfalls in existing research and then formulate a roadmap for next generation exposome studies in the field.
Results: Overall, current evidence is heterogeneous, with a majority of research focused on occupational exposure to pesticides, solvents and metals trace element and, regarding non-occupational exposures, ambient air pollution. Many chemicals, including pesticides of emerging concern (e.g., pyrethrinoids, neonicotinoids) and ubiquitous contaminants (dioxins, flame retardants, plasticizers, food/cosmetic additives, etc.) have received little attention so far in epidemiology in spite of evidence of their involvement in neurodegeneration-related pathways. There is an acute need to push towards future application of high throughput omics-based molecular approaches in population studies to reveal novel chemical signatures associated with neurodegenerative diseases.
Conclusions: We intend with this state of the art to serve as a basis knowledge for the development of new-generation exposomics research in neurosciences.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0579 / #1482

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

ASSESSING THE RELATIONSHIP BETWEEN EARLY LIFE STRESS AND NEURODEGENERATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Angus Shorthouse, Arthur Brookes, Holly Spence, Jenna Gregory, Fergal Waldron
University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom

Aims: Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's Disease (AD) collectively share hallmark characteristics of protein aggregation and progressive loss of nerve cell structure and function. Several studies have indicated that early life stress (ELS) may increase the incidence of neurodegenerative conditions. The purpose of this review and meta-analysis was to evaluate the pathological changes caused by ELS and their links to neurodegenerative disease.
Methods: A priory protocol was published (https://www.protocols.io/private/797679561B2411EEAFD80A58A9FEAC02) and searches were performed on Pubmed and Medline & Embase to identify potential studies for data extraction and screened against an inclusion & exclusion criteria. For applicable studies, individual outcomes as well as data related to the type & timing of the ELS was retrieved. Where three or more studies had assessed the same quantitative variable, a meta-analysis was performed.
Results: 51 out of 774 studies were suitable for data extraction. Numerical outcomes were then categorised into biochemical, phenotypic, and histological subsets. In ELS individuals, there was a significant increase in lipid peroxidation, Amyloid-beta 42, total tau levels, caspase-3 and amyloid plaque deposition relative to non-ELS controls. Impaired limb use in PD mice, dopamine, neuronal cell counts, and ChAT fibres were significantly decreased in ELS exposure groups. No significant differences were found for alpha-synuclein, Amyloid-beta 40 levels, and hippocampal amyloid plaque deposition.
Conclusions: In this study we identify protein misfolding pathology and brain region specific changes in response to early life stress, positing lipid peroxidation as a driving mechanistic link with neurodegeneration in later life. In light of this review and in order to mitigate disease in those at risk, there is now an added emphasis on early life stress as a driving factor influencing later life brain health.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0580 / #2585

Poster Topic: *Theme A: β-Amyloid Diseases / A05.f. Genetics, Epidemiology: Metabolic and cardiovascular*

MORTALITY IN HYPERTENSIVE PATIENTS WITH DEMENTIA TREATED WITH RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) INHIBITORS. A LONGITUDINAL NATIONWIDE COHORT STUDY.

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: METABOLIC AND CARDIOVASCULAR

Marta Villa Lopez[1,2,3], Hong Xu[4], Minjia Mo[5], Maria De La Luz Cuadrado Pérez[2,6], Maria Eriksdotter[5,7,8], Sara Garcia-Ptacek[5]
[1]Karolinska Institute, Division Of Clinical Geriatrics, Department Of Neurobiology,, Stockholm, Sweden, [2]Complutense University, Department Of Medicine, Madrid, Spain, [3]University of Alberta, Medical Genetics, EDMONTON, Canada, [4]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, Huddinge, Sweden, [5]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, STOCKHOLM, Sweden, [6]Hospital Clinico San Carlos, Department Of Neurology, Madrid, Spain, [7]University of Gothenburg, Wallenberg Centre For Molecular And Translational Medicine, Gothenburg, Sweden, [8]Institution for Neuroscience and Physiology, Department Of Neurochemistry And Psychiatry, Gothenburg, Sweden

Aims: This study evaluates the impact of the use of renin-angiotensin-aldosterone system (RAAS) inhibitors on mortality rates in hypertensive patients diagnosed with dementia, aiming to inform treatment strategies for this growing patient population.
Methods: In a longitudinal nationwide cohort study, we scrutinized data from the Swedish national health registers, specifically examining individuals diagnosed with hypertension up to 2018. We conducted a comparative analysis of RAAS inhibitor users and non-users, employing propensity score matching to account for potential confounding factors. Additionally, we stratified the results by dementia status for further insight.
Results: In a study of 158,176 hypertensive patients, 21,152 of whom initiated RAAS inhibitors, their use was linked to reduced mortality risk (HR=0.92, 95% CI: 0.90-0.94) across the entire cohort. This effect was even more significant when concentrating on patients with confirmed clinical dementia, where the HR decreased to 0.86 (95% CI: 0.77-0.96). Comparing the two major classes of RAAS inhibitors, angiotensin receptor blockers (ARBs) showed a lower mortality risk in the overall cohort (HR=0.89, 95% CI: 0.83-0.94) compared to angiotensin-converting enzyme inhibitors (ACEIs). However, this advantage disappeared when evaluating the subgroup with clinically confirmed dementia, as the HR for the comparison between ACEIs and ARBs was 1.04 (95% CI: 0.92-1.17).
Conclusions: In conclusion, our analysis reveals a significant reduction in all-cause mortality among hypertensive patients, even when specifically considering those with dementia, who are prescribed RAAS inhibitors. While these findings point to a potential survival advantage, it is essential to approach these conclusions with caution given their derivation from observational studies. Nevertheless, these results offer valuable insights that should inform personalized treatment strategies for hypertensive patients with dementia, and they may serve as a foundation for designing future clinical trials in this area

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0581 / #2012

Poster Topic: *Theme A: β-Amyloid Diseases / A05.e. Genetics, Epidemiology: Environmental risk factors*

LIGHT POLLUTION IS ASSOCIATED WITH ALZHEIMER'S DISEASE

POSTERS: A05.E. GENETICS, EPIDEMIOLOGY: ENVIRONMENTAL RISK FACTORS

Robin M Voigt[1], Bichun Ouyang[2]
[1]Rush University Medical Center, Internal Medicine, Chicago, United States of America, [2]Rush University Medical Center, Neurological Sciences, Chicago, United States of America

Aims: Alzheimer's disease (AD) prevalence has increased dramatically in the last century. Extension of lifespan due to improved sanitation and health care certainly contribute to the observed increase in prevalence, but data demonstrate that environment also influences AD development and progression. Artificial light at night (i.e., light pollution) is pervasive in modern day society and could be a factor that influences AD. The objective of this study was to evaluate the relationship between outdoor nighttime light intensity and AD prevalence in the United States.
Methods: AD and covariate prevalence were obtained from Medicare Chronic Conditions Database or the Centers for Disease Control and Prevention and nighttime light intensity data were calculated from satellite acquired images.
Results: Light pollution was associated with higher prevalence of AD at the state level and when comparing counties of approximately equal population and population density. This observation was true in those above the age of 65, below the age of 65, in men and women, and across race/ethnicity (except Asian Pacific Islander). While atrial fibrillation, diabetes, hyperlipidemia, hypertension, and stroke were associated more strongly with AD prevalence than light pollution, average nighttime light intensity was more strongly associated with AD prevalence than alcohol abuse, chronic kidney disease, depression, heart failure, and obesity. Startlingly, light pollution was more strongly associated with AD prevalence in those under the age of 65 than any other factor examined.
Conclusions: The data suggest a relationship between nighttime light exposure and AD, but there is a need to carefully investigate how exposure to light at night (outdoor and indoor) influences AD pathogenesis and evaluate mechanisms. Such information may guide public policy and individual recommendations about exposure to light at night.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0582 / #1379

Poster Topic: *Theme A: β-Amyloid Diseases / A05.f. Genetics, Epidemiology: Metabolic and cardiovascular*

CARDIOVASCULAR RISK SCORES EVALUATION TO PREDICT ALZHEIMER'S DISEASE THROUGH MACHINE LEARNING MODELS

POSTERS: A05.F. GENETICS, EPIDEMIOLOGY: METABOLIC AND CARDIOVASCULAR

Juan Pardo[1], Gemma Garcia-Lluch[2,3,4], Angélica Resendiz[1], Lucrecia Moreno[2,3], Miguel Baquero[2,4], Consuelo Cháfer-Pericás[2,4], Lourdes Álvarez[2]
[1]Universidad Cardenal Herrrera CEU, Embedded Systems And Artificial Intelligence Group, Valencia, Spain, [2]Cátedra DeCo, Research, Valencia, Spain, [3]Universidad Cardenal Herrera CEU, Pharmachology, Valencia, Spain, [4]Instituto de Investigación Sanitaria La Fe, Grupo De Investigación En La Enfermedad De Alzheimer (ginea), Valencia, Spain

Aims: The present work aims to identify the relevant factors to predict Alzheimer's Disease (AD) presence, mainly focused on cardiovascular risk scales and related variables.
Methods: Patients between 50 and 75 years old with AD screened between 2017 and 2020 in a Cognitive Disorders Unit of a Hospital in Valencia, Spain, were included. Patients were classified as AD when the t-tau/Abeta42 was >0.51 or the Abeta42/Abeta40 ratio was <0.069. In addition, non-AD patients who failed a maximum of one neuropsychological test were included as a control group. Medications were classified according to the ATC/DDD guidelines 2021 and grouped according to their 3rd ATC level. Machine learning techniques were assessed to determine the most influential variables for AD presence.
Results: A highly imbalanced dataset was obtained, with 177 diagnosed subjects and 50 controls. Ensemble models resulted in better F1-Score metrics, and cardiovascular risk factors were essential to the prediction algorithms. Drugs like anticholinergics, antidepressants, or angiotensin-converting enzyme inhibitors seem positively related to AD prediction, whereas non-steroidal anti-inflammatory drugs and angiotensin receptor blockers showed the opposite effect. Finally, ensembled models considering age, educational level, cardiovascular risk as SCORE2, and specific treatments resulted in interest in AD risk detection.
Conclusions: Machine Learning techniques may improve the identification of patients at risk of AD, allow personalized rationalizing of healthcare costs and improve preventive patient care.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0583 / #1280

Poster Topic: *Theme A: β-Amyloid Diseases / A05.g. Genetics, Epidemiology: Infectious and inflammation*

IMPACT OF MULTIPLE INFECTION ON RISK OF INCIDENT DEMENTIA ACCORDING TO SUBJECTIVE COGNITIVE DECLINE STATUS: A NATIONWIDE POPULATION-BASED COHORT STUDY

POSTERS: A05.G. GENETICS, EPIDEMIOLOGY: INFECTIOUS AND INFLAMMATION

Dong Woo Kang
Seoul Saint Mary's hospital, Department Of Psychiatry, Seoul, Korea, Republic of

Aims: The significant roles of both single and multiple infections, coupled with subjective cognitive decline (SCD), as prominent contributors to dementia development are increasingly acknowledged. Yet, their combined effect remains unexplored. This study investigates the influence of infections like Helicobacter pylori, Herpes simplex virus, Varicella-zoster virus, and Human papillomavirus on dementia risk, categorized by cognitive status.
Methods: Utilizing data from a nationwide health screening program (2009-2020) involving 1,100,540 individuals aged 66, participants were categorized as cognitively preserved (CP, n=825,405) or experiencing subjective cognitive decline (SCD, n=275,135). We evaluated the adjusted hazard ratios to ascertain the impact of infection count and cognitive status on dementia types within each group.
Results: Preliminary results indicate an escalated risk of dementia and Alzheimer's disease (AD) with single to triple infections in the CP group in unadjusted analyses. In the SCD group, triple infections significantly amplified the risk for AD dementia. However, risk was slightly mitigated with single and dual infections after adjusting for covariates. A noticeable trend revealed increasing incidence rates per 1000 person-years with a rising count of infectious agents in both groups. Notably, the SCD group faced a twofold increase in dementia risk compared to the CP group.
Conclusions: The study suggests that dementia risk, heightened by single or multiple infections, is potentially less than the risk presented by SCD. The CP group exhibited a comparatively higher risk for infection-triggered AD compared to a nonsignificant risk in the SCD group. Further meticulous research is necessary to affirm these initial findings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0584 / #1571

Poster Topic: *Theme A: β-Amyloid Diseases / A05.g. Genetics, Epidemiology: Infectious and inflammation*

GENETIC RISK FACTOR CLUSTERING OF NEURODEGENERATIVE AND AUTOIMMUNE DISEASES

POSTERS: A05.G. GENETICS, EPIDEMIOLOGY: INFECTIOUS AND INFLAMMATION

Mathew Koretsky[1], Nicole Kuznetsov[1], Sara Bandres-Ciga[1,2], Jeffrey Kim[1,2], Michael Nalls[1,2,3], Hampton Leonard[1,2,3,4]
[1]Center for Alzheimer's and Related Dementias, National Institutes Of Health, Bethesda, United States of America, [2]Laboratory of Neurogenetics, National Institute on Aging, National Institutes Of Health, Bethesda, United States of America, [3]DataTecnica LLC, Datatecnica Llc, Washington, United States of America, [4]DZNE, Dnze, Tuebingen, Germany

Aims: In an effort to find alternative drug targets for neurodegenerative diseases (NDDs), evidence that autoimmunity and inflammation have an effect on NDD etiology has been established. Here, we use a clustering approach to investigate overlapping genetic risk factors between NDDs and autoimmune and inflammatory diseases to further elucidate the potential of inflammation-based drug targets as a treatment for NDDs.
Methods: UK Biobank imputed genotype data for patients with two NDDs (Alzheimer's disease [AD] and Parkinson's disease [PD]) and five autoimmune and inflammatory diseases (multiple sclerosis [MS], rheumatoid arthritis [RA], type 1 diabetes [T1D], ulcerative colitis [UC], and Crohn's disease [CD]) were used. Genome-wide association study (GWAS) summary statistics were used to identify and extract risk variants for each disease, as well as calculate polygenic risk scores (PRS). UMAP was used to perform dimensionality reduction. Clustering was performed to identify patterns in the genotype data in an unsupervised manner, without the use of disease labels.
Results: Preliminary multi-disease analysis identified three clusters that each contained members from all studied diseases (Supplementary Figure 1). Regressions of PRS against cluster membership were performed to identify groups of patients who are generally genetically protected or at risk for the studied diseases. Individuals in cluster 0 generally showed significant genetic protection from both AD and T1D and significant risk for PD based on the PRS associations. Cluster 1 contained patients who had genetic risk for AD and T1D.

Conclusions: Planned analyses to further investigate the genetic overlap between these diseases include single-disease clustering and genomic structural equation modeling. We will also run regressions to determine variants that drive the establishment of the clusters, and perform OpenTargets and omicSynth searches to nominate inflammation-based drug targets for downstream analyses.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0585 / #1596

Poster Topic: *Theme A: β-Amyloid Diseases / A05.g. Genetics, Epidemiology: Infectious and inflammation*

ASSOCIATION BETWEEN HERPES SIMPLEX VIRUS INFECTION AND ALZHEIMER'S DISEASE BIOMARKERS ? ANALYSIS WITHIN THE MAPT TRIAL

POSTERS: A05.G. GENETICS, EPIDEMIOLOGY: INFECTIOUS AND INFLAMMATION

Morgane Linard[1], Isabelle Garrigue[2,3], Bruno Vellas[4,5], Nicola Coley[5,6], Jean-François Dartigues[1,7], Joachim Mazere[8,9], Sandrine Andrieu[5,6], Catherine Helmer[10]
[1]University of Bordeaux, INSERM, Bordeaux Population Health Research Center (u1219), Lifelong Exposures, Health And Aging Team, Bordeaux, France, [2]University of Bordeaux, CNRS, U5234, Bordeaux, France, [3]University hospital of Bordeaux, Virology, Bordeaux, France, [4]University Hospital of Toulouse, Gérontopôle de Toulouse, Institut Du Vieillissement, Toulouse, France, [5]Uiversity of Toulouse, INSERM, Cerpop, U1295, Toulouse, France, [6]University Hospital of Toulouse, Clinical Epidemiology And Public Health, Toulouse, France, [7]University hospital of Bordeaux, Memory Consultation, Cmrr, Bordeaux, France, [8]University of Bordeaux, CNRS, INCIA, Umr 5287, Bordeaux, France, [9]University Hospital of Bordeaux, Nuclear Medicine, Bordeaux, France, [10]University of Bordeaux, INSERM, Bergonié Institute, Bph, U1219, Cic-p 1401, Bordeaux, France

Aims: Several *in vitro* or animal studies have shown that inoculation with herpes simplex virus type 1 (HSV-1) could lead to the appearance of amyloid deposits, hyperphosphorylation of the Tau protein or neuronal loss. Our objective was to study a potential impact of HSV-1 on biomarkers of Alzheimer's disease in humans (in whom such studies are rare).
Methods: Our sample included 182 subjects at risk of cognitive decline from the MAPT trial and having HSV-1 plasma serology (at inclusion) and an amyloid PET scan (during follow-up). Among these, 164 subjects benefited from plasma assays of the aβ42/40 ratio and NfL (at 12 months) and 138 subjects of p-tau181 (at inclusion and at 36 months). Multivariate linear regressions were performed to investigate associations between HSV-1 serostatus and Alzheimer's disease biomarkers. Analyzes were also stratified by APOE4 genotype.
Results: The median age was 74.0 years, 85.2% were infected with HSV-1 and 42.9% had a cortical amyloid load above the positivity threshold. Infected participants tended to have a lower cortical amyloid load than uninfected participants (β=-0.08 p-value=0.06), especially those suspected of reactivating HSV-1 most frequently (i.e. with a high anti-HSV-1 IgG level; n=58, β=-0.09 p-value=0.04). After stratification, the association was only significant in APOE4 carriers (n=43, β=-0.21 p-value=0.01). No association was found between HSV-1 serostatus and any of the studied plasma biomarkers.
Conclusions: Our results regarding cortical amyloid load are unexpected and may be due to the exclusion of demented subjects at inclusion in the MAPT trial. Our results concerning plasma biomarkers are consistent with the rare pre-existing results on the topic. Nevertheless, the discrepancies between data *in vitro*, in animals and in humans are not easily explained and will require additional investigations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0586 / #860

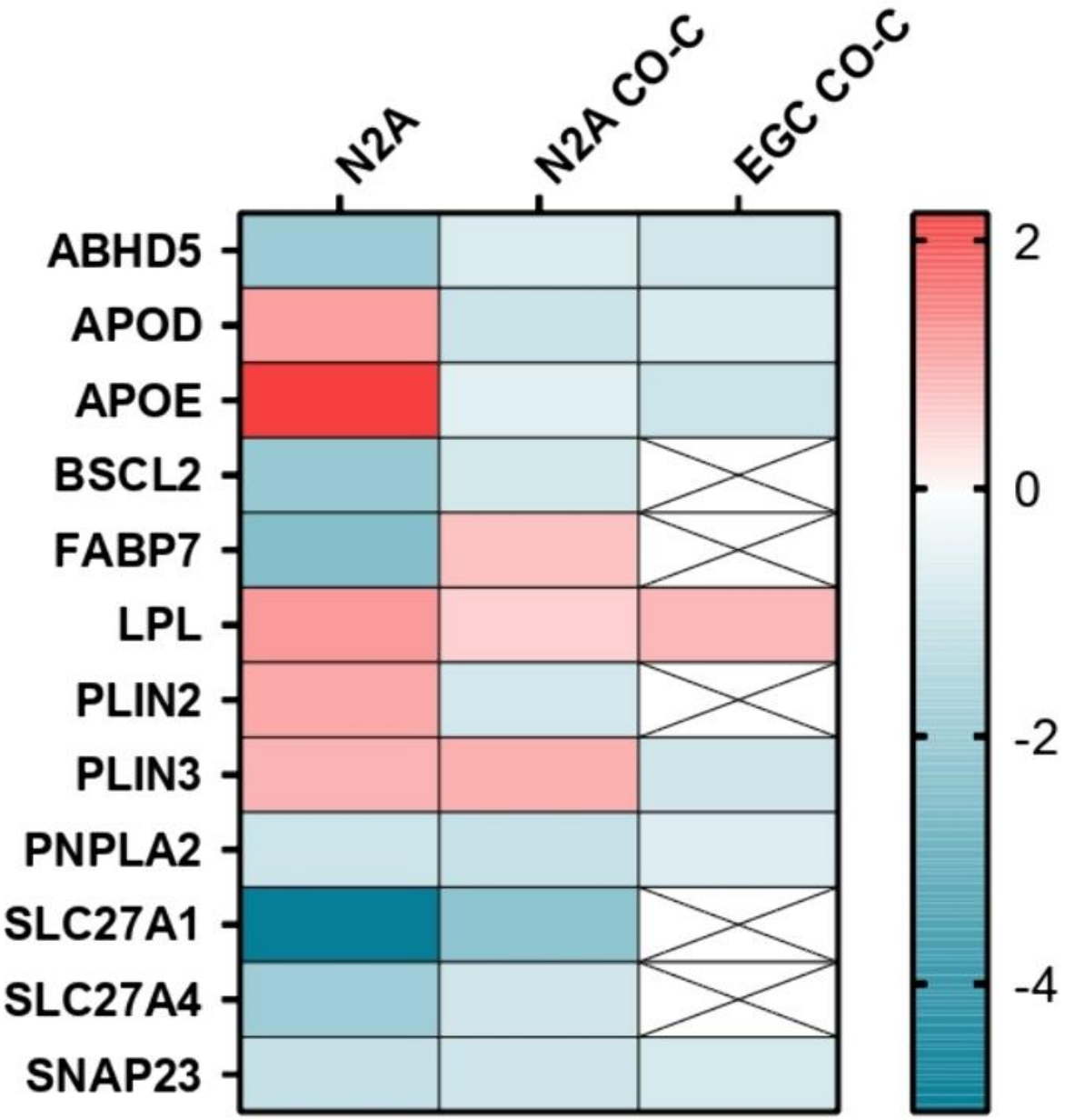
Poster Topic: *Theme A: β-Amyloid Diseases / A05.g. Genetics, Epidemiology: Infectious and inflammation*

LIPID DROPLETS AS THE LINK BETWEEN HSV-1 INFECTION, OXIDATIVE STRESS AND NEUROPATHOLOGY

POSTERS: A05.G. GENETICS, EPIDEMIOLOGY: INFECTIOUS AND INFLAMMATION

Veronica Zatta[1], Massimo Bellato[2], Alice Pegoraro[1], Paola Brun[1], Ignazio Castagliuolo[1]
[1]University of Padua, Department Of Molecular Medicine, Padua, Italy, [2]University of Padua, Department Of Information Engineer, Padua, Italy

Aims: In the last decades the involvement of Herpes Simplex Virus 1 (HSV-1) infection in Alzheimer's Disease (AD) has emerged. HSV-1 is considered a possible agent triggering neurodegeneration due to its neuro-tropism and ability to undergo multiple cycles of latency and reactivation in neurons. Lipid droplets (LDs) seem to be related to several viral infections and their increased abundance in ageing and neurodegenerating neurons has been reported. In this study we investigated the role of LDs in HSV-1 induced neurodegeneration.
Methods: Mice were inoculated intranasally with a replication deficient HSV-1 (HSV-MUT) (10^2 pfu), intragastrically after 4 weeks (W) (10^8 pfu) and sacrificed after 4W to determine Amyloid Precursor Protein (APP), β-amyloid, and LDs presence in LMMP (Longitudinal Muscle/Myenteric Plexus) by confocal microscopy. Neuro2A cells were infected with HSV-MUT to assess both the induction of LDs in vitro and the impact on the expression of LDs-related genes by qRT-PCR. Finally, HSV-1 MUT-infected Neuro2A were co-cultured with enteric glial cells (EGCs), isolated from healthy mice, to assess the expression of LDs-related genes by qRT-PCR.
Results: Persistent HSV-MUT infection induced neuronal accumulation of APP, β-amyloid and LDs in the LMMP. Moreover, HSV-MUT infected Neuro2aìA show increased ROS production and lipid peroxidation, as well as differential expression of LD-related genes (Figure1): bioinformatic analysis disclosed that such alterations involve several genes implicated in neurodegeneration. EGCs co-cultured with HSV-MUT infected Neuro2A show significantly increased LDs and alteration in the gene expression signature of LDs-related genes, as well as increased peroxidated lipids.



Conclusions: HSV-MUT infection causes the appearance of neurodegeneration markers, oxidative stress and LDs in neurons, in vivo and in vitro. Moreover, EGCs seem to act as "sponge" for LDs thus potentially counteracting HSV-MUT-induced effects.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0587 / #1437

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

PROGRESSION FROM ALL-CAUSE MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE DEMENTIA IN UK BIOBANK: EPIDEMIOLOGY, HEALTHCARE RESOURCE UTILISATION AND COSTS

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Craig Ritchie[1], Sophie Edwards[2], Dominic Trepel[3], Julie Hahn-Pedersen[4], Mei Sum Chan[5], Ben Bray[5], Alice Clark[6], Christian Wichmann[7], Alex Mourer[6], Marc Evans[8]
[1]Scottish Brain Sciences, Neuropyschology, Edinburgh, United Kingdom, [2]Barts Health NHS Trust, Geriatrics, London, United Kingdom, [3]Trinity College Dublin, School Of Medicine, Dublin, Ireland, [4]Novo Nordisk A/S, Payer Evidence Generation, Søborg, Denmark, [5]Lane Clark & Peacock LLP, Health Analytics, London, United Kingdom, [6]Novo Nordisk A/S, Real World Science, Søborg, Denmark, [7]Novo Nordisk A/S, Global Medical Affairs, Søborg, Denmark, [8]University Hospital Llandough, Endocrinology, Llandough, United Kingdom

Aims: To describe the natural history, healthcare resource utilisation and costs of progression from all-cause mild cognitive impairment (MCI) to Alzheimer's disease dementia (ADD).
Methods: UK Biobank participants were followed until end of primary care or hospital record linkage or loss to follow-up. Cognitive tests at baseline were utilised to identify participants with cognition scores consistent with MCI, using principal component analysis. Participants with and without MCI were matched using propensity scores to compare healthcare utilisation and costs. ADD diagnosis was defined using diagnostic codes in electronic health records.
Results: Of 502,394 UK Biobank participants, 33% (164,508) underwent cognitive assessments of which 6,605 (4%) were classified as having all-cause MCI. ADD incidence rates for participants with MCI were 9.5 times (95% CI, 7.9-10.9) higher than participants without MCI at 5 years (67.5 versus 7.1 per 100,000 person-years). The mean time to ADD in those with MCI who progressed to ADD was 6.9 years. 5,419 participants with MCI were matched to 21,676 participants without MCI, 40% of which had linked primary care records. Hospital inpatient costs were £866 (Standard Deviation, SD £3,205) per person per year in the MCI population versus £789 (SD £3,479) in matched participants without MCI at baseline, and £1,978 (SD £8,890) versus £1,669 (SD £9,096) 10 years after baseline, whilst primary care and prescription costs over 6 years were 9.6% higher in those with MCI. The difference in cumulative inpatient costs over 10 years between those with (n=75) and without (n=5344) eventual ADD diagnosis was £20,200 per participant with MCI.
Conclusions: Hospital and primary care costs in individuals with cognition scores consistent with MCI are modestly higher overall and much higher in individuals who subsequently develop ADD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0588 / #2735

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

DEATH RATES OF ALZHEIMER DISEASE AND OTHER DEMENTIAS IN PSYCHIATRIC HOSPITALS.

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Kengo Sato, Katsutoshi Shioda, Shiro Suda
Jichi Medical University, Department Of Psychiatry, Tochigi, Japan

Aims: We presume that this includes cases in which Alzheimer disease or other dementias are frequently associated with cause of death, or in which Alzheimer disease or other dementias should be the cause of death.This study examined death certificates and medical records in psychiatric hospitals in Japan to clarify instances where the cause of death could have been Alzheimer disease or other dementias.
Methods: We examined death certificates from three psychiatric hospitals in Japan from 2010 to 2020 for cases in which senility, pneumonia, aspiration pneumonia, multiple organ failure, urinary tract infection, and heart failure were listed as disease or condition directly leading to death, and investigated whether dementia was diagnosed or whether the patient might have had dementia in those cases. We further examined the medical records of each of these cases to determine whether dementia played a significant part in their cause of death.
Results: Of the 496 total deaths, 124 patients (75 pneumonia, 17 aspiration pneumonia, 13 heart failure, 12 multi-organ failure, 4 senility, and 2 urinary tract infection) had dementia on the death certificate. All patients had such advanced dementia that they had to be admitted to a psychiatric hospital. Despite being admitted to a psychiatric hospital, 35 patients had no psychiatric diagnosis listed on their death certificates. However, in their medical records, they had been diagnosed with dementia or were thought to have dementia.
Conclusions: In about one-third of the patients who died in psychiatric hospitals, the cause of death was related to dementia. The study suggested that dementia may in fact be the leading cause of death, with a potentially high number of cases in which dementia should be the cause of death in Japan.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0589 / #2234

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

TRANSCRIPTS PATTERN OF MONOCYTES ACCORDING TO AMYLOID-B AND TAU PATHOLOGY

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Pyungjun Choi[1], Hyuna Jeon[1], Jin Kim[1], Sun Ah Park[1], Sun Min Lee[2], So Young Moon[2], Kyung Hwa Sun[2]
[1]Ajou University School of Medicine, Anatomy, Suwon, Korea, Republic of, [2]Ajou University School of Medicine, Neurology, Suwon, Korea, Republic of

Aims: This study aims to investigate the transcription patterns in peripheral monocytes in relation to amyloid-β (Aβ) and tau biomarkers in individuals with memory impairments.
Methods: RNA was extracted from peripheral blood mononuclear cells (PBMCs), and mRNA expression profiles were generated using RNA-sequencing technology. The data were subsequently analyzed using bioinformatics tools to identify differentially expressed genes associated with amyloid-β (Aβ) and tau pathology.
Results: A total of forty-four subjects visiting a memory clinic were enrolled in this study. The mean age of the participants was 64 years, with a male-to-female ratio of 17:27. Our analysis revealed that the cellular components of the transcripts overlapped between Aβ and tau pathology, but the biological processes differed.
Conclusions: The distinct transcription patterns observed in peripheral monocytes in response to Aβ and tau pathology suggest the existence of separate processes through which systemic immune function interacts with these pathologies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0590 / #736

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

CAG REPEATS WITHIN THE NON-PATHOLOGICAL RANGE IN THE HTT GENE INFLUENCE PLASMA NEUROFILAMENT LIGHT CHAIN CONCENTRATION IN PRODROMAL ALZHEIMER'S DISEASE

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Assunta Ingannato[1], Chiara Crucitti[1], Salvatore Mazzeo[1,2], Silvia Bagnoli[1], Giulia Giacomucci[1], Valentina Moschini[2], Juri Balestrini[1], Carmen Morinelli[2], Giulia Galdo[1], Filippo Emiliani[1], Arianna Cavaliere[1], Daniele Frigerio[1], Diletta Piazzesi[1], Sonia Padiglioni[2], Sandro Sorbi[2], Valentina Bessi[2], Benedetta Nacmias[1]
[1]University of Florence, Department Of Neuroscience, Psychology, Drug Research And Child Health, Firenze, Italy, [2]Azienda Ospedaliero-universitaria Careggi, Research And Innovation Centre For Dementia-cridem, Firenze, Italy

Aims: Objectives: The Huntington's gene (HTT) contains a key region of CAG repeats that, when expanded beyond 39 repeats, Huntington's Disease (HD) develops. Intermediate alleles (IAs) are the CAG triplet expansion in the range between 27 and 35 repeats. Recent data showed an association between IAs and an increased risk of Alzheimer's disease (AD). Moreover, in a previous study, we reported a correlation between IAs and a higher risk to progress from SCD to MCI. Here, we investigated if a possible association does exist between CAG number repeats and CSF biomarkers and plasma neurofilament light chain (NfL) in AD patients.
Methods: Methods: *HTT* genotype, CSF biomarkers and plasma NfL concentration measurement were analyzed in ninety-six patients (36 SCD and 60 MCI). Study patients were classified as AP+ when A+, T+ and N+, as AP– when A– (regardless of T and N classification), or as A+/T-/N (A/T(N) system).
Results: Results: A significant relationship emerged between HTT length and plasma NfL concentration (p=0.009) in AP+ group, characterized by a nonlinear distribution. The IAs carriers were four in ATN+ group. A linear regression analysis was performed, considering plasma NfL as dependent variable, while age at baseline, age at onset, *APOE* ε4^{+}, CSF biomarker concentration and CAG number repeats as covariates. The final model was significant (p=0.031) and included only HTT CAG repeats (p=0.031) as significant variable.
Conclusions: Conclusions: Our results suggest that increasing number of CAG repeats, below the IAs threshold, may protect against neurodegeneration in AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0591 / #135

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

APOE4, IN-HOSPITAL DELIRIUM AND LONG-TERM COGNITIVE IMPAIRMENT: A LONGITUDINAL MEMORY CLINIC STUDY

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Chi-Hun Kim[1], Jong Hun Kim[2]
[1]Hallym University Sacred Heart Hospital, Neurology, Anyang, Korea, Republic of, [2]Ilsan Hospital, National Health Insurance Service, Neurology, Goyang, Korea, Republic of

Aims: To examine the association of *APOE*ε4 allele with in-hospital delirium and long-term cognitive outcomes following the delirium
Methods: DESIGN Retrospective cohort study **SETTING** Electronic medical records (EMRs) from the Ilsan Hospital memory clinics in South Korea were linked to the Korean National Health Insurance Service (NHIS) database, which contains hospitalization, medication, and diagnosis records of all citizens in South Korea from January 2002 to July 2019. **PARTICIPANTS** 1057 memory clinic visitors with *APOE* genotype, longitudinal neuropsychological tests, and hospitalization records. **MEASUREMENTS** Incident in-hospital delirium was defined as the initiation of antipsychotics during hospitalization after excluding prevalent users. Longitudinal outcomes were three cognitive scales and two functional measurements. Incidence analysis was conducted using Cox proportional hazards models, while longitudinal outcomes were analyzed using multivariable mixed models with an interrupted time series design.
Results: At baseline, *APOE*ε4 carriers (N=298, 28.2%) performed poorly cognitive tests compared to non-carriers (CDR-SB mean ± SD: 3.3 ± 3.5 vs 2.8 ± 2.9, *P*=0.016; MMSE 22.3 ± 5.8 vs 23.2 ± 5.2, *P*=0.029). Over the 17-year follow-up, the carriers developed more in-hospital delirium than non-carriers after covariate adjustments (hazard ratio 1.96, 95% confidence intervals 1.30–2.96, *P*=0.0015). The *APOE*ε4 allele also had a more detrimental impact on four out of the five cognitive and functional measurements after the delirium (beta estimates of post-delirium change by *APOE*e4 for CDR-SB = 3.20, *P*<0.0001; CDR=0.60, *P*<0.0001; KIADL = 0.99, *P*<0.0001; SIADL = 14.07, *P*<0.0001). These findings remained robust even after adjusting for covariates.
Conclusions: Throughout the 17-year follow-up, *APOE*ε4 carriers demonstrated robust associations with in-hospital delirium and exhibited more post-delirium cognitive and functional impairment compared to non-carriers. Individuals with *APOE*ε4 allele may need more attention to prevent in-hospital delirium and post-delirium cognitive impairment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0592 / #339

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

INCREASED RISK OF DEMENTIA AFTER TRANSIENT GLOBAL AMNESIA: A NATIONWIDE POPULATION-BASED, LONGITUDINAL FOLLOW-UP STUDY IN SOUTH KOREA

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Seung-Jae Lee[1], Yoon-Jong Bae[2]
[1]Soonchunhyang University Bucheon Hospital, Department Of Neurology, Bucheon, Korea, Republic of, [2]Hanmi Pharm. Co., Ltd., Data Science Team, Seoul, Korea, Republic of

Aims: Long-term cognitive outcome after transient global amnesia (TGA) is contradictory in the literature to date. Our study aimed to longitudinally investigate the association of TGA with incident dementia, using the long-term data of nationwide population-based cohort in South Korea.
Methods: From the database of the Korean National Health Insurance Service between 2002 and 2018, study population was recruited using International Classification of Diseases, Tenth Revision codes. Cumulative incidence curve was plotted to compare the incidence rate of dementia between the TGA (G 45.4; n=10,276) and the non-TGA (n=27,389) groups determined using a 1:3 propensity score matching. Using Cox proportional hazard regression models, we obtained crude and adjusted hazards ratios (aHRs) and 95% confidence intervals (CIs) for the incident dementia in patients with TGA compared with non-TGA control. To exam independent variables determining dementia in TGA group, logistic regression analysis was performed, and adjusted odds ratios (aORs) and 95% CIs were produced. All statistical tests were two-tailed, and p values <0.05 were considered statistically significant.
Results: The TGA group had higher cumulative incidence of dementia than the non-TGA group ($p < 0.001$ by long-rank test). TGA was significantly associated with incident dementia in the univariate and multivariate Cox models (HR 1.34, 95% CI 1.28–1.39 and aHR 1.40, 95% CI 1.34–1.46, respectively). The adjusted logistic regression showed that age (per 1 year, OR 1.09, 95% CI 1.09–1.10), female sex (OR 1.31, 95% CI 1.18–1.45), diabetes (OR 1.21, 95% CI 1.08–1.35), stroke (OR 1.30, 95% CI 1.16–1.46), depression (OR 1.53, 95% CI 1.33–1.76), anxiety (OR 1.24 , 95% CI 1.01–1.39), and rural residence (OR 1.24, 95% CI 1.10–1.41) were independently associated with the incident dementia.
Conclusions: Our results suggest the longitudinal association of TGA with incident dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0593 / #866

Poster Topic: *Theme A: β-Amyloid Diseases / A05.g. Genetics, Epidemiology: Infectious and inflammation*

PERSISTENT HSV-1 INFECTION IN MOUSE ENTERIC NEURONS TRIGGERS ALZHEIMER'S DISEASE-LIKE NEURODEGENERATION HALLMARKS

POSTERS: A05.G. GENETICS, EPIDEMIOLOGY: INFECTIOUS AND INFLAMMATION

Veronica Zatta, Paola Brun, Ignazio Castagliuolo
University of Padua, Department Of Molecular Medicine, Padua, Italy

Aims: A growing body of evidence is supporting the profound link between Alzheimer's disease (AD) onset and infectious agents. The neurotropic Herpes simplex virus type 1 (HSV-1) is extremely attractive for a number of experimental and clinical observations, however the absence of a handy *in vivo* model hampers further investigations. The current study was designed to investigate whether persistent HSV-1 infection of enteric neurons would cause neuropathology suggestive of neurodegenerative diseases.
Methods: Mice were inoculated intranasally with HSV-1 (10^2 pfu), intragastrically after 4 weeks (W) (10^8 pfu)* and sacrificed after 4-6-8-10 W. In the ileum LMMP (Longitudinal Muscle/Myenteric Plexus) we determined: a) Amyloid Precursor Protein (APP), β-amyloid, synaptophysin expression by IHC and IF; b) inflammatory cytokines and α-, β- and γ-secretase mRNA by qRT-PCR; c) content of Ach in myenteric neurons by LC-MS/MS. Neurons from myenteric plexus were isolated and cultured and levels of free radicals determined using specific probes.
Results: APP and β-amyloid immunoreactivity progressively increased and peaked at 10W of infection. In contrast, the strong neuronal immunoreactivity for synaptophysin progressively vanished. Ach content in the myenteric plexus was significantly reduced starting at 6W. BACE1 and PSEN2 mRNA significantly increased starting at 4W, whereas ADAM10 transcripts were not significantly affected. IL-1β and IL-6 mRNA levels significantly increased in myenteric plexus starting at 4W. Moreover, redox homeostasis analysis in cultured enteric neurons, obtained from *in vivo* infected mice, revealed peroxidation of membrane lipids and increased mitochondrial production of free radicals.
Conclusions: Persistent HSV-1 infection of enteric neurons causes synaptic damage, accumulation of APP and β-amyloid, neuroinflammation and oxidative damage in neurons: hallmarks of neurodegeneration. Overall our data further support an involvement of HSV-1 in the pathogenesis of neurodegenerative diseases. * Brun et. al. Front Microbiol. 2018

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0594 / #455

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

CHARACTERISTICS AND CO-MORBIDITIES OF PATIENTS WITH ALZHEIMER'S DISEASE AT DIAGNOSIS, PRE- AND POST-DIAGNOSIS VERSUS NON-ALZHEIMER´S-DISEASE CONTROLS IN ISRAEL

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Olga Sánchez-Soliño[1], Yael Barer[2], Lisa Vinikoor-Imler[1], Gabriel Chodick[2]
[1]AbbVie Inc., R&d, North Chicago, United States of America, [2]Maccabi Institute for Research and Innovation, R&d, Tel-Aviv, Israel

Aims: To characterize patients with Alzheimer's Disease (AD) versus matched controls in Israel, at diagnosis, 10 years prior and 2 years post-AD diagnosis.
Methods: This longitudinal, patient-level, retrospective cohort study using the Maccabi healthcare services (MHS) database included adult patients diagnosed with AD, as per the ICD-9 code 331.0 or corresponding MHS internal codes. Date of first AD diagnosis was defined as the Index date (ID). Patients were included if they had at least 10 years prior ID and at least 2 years post ID (apart from death) of continuous MHS enrollment. MHS members without AD diagnosis were matched to patients with AD by age and sex. The ID was required to occur during 01-01-2010 to 31-12-2019.Comparison between groups was performed using standardized mean difference [SMD]. Risk of morality was assessed using COX proportional hazard model adjusted to baseline characteristics.
Results: 44,128 subjects (22,064 AD and 22,064 matched non-AD) were included in the analysis. Mean age at ID was 80.02 (SD 8.4) years and 57.6% were female. At ID, patients with AD were more likely to have mild cognitive impairment, cerebrovascular-disease, type 2 diabetes, depression and/or anxiety, recurrent seizures, falls, psychosis, post-traumatic brain degeneration and other neurological conditions. Patients with AD had a 1.76-fold increased risk of mortality compared to those without. The most common dementia-related diagnoses other than AD prior and post-ID were vascular dementia and dementia due to medical condition.
Conclusions: A higher proportion of AD patients were diagnosed with prior neurological conditions and type 2 diabetes compared to non-AD controls. Patients with AD had an increased risk for death throughout follow-up. Comorbidities should be considered when providing care for patients

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0595 / #2236

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

ARE PREDICTIONS OF PHENOTYPIC COGNITIVE SCORES BY POLYGENIC COGNITIVE SCORES DRIVEN BY THE COGNITIVE COMPLEXITY OF PHENOTYPIC MEASURES? A META-ANALYSIS

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Jan Te Nijenhuis, Balaji Kannappan, Kun Ho Lee
Chosun University, Biomedical, Gwangju, Korea, Republic of

Aims: Intelligence is highly heritable and crucial in biomedical research. Recent genome-wide association studies (GWASs) have identified SNPs that account for a modest portion of the heritability of intelligence. There are many studies where cognitive polygenic scores (PGSs) are used to predict scores on intelligence tests; the resulting rs are all over the place. Various unconvincing explanations are offered for this high variability in resulting rs. The most important difference between intelligence tests is their difference in cognitive complexity. We hypothesize that the predictions of phenotypic cognitive scores by polygenic cognitive scores are a function of the cognitive complexity of the phenotypic cognitive scores.
Methods: We carried out a meta-analysis of studies reporting 1) cognitive polygenic scores (IQ, Cognitive achievement, Educational attainment) and 2) the correlation between cognitive polygenic scores and at least four cognitive test scores. We computed the cognitive complexity of the cognitive tests. We then computed the correlation between 1) the cognitive complexity of the cognitive tests and 2) the correlation between cognitive polygenic scores and at least four cognitive test scores. A strong positive correlation means that the predictions of phenotypic cognitive scores by polygenic cognitive scores are strongly driven by the cognitive complexity of the phenotypic measures.
Results: A substantial number of studies were found and many of them were based on a large number of subjects. The studies analyzed so far show large to very large correlations, strongly confirming the hypothesis.
Conclusions: Cognitive polygenic scores predict most strongly for difficult IQ tests and least strongly for easy IQ tests. So, we conclude that the predictions of phenotypic cognitive scores by polygenic cognitive scores are strongly driven by the cognitive complexity of the phenotypic measures

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0596 / #2827

Poster Topic: *Theme A: β-Amyloid Diseases / A06.a. Cell, Molecular and Systems Biology: APP, APLP, Abeta*

NOVEL KNOCKIN MICE LACKING THE ALPHA- AND BETA-SECRETASE SITES

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

Lara Kilian[1], Marija Banicevic[1], Jennifer Just[2], Michaela Back[3], Irmgard Amrein[4], Jakob Von Engelhardt[3], David Wolfer[4], Stefan Kins[5], Martin Korte[2], Ulrike Müller[1]
[1]Ruprecht-Karls Universität Heidelberg, Institute Of Pharmacy And Molecular Biotechnology (ipmb), Heidelberg, Germany, [2]TU Braunschweig, Zoological Institute, Braunschweig, Germany, [3]Johannes Gutenberg-Universität Mainz, Universitätsmedizin, Institute Of Pathophysiology, Mainz, Germany, [4]University of Zurich, Institute of Anatomy, Division Of Functional Neuroanatomy, Zurich, Switzerland, [5]TU Kaiserslautern, Department Of Human Biology And Human Genetics, Kaiserslautern, Germany

Aims: The pivotal role of the amyloid precursor protein (APP) in the pathogenesis of Alzheimer's Disease is well established. However, the precise physiological role of APP and its various proteolytical fragments is still not fully understood. Both, transmembrane APP signaling and secreted APP ectodomain fragments are required for normal development of the nervous system. Previous studies indicated that cell surface APP and the APLPs mediate synaptic adhesion, which is important during development and in the adult for processes that require synaptic stabilization. However, proteolytic cleavage of cell surface APP leads to APPsα secretion, which has been shown to support both structural and functional synaptic plasticity. Our goal is to understand the interdependence and regulation of these processes at the synapse *in vivo*.
Methods: Here, we have generated novel APP knockin mice expressing solely a secretion-deficient APP variant by introducing a genomic deletion (APPΔS622) encompassing the α- and β-secretase cleavage sites.
Results: APPΔS622 mice proved fully viable. Western blot analysis of APP processing in brain lysates indicated an accumulation of full-length, uncleaved APP at the cell surface that was paralleled by a prominent reduction of secreted, soluble APPs fragments and APP-CTFs. Intriguingly, the levels of post-synaptic proteins PSD-95 and Homer1 were significantly reduced. Moreover, electrophysiological recordings conducted in the hippocampus of adult APPΔS622 mice revealed a synaptic phenotype characterized by pronounced deficits in the induction and maintenance of hippocampal Long-Term Potentiation (LTP).
Conclusions: APPΔS622 mice represent a novel mouse line which will be further used to gain a deeper understanding of the role of APP as a soluble ligand. Collectively, our findings suggest that soluble APPs plays a fundamental role in modulating and regulating the dynamic processes underlying synaptic plasticity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0597 / #2316

Poster Topic: *Theme A: β-Amyloid Diseases / A06.a. Cell, Molecular and Systems Biology: APP, APLP, Abeta*

TARGETED CO-EXPRESSION NETWORKS PRECISELY DELINEATE THE PATHWAYS ASSOCIATED WITH THE AMYLOID BETA PRECURSOR PROTEIN WITHIN ALZHEIMER´S BRAINS

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

Juan Botia[1], Alicia Gómez-Pascual[1], Guillermo Rocamora[1], Laura Ibanez[2]
[1]University of Murcia, Information And Communications Engineering, Espinardo, Spain, [2]Washington University School of Medicine in Saint Louis, Psychiatry, Washington, United States of America

Aims: We investigated the gene expression context of the beta-amyloid precursor protein (APP) gene in Alzheimer´s Disease (AD) brains, using its gene expression as the target of a targeted co-expression network.
Methods: Gene co-expression networks (GCNs) on transcriptomes are too coarse grain models to specifically investigate associations of gene expression with phenotypes of interest. Targeted GCNs (TGCNs) are a new modelling approach we designed that creates more specific networks, focused on a phenotype, APP in this case. A TGCN tries to explain as much variation of the phenotype as possible within the sample while describing, functionally, the genes involved (available at https://github.com/aliciagp/TGCN). We created APP-TGCNs on the ROSMAP gene expression profiles and replicated results on the MSBB cohort.
Results: The APP-TGCN has 25 modules 880 genes size. The hubs explain most of the gene expression variation in APP (R^2 0.96). Within the hubs we find the ATP1B1 gene (leading a module enriched for *dopaminergic* neurons and GO terms like synaptic vesicle cycle). ATP1B1 replicates as hub in the MSBB TGCN. ABCD3 leads genes enriched for astrocytes and activity located mainly in the cell plasma membrane. FRZB is hub in a module enriched for endothelial and mural cells. NFASC module is enriched for oligodendrocytes and neuron development related terms, and replicates in the MSBB TGCN. In association to AD as a phenotype, the APP-TGCN shows APP involvement through the HNRNPA2B1 module (enriched with mRNA metabolism and splicing annotations), and ATP1B1 and NFASC module.
Conclusions: We show that APP expression in brain plays cell-specific key roles in several biological processes: neuron development through oligodendrocytes and in regulation of the synaptic vesicle cycle in dopaminergic neurons, which we found associated with AD pathobiology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0598 / #1204

Poster Topic: *Theme A: β-Amyloid Diseases / A06.a. Cell, Molecular and Systems Biology: APP, APLP, Abeta*

TMCC2 PATHOLOGY IN ALZHEIMER'S DISEASE AND DOWN SYNDROME

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

Paul Hopkins[1], Claire Troakes[2], Andrew King[2], Guy Tear[1]
[1]King's College London, Centre For Developmental Neurobiology, London, United Kingdom, [2]King's College London, Institute Of Psychiatry, Psychology And Neuroscience, London, United Kingdom

Aims: To investigate the apoE-binding and APP-interacting protein TMCC2 in post-mortem human brain.
Methods: We compared TMCC2 immunoreactivity and pathology in post-mortem brain of late onset AD cases as well as in age-matched non-demented controls. We also investigated TMCC2 immunoreactivity in post-mortem brain tissue from cases with early onset AD associated with Down syndrome.
Results: In both early and late onset AD, TMCC2 immunoreactivity was closely associated with neuronal APP, as well as found specifically in dense cored senile plaques. In Down syndrome AD, TMCC2 immunoreactivity was also found prominently associated with putative amyloid having a spicular or thread-like appearance. This TMCC2- and methoxy-X04-positive was not observed in the 10 late onset AD cases examined. Our observations may recapitulate those previously made using thioflavin S, variously named "birds nest plaques" or "fibrous plaques" which showed Aβ- and tau-negative amyloid in Down syndrome that was not observed in AD associated with other genetic risk factors.
Conclusions: Association of TMCC2 with APP-related pathology in both early and late onset AD positions this protein as mediator between apoE and APP in AD pathogenesis. The association of TMCC2 immunoreactivity with an amyloid-dye reactive pathological feature potentially enriched in Down syndrome AD suggests that TMCC2 may be a target of chromosome 21 genes, and have the potential to adopt a β-pleated sheet amyloid conformation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0599 / #1839

Poster Topic: *Theme A: β-Amyloid Diseases / A05.h. Genetics, Epidemiology: Other*

IN-DEPTH DNA METHYLATION PROFILING OF AD ASSOCIATED LOCI.

POSTERS: A05.H. GENETICS, EPIDEMIOLOGY: OTHER

Greg Wheildon[1], Adam Smith[2], Darren Soanes[1], Rebecca Smith[1], Karen Moore[3], Paul O'Neill[3], Kevin Morgan[4], Paul Francis[5], Jonathan Mill[6], Ehsan Pishva[7], Katie Lunnon[2]
[1]University of Exeter, Clinical And Biomedical Sciences, Exeter, United Kingdom, [2]University of Exeter, Department Of Biomedical And Clinical Sciences, Exeter, United Kingdom, [3]University of Exeter, Biosciences, Exeter, United Kingdom, [4]University of Nottingham, Life Sciences, Nottingham, United Kingdom, [5]University of Exeter, Medical School, Exeter, United Kingdom, [6]University of Exeter Medical School, Department For Clinical And Biomedical Sciences, Exeter, United Kingdom, [7]University of Maastricht, Department Of Psychiatry & Neurophysiology, Maastricht, Netherlands

Aims: Recent epigenome-wide association studies (EWAS) identified loci in specific genes showing robust DNA methylation alterations in Alzheimer's disease (AD) brain samples. Microarrays used in these studies target a limited number of methylation sites in each gene. We performed targeted bisulfite sequencing (TBS) for genes associated with AD, aiming to determine the exact extent of methylation changes in disease within these loci, and to conduct technological comparisons between the Illumina EPIC array and TBS.
Methods: Prefrontal cortex (PFC) brain samples from 58 individuals were selected and grouped by Braak stage (Control 0-II; intermediate III-IV; AD V-VI). DNA was extracted, before 14 AD genomic regions of interest, were captured using Agilent SureSelect target baits. The DNA was bisulfite sequenced, aligned and CpG methylation called. Differentially methylated positions (DMPs) were analysed across the three groups. We also compared the data to EPIC array data generated in the same samples
Results: Methylation levels were quantified, and group differences were examined using a one-way ANOVA, controlling for co-variation. Sites in several genes showed differential DNA methylation, with several of the most robust sites not being present on current methylation arrays. Enrichment of nominally significant sites at genomic features was observed. Non-linear changes in methylation with AD pathology were also observed. Correlation of effect sizes showed concordance at shared CpGs between the two technologies, particularly when stratifying by strength of association.
Conclusions: This work provides further evidence that methylation dysregulation is associated with AD pathology in the PFC. That sites not presented on existing methylation arrays showed significant changes suggests the need for better characterisation. Future work should focus on long-read sequencing methods to allow full characterisation of DNA methylation on native DNA, overcoming issues associated with short-read sequencing.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0600 / #1747

Poster Topic: *Theme A: β-Amyloid Diseases / A06.a. Cell, Molecular and Systems Biology: APP, APLP, Abeta*

THE REGION 35-HAEE-38 OF ALPHA4 SUBUNIT PLAYS A KEY ROLE IN THE BINDING OF ALPHA4BETA2 NICOTINIC ACETYLCHOLINE RECEPTOR TO BETA-AMYLOID

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

Olga Kechko[1], Lucy Ojomoko[2], Vladimir Mitkevich[1], Alexander Makarov[1]
[1]Engelhardt Institute of Molecular Biology RAS, Laboratory Of Protein Conformational Polymorphism In Health And Disease, Moscow, Russian Federation, [2]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS, Department Of Molecular Neuroimmune Signaling, Moscow, Russian Federation

Aims: Progression of Alzheimer's disease is accompanied by the dysfunction of cholinergetic system and massive loss of cholinergetic neurons containing the nicotinic acetylcholine receptors (nAChRs). NAChRs agonists protect neuronal cells against amyloid toxicity, eliminate the senile plaques and improve learning and memory of transgenic mice. Moreover, nAChRs antagonists, that blocks binding of Abeta to the receptor, inhibits Abeta-induced tau protein phosphorylation in neuronal cells. It is mean that the toxicity of Aβ is mediated through a direct interaction between Abeta and nAChRs. The most abundant form of nAChRs in the brain is alpha4beta2 nAChR. It is known that Abeta binds alpha4beta2 nAChR and inhibits its function but little known about this interaction.
Methods: Microscale thermophoresis and isothermal titration calorimetry were used to measure the binding of Abeta and extracellular domain (32-242aa) of nAChR alpha4 subunit. *Xenopus laevis* oocytes expressed alpha4beta2 nAChR or its mutant alpha4(35-HAAA-38) were used to define inhibition effect of Abetas on the receptor. The acetylcholine-induced ion currents were measured by two-electrode voltage clamp. Dynamic light scattering was used to evaluate the aggregation of Abeta.
Results: Abeta forms a strong complex with alpha4 nAChR through the region 35-HAEE-38 of alpha4. Isomerization of Asp7, the well-known pathogenic modification of Abeta, enhance this interaction 10-fold. Mutation 35-HAAA-38 completely abolishes the binding of alpha4 nAChR and Abetas, as well as Abeta-induced inhibition of alpha4beta2 nAChR in oocytes. The initial binding of Abeta peptides to the alpha4 nAChR promotes their aggregation on the receptor matrix.
Conclusions: The region 35-HAEE-38 of alpha4 nAChR is essential for interaction with Abeta. Increase of Abeta level induces its aggregation on the receptor and results in the inhibition of the nAChR.
Supported by the Russian Science Foundation (grant #19-74-30007)

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0601 / #1656

Poster Topic: *Theme A: β-Amyloid Diseases / A06.a. Cell, Molecular and Systems Biology: APP, APLP, Abeta*

AUTOPHAGY DEFICIENCY ALTERS INTRACELLULAR APP TRANSPORT, LEADS TO INCREASED APP PROCESSING AND SOLUBLE APP SECRETION

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

Johanna Mayer[1], Dominik Boeck[1], Michelle Werner[1], Makoto Shimozawa[1], Hesso Farhan[2], Per Nilsson[1]
[1]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden, [2]Medical University of Innsbruck, Institute Of Pathophysiology, Innsbruck, Austria

Aims: Alzheimer's disease pathology is characterized by amyloid beta (Abeta) plaques and dysfunctional autophagy as seen by an accumulation of autophagic vacuoles in patient brains. Abeta is generated by sequential proteolytic cleavage of amyloid precursor protein (APP) and the site of intracellular APP processing is highly debated and may include autophagosomes.
Methods: Here we investigated the involvement of autophagy in APP intracellular trafficking and processing by applying the retention using selective hooks (RUSH) system. Thereby we could follow the transport of fluorescently labeled mCherry-APP-EGFP in a systematic way starting from the endoplasmic reticulum. Autophagy-deficient, ATG9 knockout HeLa cells stably expressing the RUSH mCherry-APP-EGFP system were investigated by live-cell imaging, immunofluorescence, and Western blot.
Results: We found that mCherry-APP-EGFP passed through the Golgi faster in ATG9 knockout cells potentially due to a fragmented Golgi. ATG9 depletion further resulted in an intracellular relocation of mCherry-APP-EGFP away from early endosomes and towards the plasma membrane. Eventually, the intracellular re-routing of mCherry-APP-EGFP resulted in an increased amount of secreted mCherry-soluble APP and intracellular C-terminal fragment-EGFP.
Conclusions: These findings contribute to the understanding of the role of autophagy in APP metabolism and could potentially have implications for new therapeutic approaches for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0602 / #1669

Poster Topic: *Theme A: β-Amyloid Diseases / A06.a. Cell, Molecular and Systems Biology: APP, APLP, Abeta*

SPATIOTEMPORAL EXPRESSION OF MEMBRANE-TETHERED APP INTRACELLULAR DOMAIN PLAYS A CRITICAL ROLE IN SLEEP AND COGNITIVE BEHAVIORS OF AD MOUSE MODELS

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

Angèle Parent[1,2], Anjana Sadanand[1], Clémentine Puech[3], Emily Sandefur[1], Alex Torrelli-Diljohn[1], Neil Coleman[1], Vanity Spruill[2], Gini Besant[2], Mohammad Badran[3], Mary Weinrich[1], Rong Wang[1], David Gozal[3,4]
[1]University of South Florida, Molecular Medicine, Tampa, United States of America, [2]University of Chicago, Neurobiology, Chicago, United States of America, [3]University of Missouri, Department Of Child Health, Columbia, United States of America, [4]Marshall University, Joan C Edwards School Of Medicine, Huntington, United States of America

Aims: We previously reported that membrane-tethered APP intracellular domain (mAICD) interacts with GalphaS and activates adenylate cyclase. We established that mAICD expression in the brain since birth rescued cognitive impairment observed in 5XFAD, an effect that required mAICD interaction with GalphaS protein. Here, we explored if mAICD expression in adult mouse brains with advanced AD conditions is sufficient to preserve spatial memory and sleep, underlying AD pathology, which can interfere with cognitive behavior.
Methods: We expressed mAICD or mAICDmutAAA variant (lacking the GalphaS interacting site) in the brain of amyloidogenic 5XFAD and tauopathy PS19 mouse models using AAV brain delivery strategy. We injected the AAV plasmids in neonates, young and old adults, and performed sleep and cognitive behaviors 3-6 months later.
Results: We observed that 5XFAD mice sleep less than non-transgenic (NTg) littermates. mAICD expression since birth in 5XFAD prevented sleep disturbance, an effect not seen in 5XFAD mice expressing mAICDmutAAA. NTg mice expressing mAICDmutAAA exhibit an overall reduction of sleep, which was correlated with cognitive impairment. Noteworthy, NTg mice expressing mAICD in the dentate gyrus since a young age exhibited cognitive impairment, an effect not seen in older cohorts. 5XFAD mice did not improve their cognitive behaviors when expressing mAICD in the dentate gyrus, whereas they showed less memory decline if injected in the CA3. We also found that expression of mAICDmutAAA in the suprachiasmatic nucleus markedly reduced contextual fear conditioning responses in PS19 and 5XFAD mice.
Conclusions: Our results suggest that altered APP-mediated cAMP/PKA downstream signaling could contribute to the sleep pattern discrepancy seen in AD mouse models, therefore impacting memory performance. mAICD overexpression in select brain areas at a given period during lifespan might affect cognition.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0603 / #2149

Poster Topic: *Theme A: β-Amyloid Diseases / A06.a. Cell, Molecular and Systems Biology: APP, APLP, Abeta*

MOLECULAR PATHWAYS OF PATHOGENIC SORLA PROTEIN IN ALZHEIMER'S DISEASE DEVELOPMENT.

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

Jan Raska[1,2], Petr Fojtik[1,2], Klara Plesingrova[1], Veronika Pospisilova[1], Simona Bartova[1], Jiri Sedmik[1], Tereza Vanova[1,2], Sona Kadakova[1], Hana Hribkova[1], Victorio Devoto[1,2], Marko Mecava[1], Miriam Satkova[1], Olav Andersen[3], Dasa Bohaciakova[1,2]
[1]Masaryk University, Department Of Histology And Embryology, Brno, Czech Republic, [2]International Clinical Research Center (ICRC), St. Anne's University Hospital, Brno, Czech Republic, [3]Aarhus University, Department Of Biomedicine, Aarhus, Denmark

Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a gradual decline in memory function and the presence of distinct pathological features, including amyloid-β plaques and Tau neurofibrillary tangles. While most AD cases are sporadic, a subset of cases is linked to specific mutations in genes such as *APP*, *PSEN1*, and *PSEN2*, which lead to early-onset AD. More recently, genetic variations in the *SORL1* gene, which encodes the SORLA protein, have also been associated with the development of AD, suggesting that *SORL1* may be considered the fourth AD causative gene. We aimed to investigate the mechanisms underlying the development of AD-related pathology caused by pathogenic *SORL1* mutations.
Methods: We used CRISPR/Cas9 technology to introduce several pathogenic *SORL1* mutations into induced pluripotent stem cells and employed advanced *in vitro* models to produce 2D inducible neurons and 3D neural organoids. SORLA was investigated by WB, and endosome morphology, and APP accumulation were investigated using confocal microscopy and the Proximity ligation assay.
Results: We successfully adapted advanced 2D and 3D *in vitro* models and introduced mutations in the *SORL1* gene to investigate the molecular consequences of pathological SORLA in AD development. As controls, we utilized wild-type and complete *SORL1* knock-out cells. Using these novel disease models, we observed how decreased maturation and the total SORLA protein level was unifying feature of all tested pathogenic variants. A concomitant decrease in mutant SORLA shedding was observed. Notably, we identified the presence of enlarged endosomes with increased accumulation of APP, a major pathological marker in these cell models.
Conclusions: We have successfully validated the utility of stem-cell *in vitro* models for SORLA research, paving the way for more in-depth investigations into the molecular pathways underlying SORLA-associated AD development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0604 / #1621

Poster Topic: *Theme A: β-Amyloid Diseases / A06.b. Cell, Molecular and Systems Biology: ApoE*

EVALUATING ALZHEIMER'S DISEASE PHENOTYPES IN APOE ALLELIC VARIANTS ENGINEERED INTO IPSC-DERIVED NEURONS

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

Amr Othman[1], Scott Schachtele[2], Rebecca Fiene[1], Megan Livingston[1], Carole Crittenden[3], Oksana Sirenko[3], Coby Carlson[1]
[1]FUJIFILM Cellular Dynamics, Applications, Madison, United States of America, [2]FUJIFILM Cellular Dynamics, Product Management, Madison, United States of America, [3]Molecular Devices, LLC., Applications, San Jose, United States of America

Aims: Apolipoprotein E (APOE) is a gene involved in cholesterol transport and has a well-known link to Alzheimer's Disease (AD). An individual's composition of APOE alleles (e.g., epsilon(E)2, E3, E4) is related to AD risk; inheriting two APOE E4 alleles increases risk of AD compared to individuals containing just one E4 allele. Conversely, two APOE E2 alleles reduces risk of developing AD. Understanding the functional role of APOE allele combinations may identify new methods for prevention or delay of AD. In this study, we investigated phenotypes of common APOE allele combinations in GABAergic neurons derived from human induced pluripotent stem cells (iPSCs) and cultured in either 2D or advanced multi-cell 3D neurospheres.
Methods: A human iPSC donor with APOE 3/3 (wild-type) was engineered to create isogenic APOE E2/2, E3/4, and E4/4 iPSCs. iPSCs were differentiated into GABAergic neurons (iCell GABANeurons) at scale and across multiple lots. We monitored the effect of APOE allele combinations on neurite outgrowth and alpha-synuclein production. iCell GABANeurons were cultured with other iPSC-derived brain cells (i.e., glutamatergic neurons, astrocytes) to generate 3D neurospheres. Using a high-throughput calcium oscillation assay, baseline activity was measured in APOE allele AD-based neurospheres. Neurosphere cultures were subsequently screened with neuromodulatory and AD-relevant compounds.
Results: Neurospheres containing APOE allele GABANeurons yielded unique functional differences using the calcium oscillation assay. APOE E4/4 GABANeurons displayed the strongest deviation compared to control APOE E3/3 neurons. Preliminary data showed memantine treatment returned APOE4/4 neuron calcium oscillations back to control cultures.
Conclusions: Human iPSC-derived neurons composed of AD-relevant APOE allele combinations present phenotype differences in culture and can be a useful model for identifying mechanism of AD pathogenesis and potential targets for therapeutic treatments.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0605 / #1640

Poster Topic: *Theme A: β-Amyloid Diseases / A06.b. Cell, Molecular and Systems Biology: ApoE*

THE INTERRELATION BETWEEN APOE AND MATRIX METALLOPROTEINASE-9 WITH HIPPOCAMPAL VOLUMETRY IN PATIENTS WITH ALZHEIMER'S DISEASE

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

Jelena Bašić[1], Vuk Milošević[2], Branka Đorđević[1], Vladana Stojiljković[1], Milica Živanović[3], Tatjana Jevtović Stoimenov[1], Ivana Stojanović[1]
[1]Faculty of Medicine, University of Niš, Department Of Biochemistry, Niš, Serbia, [2]University Clinical Center Niš, Clinic Of Neurology, Niš, Serbia, [3]University Clinical Center Niš, Radiology Center, Niš, Serbia

Aims: Although APOE ε4 carrier status, matrix metalloproteinases-9 (MMP-9), and its tissue inhibitor (TIMP-1) are associated with the disruption of blood-brain barrier integrity, prolonged neuroinflammation, and Aβ clearance, the role of matrix remodeling enzymes in neurodegeneration remains unclear. This study aimed to investigate the influence of APOE ε4 carrier status on plasma MMP-9, TIMP-1 levels, and hippocampal volume, and to assess the correlation between MMP-9/TIMP-1 ratio with hippocampal volumetric measurements in patients with dementia due to Alzheimer's disease (AD).
Methods: We enrolled 53 patients with probable dementia due to AD. The positivity of selected CSF AD biomarkers was determined using the A/T/N classification. Brain magnetic resonance imaging (MRI) was performed according to the dementia protocol, and hippocampal volumetry was analyzed using Vol2Brain. Plasma MMP-9 and TIMP-1 levels were determined by ELISA. APOE rs429358 and rs7412 were analyzed using the Real-Time PCR method with allele-specific TaqMan assays, followed by the analysis of APOE ε2/ε3/ε4 allele carrier status.
Results: Volumetric analysis based on brain MRI scans showed that APOE ε4+ patients exhibited a decline in hippocampal volume, including total volume (p=0.008), total/intracranial volume (ICV)(p=0.008), right hippocampus (p=0.002), right/ICV (p=0.000), and left hippocampus (p=0.033), when compared to APOE ε4- patients. Although we didn't find a significant difference in levels of plasma MMP-9, TIMP-1, and MMP-9/TIMP ratio between APOE ε4+ and APOE ε4- patients, we observed a positive correlation between the plasma MMP-9/TIMP-1 ratio and the Asymmetry Index (AI) of hippocampus in volumetry, as a neuroradiological biomarker of disease progression (r= 0.437; p=0.018).
Conclusions: Our findings suggest that the MMP-9/TIMP-1 ratio may be involved in neurodegeneration and could potentially serve as a promising plasma biomarker for monitoring disease progression in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0606 / #2646

Poster Topic: *Theme A: β-Amyloid Diseases / A06.b. Cell, Molecular and Systems Biology: ApoE*

MOLECULAR AND BEHAVIORAL EFFECTS OF APOE4 FRAGMENTATION IN TRANSGENIC ZEBRAFISH

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

Troy Rohn, Emily Egan, Sofi Leon-Gonzalez, Alex Lafollette
Boise State University, Biological Sciences, Boise, United States of America

Aims: Of the genetic risk factors identified, the 34 kDa protein, apolipoprotein (Apo) E4, is of significant importance as *APOE4* carriers account for 65-80% of all AD cases. Although ApoE4 plays a normal role in lipoprotein transport, how it contributes to AD pathogenesis is currently unknown. The overall objective of this project is to determine the potential deleterious effects of an endogenously generated 151 amino-terminal fragment of ApoE4 ($nApoE4_{1-151}$) Zebrafish.
Methods: We propose to generate a new zebrafish strain that expresses $nApoE4_{1-151}$ to determine whether low-level chronic expression leads to developmental and behavioral impairments. By employing a Tol2 transposase method, we have generated a permanent transgenic zebrafish line that can now be bred indefinitely to allow for the study of deleterious effects from embryos into adulthood. Using such a model, we hypothesize that the $nApoE4_{1-151}$ fragment will demonstrate significant developmental abnormalities, motor dysfunction, and memory impairments that will further support a novel role of this fragment in the etiology associated with AD.
Results: •Confocal microscopy showed strong immunofluorescent labeling of the $nApoE4_{1-151}$ within the CNS of mutant zebrafish •T-maze behavioral studies indicated both color preference and enriched environment of wild-type zebrafish as compared to $nApoE4_{1-151}$ fish. •$nApoE4_{1-151}$ zebrafish show a significant decrease in survivorship as compared to wild-type fish
Conclusions: Although it is well established that inheritance of the *APOE4* allele increases the risk of AD the mechanism of how this protein contributes to AD pathogenesis remains unknown. Our findings in $nApoE4_{1-151}$ mutant zebrafish provide proof-of-concept *in vivo*, that this amino-terminal fragment induces toxicity and behavior deficits. These data provide further support for the novel role of this important risk factor in the etiology associated with AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0607 / #1986

Poster Topic: *Theme A: β-Amyloid Diseases / A06.b. Cell, Molecular and Systems Biology: ApoE*

DETERMINING HOW COMPLEX INTERACTIONS BETWEEN APOE ALLELIC SERIES AND GENETIC BACKGROUND CONTRIBUTE EARLY TO ALZHEIMER'S DISEASE RISK

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

Kristen Onos[1], Asli Uyar[2], Kelly Keezer[1], Kevin Elk[1], Ravi Shanker Pandey[2], Kierra Eldridge[3], Scott Persohn[3], Amanda Bedwell[3], Mike Sasner[1], Gregory Carter[2], Paul Territo[3], Gareth Howell[1]
[1]The Jackson Laboratory, Research, Bar Harbor, United States of America, [2]The Jackson Laboratory, Research, Farmington, United States of America, [3]Indiana University, School Of Medicine, Indianapolis, United States of America

Aims: OBJECTIVES: Apolipoprotein E4 is the strongest genetic risk factor for late-onset Alzheimer's disease(AD), leading to an 3-12x increase dependent on copy number, and significant decrease in age of onset. APOE is implicated to play central roles in multiple pathways such as neuroinflammation, lipid metabolism and vascular health. E4 has also been identified as an independent risk factor for Type-2 diabetes and cardiovascular disease. Here, we aimed to identify how differences in copy number and genetic context may interact to elevate risk for AD.
Methods: METHODS: We performed a comprehensive analysis of neurovascular coupling in aging in $APOE^{3/3}$, $APOE^{4/4}$ and $APOE^{3/4}$ animals. PET/MRI measures of ^{64}Cu-PTSM, blood-flow and ^{18}F-FDG, glucose uptake were utilized. Furthermore, we introduced APOE4 into genetically diverse mouse strains that had previously been shown to be resilient or susceptible to amyloid-induced neuronal loss. Neuropathology and brain transcriptomics were performed across multiple strains.
Results: RESULTS: PET/MRI data collected across 27 brain regions was analyzed per tracer as well as combined into a novel measure of neurovascular metabolic uncoupling. Age, sex and APOE genotype directly contributed to significant disruptions in blood-flow and metabolism, with $APOE^{3/4}$ exhibiting earlier and more severe Type II uncoupling. In genetically diverse strains carrying $APOE^{4/4}$, the PWK background showed the greatest transcriptomic change and impact to neuronal health despite previously being shown to be resistant to age-related synaptic loss and resilient to amyloid-induced neuronal loss.
Conclusions: CONCLUSIONS: Overall, these combined data highlight new ways to identify early metabolic changes in novel mouse models of APOE, as well as the importance of assessing risk alleles for AD in a variety of genetic contexts. These approaches hold great promise for identification and development of novel therapeutic targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0608 / #963

Poster Topic: *Theme A: β-Amyloid Diseases / A06.b. Cell, Molecular and Systems Biology: ApoE*

APOE ISOFORM-DEPENDENT MODULATION OF HIGH-FAT DIET EFFECTS IN THE MOUSE BRAIN

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

Sun Ah Park[1,2], Kyeong Jae Lee[1], Pyeong Jun Choi[1], Hyuna Jeon[1], Jin Kim[1]
[1]Ajou University School of Medicine, Anatomy, Suwon, Korea, Republic of, [2]Ajou Univeristy, Neurology, Suwon, Korea, Republic of

Aims: Alzheimer's disease (AD) is influenced by both genetics and environmental factors. Among genetic risk factors, ApoE4 allele is the most significant predictor of AD. Additionally, midlife obesity is known to increase the risk of AD. This study aims to investigate the interplay between a high-fat diet (HFD)-induced obesity and the ApoE4 isoform in the brain.
Methods: We utilized human ApoE3 knock-in, ApoE knockout (KO), and ApoE4 knock-in mice to distinguish the effects specific to the ApoE isoform from those specific to ApoE itself. These mice were either fed a HFD or a normal regular diet (ND) for six months, starting at three months of age. We conducted behavioral tests, magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI), and tissue analysis to assess the impact of chronic HFD on the brain, depending on the ApoE isoform.
Results: Weight gain due to HFD was observed in all ApoE genotype groups. However, HFD led to an increase in glycated hemoglobin levels only in ApoE4 mice, not in ApoE3 and KO mice. Nest-building performance declined in ApoE4 and KO mice on HFD. DTI-MRI revealed disrupted neural integrity in response to HFD, primarily in ApoE4 knock-in mice. Western blot analysis showed consistently lower levels of lipidation and apoE protein in the cortex of ApoE4 mice compared to ApoE3 mice, regardless of HFD intake. Furthermore, synaptic and inflammatory markers exhibited apoE isoform-specific differences, not HFD-dependent changes. In different to these, the examination of axon skeletal proteins revealed a HFD-specific change: reduced levels in ApoE4 mice in response to HFD.
Conclusions: It provides the evidence that HFD feeding has differential effects on the mouse brain depending on the ApoE isoform, particularly increasing white matter pathology in ApoE4 mice.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0609 / #1796

Poster Topic: *Theme A: β-Amyloid Diseases / A06.a. Cell, Molecular and Systems Biology: APP, APLP, Abeta*

THE MITOCHONDRIAL PHOSPHATASE PGAM5 IS A NOVEL INTERACTOR OF THE AMYLOID PRECURSOR PROTEIN

POSTERS: A06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APP, APLP, ABETA

Kriti Shukla[1], Zhi Zhang[2], Charles Lacy[1], Dylan Barber[1], Samah Houmam[1], Jialing Lin[2], Heather Rice[1]
[1]University of Oklahoma Health Sciences Center, Center For Geroscience & Healthy Brain Aging, Oklahoma City, United States of America, [2]University of Oklahoma Health Sciences Center, Biochemistry & Molecular Biology, Oklahoma City, United States of America

Aims: In ongoing clinical trials, APP is being targeted by RNAi to reduce amyloid-beta levels to treat AD. However, not only does this reduce amyloid-beta but also full-length APP and its other fragments, such as CTF and sAPP. Thus, it is critical that we fully understand the functions of APP and its proteolytic products. In our previous study (Rice et al., 2019), we performed an unbiased proteomics screen for interactors of the APP ectodomain and found that the GABA B receptor and phosphoglycerate mutase family member 5 (PGAM5) were among the top candidates. Here, we aimed to investigate PGAM5, a mitochondrial phosphatase, as a candidate interactor of the APP ectodomain.
Methods: In vitro binding assays were used to confirm binding of APP and PGAM5 and to determine the domains required for binding. Subcellular fractionation of HeLa cells were performed to determine the subcellular localization of these proteins. Proximity ligation assays were used to determine the subcellular location of this interaction in mouse primary cell cultures and brain slices.
Results: The N-terminal region of PGAM5 interacts with the linker region of APP in vitro. PGAM5 is enriched in mitochondria and mitochondrial associated ER membranes (MAMs), full-length APP is enriched in MAMs, and APP CTF is enriched in mitochondria. APP and PGAM5 interact in primary neurons and astrocytes as well as brain slices, and this interaction likely occurs in MAMs.
Conclusions: We demonstrate that endogenous APP interacts with PGAM5 in multiple cell types of the brain. Ongoing work is aimed at determining the effect of this interaction on mitochondrial dynamics in health and in AD. This will lead to a better understanding of the potential consequences of targeting APP for the treatment of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0610 / #524

Poster Topic: *Theme A: β-Amyloid Diseases / A06.b. Cell, Molecular and Systems Biology: ApoE*

RECOGNITION OF ISLET AMYLOID POLYPEPTIDE'S EPITOPES IS IMMUNOGLOBULIN- AND APOE ISOTYPE-DEPENDENT

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

Dovile Poceviciute[1], Anders Olofsson[2], Bodil Roth[3], Malin Wennström[1]
[1]Lund University, Department Of Clinical Sciences, Malmö, Sweden, [2]Umeå University, Department Of Medical Biochemistry And Biophysics, Umeå, Sweden, [3]Lund University, Internal Medicine, Malmö, Sweden

Aims: Autoantibody clearance of oligomeric islet amyloid polypeptide (IAPPo) is crucial as increased plasma levels of IAPPo can induce microvascular alterations and amyloid beta depositions in the brain. The clearance is dependent on the exposure and specificity of epitopes, where epitopes in the N-terminal, but not C-terminal, are exposed when the peptide oligomerizes. Previously, we have showed that individuals carrying the *APOE4* demonstrate reduced amounts of IgA (but not IgG or IgM) against IAPPo, suggesting a specific impediment in IgA clearance of IAPPo in these individuals. Currently, we aim to investigate if this Ig- and *APOE* isotype-dependent impact can be explained by differences in epitope recognition.
Methods: The plates were coated with six IAPP peptides (P) representing the following fragments of the IAPP (1-37) sequence: P1 (1-15), P2 (6-20), P3 (11-25), P4 (16-30), P5 (21-35), P6 (26-37). Thereafter, plasma from non-demented controls (NCs) carrying *APOE33* (n=6) and AD patients carrying *APOE33* (n=6) and *APOE44* (n=6) was applied, followed by an incubation with either anti-IgA or anti-IgG secondary antibodies.
Results: While IgG in plasma from all individuals bound solely to P6, IgA bound to all six peptides, but with an increasing binding towards the C-terminal (P1<P2<P3<P4<P5<P6). Levels of IgA against P1 and P2 in AD with *APOE44* were lower (p=0.0887) and significantly lower, respectively, than the levels in NC with *APOE33.*
Conclusions: Our data indicate an Ig isotype-dependent binding to IAPP epitopes and that some IgA-specific epitopes are still exposed when IAPP oligomerizes. However, the binding to these exposed epitopes is decreased in *APOE44* carriers. We, therefore, speculate that the reduction in IAPPo-IgA levels seen in our previous studies is due to IgA-IAPP epitope specificity which is affected by oligomerization and *APOE* isotype.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0611 / #1892

Poster Topic: *Theme A: β-Amyloid Diseases / A06.d. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

METALS MODULATE PROTEIN PHOSPHATASES IMPACTING ALZHEIMER'S DISEASE RELATED PROTEINS

POSTERS: A06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

André Nadais, Steven Alves, Ana Gabriela Henriques, Odete Da Cruz E Silva
Institute of biomedicine, Department Of Medical Sciences, University Of Aveiro, Aveiro, Portugal

Aims: Alzheimer´s Disease (AD) is histopathologically characterized by hyperphosphorylation of tau protein and Aβ peptide deposition, thus forming intracellular neurofibrillary tangles (NFTs) and extracellular senile plaques (SPs), respectively. Moreover, the hyperphosphorylated states that occur in amyloid β-precursor protein (APP) and tau can result from imbalanced activities of protein phosphatases (PPs) and protein kinases (PKs) observed in AD. Additionally, SPs found in AD patients contain Zn2+, Cu2+, Al3+ and Fe3+ and previous studies have demonstrated that some metals affect both PPs and PKs activity impacting tau and APP phosphorylation. However, the correlation between metals, protein phosphorylation and AD pathology has not been fully elucidated and will be addressed in the work here presented.
Methods: *In vitro* (cell-based experiments and protein analysis) and *in silico* methods were employed to unravel the potential role of metals in AD relevant proteins.
Results: The results showed that Zn2+ and Cu2+ promote an increase in protein phosphatase 2A (PP2A) activity as well as a decrease of Glycogen Synthase Kinase 3β (GSK3β), resulting in decreased tau phosphorylation. On the other hand, with Al3+ and Fe3+, APP phosphorylation and metabolism were compromised as well as an increase in tau phosphorylation. These effects can be potentially mediated by alteration of PP1/PP2A and GSK3β activity. Moreover, using bioinformatic tools, 81 metal binding proteins, that also bind to PP1 or PP2 and that are associated with AD were identified. These represent interesting candidates for future studies among them the Glutamate Receptor Ionotropic, NMDA 2B (GluN2B).
Conclusions: This study opens the door to the use of Zn2+ and Cu2+ as potential modulators of protein phosphatases and NMDAR activity, preventing the excitotoxicity, synaptic dysfunction, and tau hyperphosphorylation observed in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0612 / #1249

Poster Topic: *Theme A: β-Amyloid Diseases / A06.d. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

DEEP LEARNING RESOLVES CELL-TYPE SPECIFIC TRANSCRIPTOMES IN MOUSE HIPPOCAMPUS AND UNVEIL SYNAPTIC CHANGES AFTER EXPOSURE TO AN EXCITOTOXIN.

POSTERS: A06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

Eloise Berson[1], Amalia Perna[2], Thanaphong Phongpreecha[2], Nima Aghaeepour[3], Thomas Montine[2]
[1]Stanford, Pathology, Palo Alto, United States of America, [2]Stanford, Pathology, PaloAlto, United States of America, [3]Stanford, Anesthesia, PaloAlto, United States of America

Aims: Single nucleus RNA sequencing (snRNA-seq) has revolutionized our ability to dissect transcriptional profiles in specific cell types. However, it captures only 20-50% of the cellular transcriptional information, limiting our comprehensive understanding of the cellular transcriptional ensemble. Therefore, we propose a computational approach to extract the cellular signal from brain tissue bulk transcriptomic data, allowing us to investigate cell type-specific transcriptomic programs underlying neurodegeneration.
Methods: We adapted Cellformer - a deep learning deconvolution model for ATAC-seq data - to RNA-seq data. We leverage an excitotoxicity mouse model to detect cell-type specific transcriptomic responses to injury.
Results: Cellformer accurately deconvoluted mouse brain bulk RNA into 9 major cell types (mean Pearson correlation of 0.97) (Figure 1A). Validation with single nucleus datasets reveals a significantly higher correlation (0.85) within the same cell type compared to different cell types (0.20) (P-value < 1e-6) (Figure 1B). We applied Cellformer to bulk RNAseq data obtained from both tissue and nuclei isolated from the same mouse hippocampus. We compared these cell-type-specific transcriptomic signatures between healthy mice and those exposed to a low dose of Kainic Acid (KA), a potent toxin for excitatory neurons (Figure 1C). More shared information was found between snRNA and deconvoluted RNA from nuclei compared to deconvoluted tissue (Figure 1D). Interestingly, differential expression analysis revealed a greater effect of low-dose KA exposure on deconvoluted bulk tissue compared to nuclei, pinpointing synaptic and lysosomal signaling to excitatory neuronal cells (Figure 1E-F).
Conclusions: We introduce a computational approach using Cellformer to deconvolute bulk RNA sequencing data into cell-type-specific profiles, enabling in-depth analysis of bulk RNAseq. By comparing deconvoluted profiles between healthy and injured hippocampi, we unveil insights previously masked by the limitations of snRNA-seq, revealing intricate synaptic signaling dynamics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0613 / #2927

Poster Topic: *Theme A: β-Amyloid Diseases / A06.d. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

EXPLORING ORGANELLE-SPECIFIC ROLES FOR PRESENILINS USING INTERACTOME PROFILING

POSTERS: A06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

Céline Vrancx[1], Rosanne Wouters[1], Ragna Sannerud[1], Iván Ramos Calvo[1], Anika Perdok[1], Francis Impens[2], Wim Annaert[1]
[1]VIB KU Leuven Center for Brain & Disease Research, Laboratory For Membrane Trafficking, Leuven, Belgium, [2]VIB-UGent Center for Medical Biotechnology, Proteomics Expertise Core, Ghent, Belgium

Aims: Presenilins (PSEN) 1 and 2 act as the catalytic core of γ-secretase, playing a pivotal role in the onset and progression of Alzheimer's disease (AD). We previously demonstrated that, opposed to the broad localization of PSEN1/γ-secretase at the cell surface and in endosomes, PSEN2 is restricted to late endosomes/lysosomes (LE/Lys). Interestingly, the endolysosomal system has been recognized a central vulnerable mechanism in AD for decades, owing to its early defects and functionally related genetic risk variants. This project aims to unravel whether the homologue-specific subcellular localization reflects PSEN1- and PSEN2-specific functions in organellar homeostasis.
Methods: We generated cell lines expressing either GFP- or APEX2-tagged versions of PSEN with the aim to identify specific interactors hinting at functional roles in distinct organelles. This allowed us to combine two orthogonal interactomics methods, i.e. affinity purification with the GFP-tag and proximity-dependent biotinylation with the APEX2-tag. Identified hits were prioritized based on their functional relevance to organellar homeostasis and next validated for their interaction using biochemical approaches and super-resolution imaging.
Results: Although some common interactors were identified, we found the PSEN1 interactome being more enriched for cell surface localized proteins whereas PSEN2/γ-secretase interactors related more to endolysosomal functions, including lysosomal transport/motility and nutrient sensing. Using super-resolution imaging and functional assays, we confirmed that PSEN2 participates in lysosomal positioning in response to e.g. nutrient availability, with its deficiency impairing these two intrinsically connected molecular pathways.
Conclusions: Our observations specifically link PSEN2/γ-secretase to endolysosomal functioning, providing new starting points for a better understanding on the etiology of endolysosomal dysfunctions which appear at early, preclinical stages of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0614 / #1648

Poster Topic: *Theme A: β-Amyloid Diseases / A06.d. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

SEX-LINKED TRANSCRIPTION FACTORS ZFX AND ZFY REGULATE MICROGLIAL EXPRESSION STATES AND DISEASE-RELATED GENES

POSTERS: A06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

Logan Brase[1], Yanbo Yu[1], Oscar Harari[1], Bruno Benitez[2]
[1]Washington University in St. Louis, Psychiatry, St. Louis, United States of America, [2]Harvard Medical School and Beth Israel Deaconess Medical Center, Neurology, Boston, United States of America

Aims: Objectives: Microglia can exhibit different expression states in Alzheimer disease (AD). Using gene regulatory networks, we sought to determine the key regulatory elements for specific microglia states and how these regulatory differences could influence AD.
Methods: Methods: We ran pySCENIC 100 times for each of five unique microglia states in discovering and replicating single nucleus RNA-seq datasets to identify consensus transcription factors (TF) and their target genes. We accessed ChIP-seq data from ChIP-Atlas[1] and isolated the MACS2 binding scores for TFs *ZFX* and *ZFY* in the HepG2 cell line. We compared the binding affinity across all target genes and the transcriptome, then used Cook's Distance to identify genes deviating from the line of best fit.
Results: Results: We identified 78 TFs that replicated across all microglia states, including TFs unique to each resting, activated, *TREM2*-reduced activation, *MS4A*-proinflammatory, and necroptosis states. *ZFX* uniquely regulated the activated state, and *ZFY* the *MS4A*-proinflammatory. These are orthologous TFs on the sex chromosomes that encode zinc-finger proteins with known residue differences in 5 of the 13 zinc-finger domains[2]. We compared the binding affinity for *ZFX* and *ZFY* to the target genes identified by pySCENIC. In general, we observed a stronger affinity from *ZFY* than *ZFX* (slope = 1.08), including for *RALGAPB,* an autism-linked gene[3]. A transcriptome-wide version of this analysis identified the strongest binding affinity difference in *NPAS4,* a gene negatively associated with Tau Braak stage[4], regulated by *APP*[5], and responsible for regulating neuronal plasticity[6].
Conclusions: Conclusions: We discovered that *ZFX* and *ZFY*, two TFs on the sex chromosomes, regulate microglia states and disease-related genes, *RALGAPB* and *NPAS4*. These findings may have implications for sex differences and therapeutic strategies in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0615 / #927

Poster Topic: *Theme A: β-Amyloid Diseases / A06.d. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

PATHWAY TRACING: KNOWLEDGE GRAPHS FROM GENE LISTS

POSTERS: A06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

Stephen Keegan[1], Gregory Cary[1], Jesse Wiley[2], Gregory Carter[1]
[1]The Jackson Laboratory, The Jackson Laboratory, Bar Harbor, United States of America, [2]Sage Bionetworks, Sage Bionetworks, Seattle, United States of America

Aims: The TaRget Enablement to Accelerate Therapy Development for AD (TREAT-AD) consortium is missioned to provide tools to the Alzheimer's research community for the discovery of novel therapeutics. Here we establish methods for developing knowledge graphs summarizing Alzheimer's disease (AD) endophenotypes.
Methods: The Pathway Commons Database contains information about biological pathway and interaction data. Using genes as nodes and the pathway and interaction data as edges, the topography of the network is established. A query gene list is used as input and the shortest path network reconstruction is the output. Data from the Accelerating Medicines Partnership® Program for Alzheimer's Disease (AMP-AD) is encoded into the knowledge graph as node and edge features. Filters, like cell type specificity, can be used to constrain the scope of the graph reconstruction.
Results: Analysis of genetic targets for AD is enhanced by constructing pathway interaction networks describing the relationships between genes. Using a reconstructed network as the basis for a suite of network analysis tools identifies relationships between genes and potential therapeutic targets. Networks derived from genes involved in the biological domains such as lipid metabolism, autophagy, and synapse are more informative than a random set of genes being traced.
Conclusions: Knowledge graphs derived from a list of genes are generated to enable network level understanding of the genes of interest. The relationships between genes that are annotated to a phenotype can be visualized and analyzed further as a network than they can in just a list form. Understanding the network effects of gene targets is imperative for identifying AD therapeutic targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0616 / #1785

Poster Topic: *Theme A: β-Amyloid Diseases / A06.d. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

ENRICHMENT OF SYNCHRONOUS GENES RELATED TO ALZHEIMER'S USING DUO

POSTERS: A06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

Bryce Paubel, Olivia Biswas, Divine Akinjiyan, Sharlee Climer
University of Missouri-St. Louis, Computer Science, St. Louis, United States of America

Aims: WGCNA, weighted correlation network analysis, is a network analysis tool that is widely used to identify combinations of genes that appear to have correlated expressions in the presence of a given phenotype. However, its network model conflates high and low expression and the correlation metric utilized doesn't adapt to phenotype heterogeneity. Herein, we apply a robust network analysis tool, Duo, to analyze gene expression data in the context of late-onset Alzheimer disease (AD).
Methods: AD gene expression dataset GSE132903 was downloaded from GEO Omnibus and split into Discovery (58 cases and 49 controls) and Validation (39 cases and 39 controls) such that sex was evenly balanced. Duo generated a network with communities of inter-correlated genes and identified significant communities. Finally, these communities were tested on the unseen Validation data.
Results: We identified five statistically significant groups of highly synchronized genes. The cardinalities of these communities ranged from 2 to 23 genes and exhibited odds ratios of **0.17** [95%CI: 0.05,0.54], **15.56** [95%CI: 3.88,16.00], **7.86** [95%CI: 3.43,18.03], **4.11** [95%CI: 1.89,8.95], **12.11** [95%CI: 4.82,30.43] in the Discovery data and **0.21** [95%CI: 0.05,0.83], **3.18** [95%CI: 1.13,8.97], **4.02** [95%CI: 1.56,10.32], **3.20** [95%CI: 1.27,8.09], **5.26** [95%CI: 1.69,16.30] in the Validation data.
Conclusions: Two of the significant communities included genes with known AD associations. Community 3 with 23 nodes includes *TTBK1*, which is a kinase that phosphorylates tau. Additional interesting genes include *UBTD1*, which is involved in cellular senescence, and *MKNK2* and *CACTIN*, which are involved in stress response. Community 10 with 6 nodes includes both *PRKX* and *TNS1*, which have been previously associated with AD risk. These results reveal highly synchronous genetic patterns that are significantly associated with AD in both Discovery and Validation datasets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0617 / #777

Poster Topic: *Theme A: β-Amyloid Diseases / A06.b. Cell, Molecular and Systems Biology: ApoE*

NOVEL KLOTHO MOUSE MODELS TO EXAMINE PROTECTION AGAINST APOE4 RISK FOR ALZHEIMER'S DISEASE

POSTERS: A06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: APOE

Mike Sasner[1], Christoph Preuss[1], Dylan Garceau[1], Kevin Kotredes[1], Ravi Shanker Pandey[2], Gregory Carter[1]
[1]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America, [2]THE JACKSON LABORATORY, For Genomics Medicine, FARMINGTON, United States of America

Aims: Several large-scale genetic studies have identified a common haplotype of the aging factor *klotho* that modifies disease risk specifically in APOE4 carriers. In humans, *klotho* harbors two common missense variants (*rs9536314*, p.F352V; *rs9527025*, p.C370S) that define the *klotho* V/S (KL-V/S) haplotype, which is protective against LOAD in APOE4 carriers, and the *klotho* F/C (KL-F/C) haplotype, which is not. We sought to understand this genetic interaction using novel mouse models.
Methods: We replaced the native mouse haplotype with protective KL-V/S and common KL-F/C haplotypes. To validate the effects of these *klotho* haplotypes, soluble klotho serum levels of young mice were compared using ELISA. We also measured klotho in amyloidogenic *App*^{SAA} mutant mice. Transcriptomic analysis on brain hemispheres was performed at 4 and 12 months of age.
Results: Secreted klotho was decreased in KL-F/C mice harboring the novel mouse risk haplotype when compared to B6 controls and KL-V/S mice. In contrast, KL-V/S mice showed no significant differences in soluble klotho serum levels when compared to B6 controls. Secreted klotho levels in KL-V/S mice were significantly elevated when compared to the *App*^{SAA} mice, whereas KL-F/C mice showed similar levels to the aged *App*^{SAA} model. Transcriptomic analysis revealed significant differential gene expression between the homozygous klotho genotypes, particularly in genes involved in metabolic pathways and in genes associated with AD.
Conclusions: Taken together, these data suggest the native mouse *klotho* allele acts similarly to the protective KL-V/S haplotype, while the KL-F/C haplotype leads to lower secreted klotho and potentially greater disease risk. These models are therefore suitable to elucidate how *klotho* variants protect from LOAD pathologies and will enable detailed studies of how this protection is specific to the APOE4 genotype.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0618 / #1719

Poster Topic: *Theme A: β-Amyloid Diseases / A06.d. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

INTERACTION BETWEEN HIPPO PATHWAY ELEMENTS AND THE E3-LIGASE CHIP REGULATES A POTENTIAL MARKER OF ALZHEIMER`S DISEASE

POSTERS: A06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

Melek Suluova, Kathryn Ball, Erisa Nita
The University of Edinburgh, Institute Of Genetics And Cancer, Edinburgh, United Kingdom

Aims: Aim: CHIP has a role in the ubiquitin-proteasome system to maintain cellular proteostasis in stress conditions. VGF is a neuronal precursor protein whose peptide-derivatives have various roles in the neuronal cells including energy homeostasis and synaptic plasticity. The transcriptional coactivator YAP1, a known CHIP substrate, that has a role in the regulation cell proliferation, tissue homeostasis and stem cell maintenance, was investigated as a potential link between CHIP and VGF which is 10X higher in CHIP KO neuroblastoma cells (our unpublished data).
Methods: Method: (1) Previously, CRISPR-Cas9 method was used to create CHIP KO neuroblastoma cell line. Then proteomic data of CHIP KO and WT neuroblastoma cells was obtained by SWATH-MS. VGF data was validated by immunoblot and IF. (2) YAP1 level and localization were assessed in both cell group. (3) RNAi method was used for YAP1 silencing, then analysis was done via immunoblot and IF. (4) Additionally, pathway analysis of upregulated and downregulated hits of the proteomics data plus YAP1 was applied.
Results: Result: (1) Based on proteomic data, CHIP KO neuroblastoma cells have 10X more VGF protein level than isogenic WT cells, validation was done by immunoblot and IF. (2) YAP1 expression and nuclear localization are higher in CHIP KO neuroblastoma cells. (3) YAP1 manipulation showed impact on the VGF expression in CHIP KO neuroblastoma cells. (4) Pathway analysis of proteomics hits plus YAP1 showed both VGF and YAP take role in organismal development pathways and stress response.
Conclusions: Conclusion: CHIP modified Hippo element YAP1 potentially can have role in VGF regulation. As VGF is an Alzheimer's disease biomarker, discovering new elements of its regulation mechanisms could support efforts to find new targets for the development of disease modifying drugs."

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0619 / #456

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

CHARACTERIZATION OF GLOBAL METHIONINE OXIDATION IN A FAMILIAL MODEL OF ALZHEIMER'S DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Filipa Blasco Tavares Pereira Lopes[1], Daniela Schlatzer[1], Rihua Wang[2], Xin Qi[2], Mehmet Koyutürk[3], Mark Chance[1]
[1]Case Western Reserve University, Center For Proteomics And Bioinformatics, Cleveland, United States of America, [2]Case Western Reserve University, Department Of Physiology & Biophysics, Cleveland, United States of America, [3]Case Western Reserve University, Department Of Computer And Data Sciences, Cleveland, United States of America

Aims: Methionine oxidation is a frequent occurrence in the ROS-rich brain, which can be reversed by methionine sulfoxide reductase (Msr). Since Msr is downregulated in AD patients and causes accumulation of methionine-oxidation, we believe that characterizing the methionine-oxidized proteome will provide clinically relevant information regarding AD pathogenesis.
Methods: The present research provides label-free methionine-oxidized proteome measurements of mouse hippocampus with a design including variables of: time (3, 6, and 9 months), genetic background (5XFAD vs. WT) and sex (male and female).LC-MS/MS was acquired by Waters NanoAcquity UPLC coupled to a Thermo Scientific™ Elite Orbitrap Elite™ mass spectrometer. Raw LC-MS/MS data was processed using Peaks, Scaffold and Protmap.
Results: We detected an age-dependent increase in global oxidation in both WT and 5XFAD mice, corroborating previous studies that found accumulation of oxidized proteins in healthy older adults. Additionally, 5XFAD mice show significantly higher expression of oxidized peptides at six and nine months, meaning that the oxidation burden is both age and disease dependent in this model. Enrichment pathway analysis revealed that glucose metabolism, recycling pathway of L1, and neurotransmitter release cycle are the main pathways involved in the AD-dependent oxidation as reflected by methionine sulfoxide profiling. While exploring our dataset of significantly expressed oxidized peptides, we found multiple proteins to be almost exclusively expressed in 5XFAD mice in oxidized forms. Using Protmap, we further validated which of these ox-peptides display a significantly higher oxidized fraction than all other proteins detected to be oxidized.
Conclusions: We have longitudinally characterized the methionine sulfoxide abundance and stoichiometry speciation in 5XFAD mice. Altogether, our characterization of 5XFAD's oxidized proteome provides insight on oxidation-impacted molecular mechanisms and identifies several methionine-oxidized proteins as a potential clinical target for antioxidant AD therapy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0620 / #1244

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

A COMPLETE PIPELINE FOR HIGH-PLEX SPATIAL PROTEOMIC PROFILING AND ANALYSIS OF NEURAL CELL PHENOTYPES ON A SPATIAL MOLECULAR IMAGER AND A SPATIAL INFORMATICS PLATFORM.

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Shilah Bonnett[1], Alyssa Rosenbloom[1], Tien Phan-Everson[1], Zachary Lewis[1], Giang Ong[1], Liu Liu Pan[2], Aster Wardhani[1], Mithra Korukonda[1], Edward Zhao[1], Sangsoon Wu[1], Jason Reeves[1], Christine Kang[1], Gary Geiss[1], Joseph Beechem[1], Yan Liang[1], Carl Brown[1], Dwayne Dunaway[1], Erin Piazza[1], Vikram Devgan[1], John Lyssand[1]
[1]NanoString(R) Technologies, Inc, R&d, Seattle, United States of America, [2]NanoString Technologies, Not Applicable, Seattle, United States of America

Aims: The brain is complex and heterogeneous where cell function and cell-to-cell communication are critical for rapid and accurate performance. The ability to explore protein-driven activities at high resolution within the spatial context of their immediate environment is critical to gaining comprehensive pictures of brain development, activity, aging, disease or dysfunction, and inflammatory responses. Many existing approaches for high-plex single-cell spatial proteomics face issues around simplicity, speed, scalability, and big data analysis.
Methods: Here, we present an integrated workflow that addresses key concerns around high-plex proteomics. The CosMx™ Spatial Molecular Imager and AtoMx™ Spatial Informatics Platform comprise an end-to-end workflow that efficiently handles highly multiplex protein analysis at plex-sizes >68 targets. The CosMx protein assays use oligonucleotide-conjugated antibodies, that are detected using universal, multi-analyte CosMx readout reagents. The CosMx Mouse Neural Cell Typing and Alzheimer's Pathology panels, are optimized to comprehensively profile neural cell lineages across the brain as well as the progression of Alzheimer's disease.
Results: The CosMx protein assay reagents were validated on the FFPE adult mouse brain, mouse embryo, and Alzheimer's positive human brain. We used the CosMx protein panels with the CosMx SMI to identify multiple neuronal subtypes, reactive states of astrocytes and microglia, cell degeneration and proliferation. In a single-cell exploration of mitochondria, we noted distinct patterning of key immune targets based on their immediate microenvironment.
Conclusions: CosMx SMI is a high-plex spatial multi-omics platform that enables the detection of >68 proteins at subcellular resolution. In combination with the high-plex CosMx Mouse Neural Cell Typing and Alzheimer's Pathology panels, we present a robust solution for comprehensive neural and disease phenotyping that captures the complexity of neuronal and glial cellular activity with full spatial context.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0621 / #709

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

COMPREHENSIVE METABOLOMIC PROFILING OF IN VIVO CEREBRAL BETA-AMYLOID DEPOSITION IN NONDEMENTED INDIVIDUALS

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Min Soo Byun[1], Da Jung Kim[2,3], Jun Ho Lee[1], Dahyun Yi[4], Joo-Youn Cho[2], Dong Young Lee[1]
[1]Seoul National University College of Medicine and Seoul National University Hospital, Department Of Psychiatry, Seoul, Korea, Republic of, [2]Seoul National University College of Medicine and Hospital, Department Of Clinical Pharmacology And Therapeutics, Seoul, Korea, Republic of, [3]Biomedical Research Institute, Seoul National University Hospital, Metabolomics Core Facility, Department Of Transdisciplinary Research And Collaboration, Seoul, Korea, Republic of, [4]Seoul National University Medical Research Center, Institute Of Human Behavioral Medicine, Seoul, Korea, Republic of

Aims: It remains unclear whether serum metabolomic signatures can differentiate early accumulation of *in vivo* cerebral beta-amyloid (Aβ), a hallmark neuropathology of AD, before onset of dementia. We investigated serum metabolomic signatures of *in vivo* cerebral Aβ deposition in nondemented individuals using comprehensive metabolomic profiling.
Methods: We recruited nondemented older adults from the Korean Brain Aging Study of the Early Diagnosis and Prediction of Alzheimer's Disease. All participants underwent comprehensive clinical assessment and ^{11}C-PiB-PET, as well as the collection of serum samples from overnight fasting blood. Participants were classified into the Aβ positive (Aβ+) and Aβ negative (Aβ-) groups after quantification of brain regional PiB uptake. For comprehensive metabolomic profiling, we conducted global metabolomics using gas chromatography time-of-flight mass spectrometry and targeted metabolomics using the AbsoluteIDQ® p400 kit (BIOCRATES Life Science AG) with an ultra-high-performance liquid chromatography-quadrupole orbitrap mass spectrometry system.
Results: A total of 247 nondemented older adults were included in the final analysis. Among them, 102 individuals were classified into the Aβ+ group, and 145 individuals were in the Aβ- group. From global metabolomic profiling and targeted metabolomics, we first identified metabolite candidates that showed significant differences between the Aβ+ and Aβ- groups after multiple comparison corrections (FDR-corrected $p<0.05$). Then, we selected five metabolic biomarkers, including Methionine, Threonic acid, 1,3-Butaneiol, L-Phenylalanine and PC-O (25:0) by adjusting a VIP score in the PLS-DA model. The diagnostic accuracy of this metabolic panel to discriminate Aβ positivity among nondemented older adults was 84.2% (CI: 79.2%-89.1%).
Conclusions: Our comprehensive metabolomic profiling found differences in serum metabolic profiles between the Aβ+ and Aβ- groups in nondemented older adults, indicating the serum metabolic signature may reflect *in vivo* cerebral Aβ deposition in this population.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0622 / #2414

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

RELATIONSHIP BETWEEN LIPID PROFILE CHANGES AND ENDOGENOUS NANOPARTICLES IN ALZHEIMER'S DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

William Dartora[1], Ana Paula Costa[1], Krista Wartchow[1], Artur Lazarian[1], Gloria Chiang[1], Nicholas Bartelo[2], Richa Batra[2], Jan Krumsiek[2], Laura Beth Mcintire[1,3]
[1]Brain Health Imaging Institute, Weill Cornell Medicine, Radiology, New York, United States of America, [2]Institute for Computational Biomedicine, Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, New York, Physiology And Biophysics, New York, United States of America, [3]Columbia University Medical Center, Pathology And Cell Biology, New York, United States of America

Aims: We generated a pipeline to analyze lipidomic data and the association with amyloid load, imaging and fluid biomarkers as well as cognitive measures in participants from Alzheimer's Disease Neuroimaging Initiative (ADNI).
Methods: We analyzed lipidomic data from ADNI which included targeted lipidomics and a metabolic panel based on nuclear magnetic resonance (NMR)including endogenous nanoparticles (eNP) composed of apolipoproteins. We determined the association of lipid dysregulation with amyloid load, imaging and fluid biomarkers including hippocampal volume and cognitive metrics including SPELL OUT (CDR-SB) AND MMSE (MMSE). Statistical models were built using linear regression and stratified by ApoE4 status (ApoE4+, harboring one or two ApoE4 alleles and ApoE4-, lacking the E4 allele). and diagnosis, including cognitively normal (CN), Mild Impairment Cognitive (MCI) and AD.
Results: In ApoE4+ individuals, several eNP, including low-density lipoprotein cholesterol ester (LDL-CE), increased with cortical amyloid burden in the temporal, parietal, and cingulate lobe regions. From targeted lipidomic data, both ApoE4+ and ApoE4-, were associated of sphingomyelin (SM) and phosphatidylethanolamine (PE). Several species of lysophosphatidylcholine (LPC) were associated with hippocampal volume, implicating changes in acyl chain remodeling. SM lipids were positively associated with CSF Abeta42 in AD+ participants and was negative associated with cognition in MCI+ participants.
Conclusions: Our findings indicate that eNP and the lipid content are associated with amyloid burden, hippocampal volume, and cognitive outcomes amongApoE4 carriers and non-carriers . Molecular mechanisms and potential for clinical intervention can be revealed by future research of the lipid signature and changes in endogenous nanoparticle content of biofluids.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0623 / #694

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

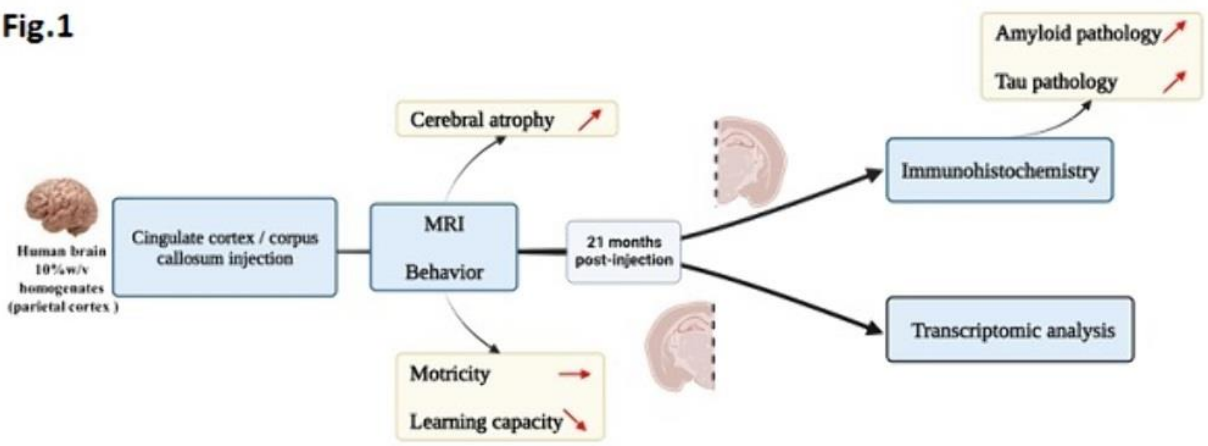
IMPACT OF TAU AND AMYLOID-BETA LESIONS ON THE TRANSCRIPTOME EXPRESSION IN A PRIMATE MODEL OF ALZHEIMER'S DISEASE.

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Leo Dupuis[1,2], Suzanne Lam[1,2], Marie-Claude Gaillard[1,2], Fanny Petit[1,2], Anne-Sophie Herard[1,2], Luc Buee[3], Susana Boluda[4,5], Stéphane Haïk[4,5], Jean-Luc Picq[1,2,6], Marc Dhenain[1,2]
[1]Commisssariat à l'Energie Atomique et aux Energies Alternatives (CEA), Direction De La Recherche Fondamentale (drf), Institut François Jacob, Mircen, Fontenay-aux-Roses, France, [2]UMR 9199 CEA CNRS, Mircen, Fontenay-aux-Roses, France, [3]University of Lille, Lille Neuroscience & Cognition, Inserm U1172, Lille, France, [4]ICM, Umr 7225, Sorbonne Université, Paris Brain Institute-icm, Cnrs, Ap-hp, Hôpital De La Pitié Salpêtrière, Inserm U1127 Dmu Neurosciences, Paris, France, [5]Brainbank NeuroCEB Neuropathology Network, Hôpital De La Pitié-salpêtrière, Paris, France, [6]Laboratory of Cognitive Functioning and Dysfunctioning (DysCo), University Of Paris 8, Saint-Denis, France

Aims: Transcriptomic approach is widely used to study changes of gene expressions in reaction to Alzheimer's Disease (AD) pathology. Most studies involve rodents but their transcriptomic profile is relatively different from humans during AD. In consequence, animal models closer of the humans are required. This work aims to study the impact of AD human brain inoculation on the transcriptomic expression of a primate model.
Methods: We induced β-amyloid (Aβ) and tau lesions in a primate (Microcebus murinus) following intracerebral inoculation of AD brain extracts (n=12)(Lam, Acta Neuropathol Com, 2021)(Fig.1). Animals inoculated with control brain extracts were used as controls (n=6). They did not display amyloid or tau lesions. Bulk transcriptomic expression was assessed by RT-qPCR 21 month after brain extracts inoculation (Fig.2). We focused on the hippocampus, entorhinal cortex, frontal cortex and caudate nucleus using selected genes for microglia (AIF1, TREM2, CD68, CX3CR1), complement (C3, C1QBP), astrocytes (GFAP, Vimentin), oligodendrocytes (Sox10, MBP, PLP, APC, PDGFR-alpha) and neurons (Bassoon, Synaptophysin, Scl17a7, Homer1, Gria1 and Dlg4).

Fig.1



Results: Mann-Whitney statistical test revealed an up-expression of MBP, GFAP and Vimentin in the entorhinal cortex in AD animals (this region displayed only tau pathology) compared to controls. Analysis

of frontal cortex (that displayed only Aβ pathology) showed a down-expression of AIF1 and an up-expression of CD68 and Gria1 in AD animals compared to control. Analysis in hippocampus (that displayed both tau and Aβ) revealed a down-expression of AIF1 and an up-expression of Bassoon in AD animals compared to control.

Fig.2 Lesions	Hippocampus	Entorhinal cortex	Frontal cortex	Caudate nucleus
Amyloid	Positive	Intermediate	Positive	Negative
Tau	Positive	Positive	Intermediate	Negative

Genes	Hippocampus	Entorhinal cortex	Frontal cortex	Caudate nucleus
	Ctrl vs AD	Ctrl vs AD	Ctrl vs AD	Ctrl vs AD
Astrocyte				
GFAP	=	↗	=	=
Vimentin	=	↗↗	=	=
Microglia				
AIF1	↘	=	↘	=
CD68	=	=	↗	=
Trem2	=	=	=	=
CX3CR1	=	=	=	=
Complement				
C1QBP	=	=	=	=
C3	=	=	=	=
Oligodendroycte				
Sox10	=	=	=	=
MBP	=	↗	=	=
PLP	=	=	=	=
PDGFR-alpha	=	=	=	=
APC	=	=	=	=
Neurons (pre-synaptic)				
Basspon	↗	=	=	=
SCl17a7	=	=	=	=
Synaptophysin	=	=	=	=
Neurons (pre-synaptic)				
Homer1	=	=	=	=
Dlg4	=	=	=	=
Gria1	=	=	=	↗

Conclusions: Our results reveal transcriptomic changed involving astrocytes, oligodendrocytes, microglia and neurons in reaction to tau and Aβ lesions. They open the way for further evaluation of transcriptomic profiles in the Microcebus Murinus as a model of AD pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0624 / #862

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

BRAIN MULTI-OMICS INTEGRATION IDENTIFIED CSF SYNAPTIC BIOMARKERS FOR ALZHEIMER'S DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Abdallah Eteleeb[1,2], Brenna Novotny[1], Carolina Tarraga[1], Christopher Sohn[1], Eliza Dhungel[3], Logan Brase[1], Aasritha Nallapu[1], Jared Buss[1], Fabiana Farias[1,4], Kristy Bergmann[1,4], Joseph Bradley[1,4], Joanne Norton[1,4], Jen Gentsch[1,4], Fengxian Wang[1,4], Albert Davis[5,6], John Morris[2,5,6], Celeste Karch[1,2,4,6], Richard Perrin[2,5,6,7], Bruno Benitez[8], Oscar Harari[1,2,6]
[1]Washington University in St. Louis, Psychiatry, St. Louis, United States of America, [2]Washington University at Saint Louis, The Charles F. And Joanne Knight Alzheimer Disease Research Center, St. Louis, United States of America, [3]University of North Carolina at Charlotte, Bioinformatics And Genomics, Charlotte, United States of America, [4]Washington University in St. Louis, Neurogenomics And Informatics Center, St. Louis, United States of America, [5]Washington University in St. Louis, Neurology, St. Louis, United States of America, [6]Washington University in St. Louis, Hope Center For Neurological Disorders, St. Louis, United States of America, [7]Washington University in St. Louis, Pathology & Immunology, St. Louis, United States of America, [8]Harvard Medical School and Beth Israel Deaconess Medical Center, Neurology, Boston, United States of America

Aims: Unbiased data-driven omic approaches are revealing the molecular heterogeneity of Alzheimer disease (AD). It has been hypothesized that by combining multiple signals from various molecules, novel significant biological pathway changes in AD will emerge that are otherwise missed with single-omic analyses. We sought to investigate whether multi-omics integration of AD brains can provide novel molecular insights into AD progression and identify potential biomarkers for synaptic dysfunction, cognition, and AD staging.
Methods: We leveraged machine learning approaches to integrate high-throughput transcriptomic, proteomic, metabolomic, and lipidomic profiles with clinical and neuropathological data from multiple AD cohorts and brain regions to identify cross-omics molecular profiles of AD, genes and pathways affected at multiple stages of AD. These profiles were then integrated with data from established mouse models of neurodegeneration to clarify the role of genes and pathways altered in these profiles in AD pathophysiology.
Results: We discovered four unique multimodal molecular profiles, one showing signs of poor cognitive function, a faster pace of disease progression, shorter survival with the disease, severe neurodegeneration and astrogliosis, and reduced levels of metabolomic profiles. This profile shows similar cellular and molecular profiles in multiple affected cortical regions associated with higher Braak tau scores and significant dysregulation of synapse-related genes and pathways altered in AD early and late stages. To monitor AD progression, the multimodal clusters uncovered cerebrospinal fluid synaptic biomarkers, including *IGF1*, *NRXN3*, and *YWHAZ*, which can be employed for early detection of synaptic dysfunction, cognition, and AD staging. Integrating AD multi-omics profiles with A53T aSyn-APOE transgenic mice transcriptomic data revealed an overlapping signature.
Conclusions: Multi-omics analyses capture molecular heterogeneity among AD cases and provide novel critical molecular insights into AD that are typically missed with single-modality omics approaches.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0625 / #1903

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

PSEUDO-TEMPORAL MODELS OF ALZHEIMER'S DISEASE ACROSS BRAIN-DERIVED TRANSCRIPTOMICS AND PROTEOMICS REVEAL UNIQUE INSIGHTS INTO EARLY MOLECULAR CHANGES LEADING TO DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Laura Heath[1], Gregory Cary[2], Jesse Wiley[1], William Poehlman[1], Abby Vander Linden[1], Gregory Carter[2], Anna Greenwood[1]
[1]Sage Bionetworks, Sage Bionetworks, Seattle, United States of America, [2]The Jackson Laboratory, The Jackson Laboratory, Bar Harbor, United States of America

Aims: We applied pseudotemporal models to brain-derived transcriptomics and proteomics data from an AD case-control study to better understand the ordering and nature of the earliest molecular changes in the brain.
Methods: Manifold learning algorithms 'order' samples based on similarity of expression patterns, and then place each sample across a 'trajectory' of disease progression. We applied this approach to transcriptomic (N=1078) and TMT-proteomic (N=602) data from human postmortem brain samples from the ROS/MAP study within the Accelerating Medicine Partnership-AD consortia (AMP-AD). Analyses were stratified by sex, which resulted in four lineages, each of which successfully recapitulated disease and neuropathological endpoints. We calculated differential expression (DE) within 'states' along each trajectory. We used gene set enrichment analyses to identify significant GO terms changing along the trajectories and grouped them into 19 AD-relevant biological domains. We compared state-specific DE to case-control analyses of DE.
Results: We identified up- and down-regulated pathways involved in biodomains encompassing immune response, synaptic function, lipid metabolism, and other realms, in sex-stratified AD case-control analyses. We then tracked them state-by-state along the lineages and identified early 'transition' states at which biodomain regulation began to resemble the case-control analysis. In these transition states, we also observed significant changes in other biodomains that were not identified in the case-control analysis. Major pathways were largely conserved between males and females.
Conclusions: Pseudotemporal modelling provided unique insights into the ordering of molecular changes leading to AD, and potentially uncovered new genes and pathways implicated in early-stage disease processes. While most major pathways were conserved between sexes, more subtle differences, especially those noted early in disease trajectories, may provide crucial insights into key processes driving disease in women and men.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0626 / #438

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

THE NEUTROPHIL LANDSCAPE OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Kilian Kleemann[1,2], Neta Rosenzweig[2], Madeline Grucci[3], Hyun-Sik Yang[3], Reisa Sperling[3], Oleg Butovsky[2]
[1]Bonn University Hospital, Institute Of Clinical Chemistry And Clinical Pharmacology, Bonn, Germany, [2]Brigham and Women's Hospital, Harvard Medical School, Neurology, Boston, United States of America, [3]Massachusetts General Hospital, Harvard Medical School, Department Of Neurology, Boston, United States of America

Aims: Neutrophils were shown to play a negative role in Alzheimer Disease (AD) mice and their depletion improved cognitive functions. In AD patients, increased neutrophil-to-lymphocytes ratio was observed. Here we aimed to dissect the neutrophil transcriptomic signature associated with cognitive impairment in AD relative to sex, age and APOE-genotype.
Methods: We utilized a balanced cohort (totalling 160 samples) of male and female patients with AD or mild cognitive impairment (MCI) across APOE genotypes. Age-matched cognitively unimpaired individuals, were analyzed as healthy controls (HC). Top differentially expressed genes were identified, and the core neutrophil signature associated with MCI/AD, adjusted for covariates, was investigated using supervised machine learning (Random-Forest-Classifier). Validation was performed on public bulk-RNAseq of blood samples from 422 patients. Bulk-RNAseq profiles were screened using immune-cell-type deconvolution. Gene-regulatory-network, upstream-regulator and custom gene-set enrichment analysis were implemented to decipher underlying neutrophil changes according to patient subgroup.
Results: We identify strong sex-dependent neutrophil gene signature changes during cognitive impairment. While neutrophils from both sexes were enriched for TGFb-signaling during MCI/AD, only female samples upregulated gene expression modules associated with IL-1 and IL-17. Utilizing neutrophil expression profile and machine learning approaches, we identified top molecular perdictors of cognitive impairment, which are enriched in carriers for the strongest AD risk gene; APOE4, and to a greater extent in female APOE4 carriers.
Conclusions: The core transcriptional signature of neutrophils associated with cognitive impairment, was predominantly sex-dependent and to a lesser extent APOE4 driven. We identify targets for therapeutic intervation, as well as molecular biomarkers of the transition to cognitive imapirment and dementia. This may result in precise therapeutic interventions for AD according to sex and APOE4 genotype, providing an alternative strategy for an unmet clinical need.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0627 / #706

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

CHARACTERIZING THE MOLECULAR MECHANISMS IN THE HUMAN AMYLOID PLAQUE NICHE USING SPATIAL TRANSCRIPTOMICS

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Hans-Ulrich Klein, Berke Karaahmet, Laurine Duquesne, Ya Zhang, Alina Sigalov, Christina Yung, Alexandra Kroshilina, Mariko Taga
Columbia University Irving Medical Center, Neurology, New York, United States of America

Aims: Glial cells exhibit distinct transcriptional responses to β-amyloid. Single-nucleus RNA-sequencing studies have carefully characterized glial cell subpopulations in the human Alzheimer's disease (AD) brain and described their association with AD pathology burden. However, without spatial information, the multicellular response at amyloid plaques remains largely unknown. Here, we combined spatial transcriptomics (ST) with immunohistochemistry to explore the molecular mechanisms in the amyloid plaque niche.
Methods: A total of 32 sections from the prefrontal cortices of 15 AD and 2 control cases were applied to ST arrays with spatially barcoded probes (spots) of 55 µm diameter. Each of the 59,588 tissue-covered spots in our dataset detected a median of 2,202 genes and included a median of 4 nuclei. Amyloid plaques in the same tissue sections were stained with Thioflavin S and then projected onto the ST profiles.
Results: Clustering the spots reconstructed the cortical layer structure. We detected 263 amyloid plaques, and spots within 150 µm of plaques were compared to distant spots (>500 µm), adjusted for cortical layer and donor. This approach confirmed plaque-associated genes reported in mice, including *GFAP*, *CLU*, *MBP* and *MOBP*. Interestingly, the two AD risk genes *RBFOX1* and *SERPINA3* were upregulated at plaques. *SERPINA3* is a marker of an inflammatory astroglial subpopulation (Ast_5). Indeed, computationally predicting the Ast_5 locations from the ST data confirmed an enrichment at plaques. Further, we found a downregulation of metallothioneins, expressed by astrocytes, indicating a potential dysfunction of zinc ion homeostasis.
Conclusions: Our unbiased approach revealed 182 plaque-associated genes, enhancing our understanding of the molecular mechanisms within the amyloid plaque environment. Many of these genes are transcribed by astrocytes and oligodendrocytes and point towards inflammatory processes and ion transport and homeostasis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0628 / #1421

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

INVESTIGATING ABCA7-MEDIATED PHENOTYPES IN A HUMANIZED, LATE-ONSET ALZHEIMER'S DISEASE MOUSE MODEL

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Kevin Kotredes[1], Adrian Oblak[2], Ravi Shanker Pandey[3], Paul Territo[4], Mike Sasner[1], Gregory Carter[1], Bruce Lamb[5], Gareth Howell[1]
[1]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America, [2]Indiana University School of Medicine, Stark Neurosciences Research Institute, Indianapolis, United States of America, [3]THE JACKSON LABORATORY, For Genomics Medicine, FARMINGTON, United States of America, [4]Indiana University School of Medicine, Medicine, Indianapolis, United States of America, [5]Indiana University School of Medicine, Stark Neuroscience Research Institute, Indianapolis, United States of America

Aims: The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) Center aims to develop, validate, and distribute novel mouse models of late-onset Alzheimer's disease (LOAD). Accordingly, risk factors associated with the etiology of LOAD were identified and expressed in a novel mouse model to investigate their impact on aging phenotypes and AD progression. Genetic studies have demonstrated that a locus containing the ATP binding cassette subfamily A member 7 (*ABCA7*) gene is correlated with increasing risk for AD. Here, we investigated the effects of the *Abca7*A1527G* humanized risk allele on LOAD phenotypes and biomarkers to better align the biology of mouse models with those observed in human disease.
Methods: Two genetic risk factors of LOAD were incorporated into C57BL/6J mice along with humanized amyloid-beta to produce the 'LOAD2' (B6.*APOE4.Trem2*R47H*.hAbeta) baseline strain. To investigate the impact of the *ABCA7*A1527G* risk factor, littermate carrier (LOAD2. Abca7*A1527G) and non-carrier (LOAD2) mice were extensively aged and an animal phenotyping pipeline was employed to correlate outcomes with phenotypes observed in human patients, including i*n vivo* PET/CT imaging and behavior assays. Post-mortem analyses of blood and brain tissue for risk-factor-related alterations in neuropathology, transcriptomics, metabolomics, and proteomics were performed.
Results: Mice expressing *Abca7*A1527G* revealed individual and synergistic transcriptional effects with genetic risk factors correlated with human AMP-AD modules. LOAD2.*Abca7*A1527G* mice showed an uncoupling of brain glycolysis and regional perfusion. Neuropathology analysis in brain tissue is in progress, as are cytokine panels in brain homogenates and plasma. Further transcriptomic, neuropathological, and histological analyses are currently underway.
Conclusions: Initial characterization of aged mice expressing genetic risk factors of LOAD indicates that *Abca7*A1527G* expression increases susceptibility to disease through interactions between cerebrovasculature, microglia and peripheral immune cells.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0629 / #1873

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

CONTRIBUTIONS OF MTHFR RISK ALLELE TO DISEASE PROGRESSION IN LATE-ONSET ALZHEIMER'S DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Kevin Kotredes[1], Alaina Reagan[1], Adrian Oblak[2], Ravi Shanker Pandey[3], Paul Territo[4], Mike Sasner[1], Gregory Carter[1], Bruce Lamb[5], Gareth Howell[1]
[1]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America, [2]Indiana University School of Medicine, Stark Neurosciences Research Institute, Indianapolis, United States of America, [3]THE JACKSON LABORATORY, For Genomics Medicine, FARMINGTON, United States of America, [4]Indiana University School of Medicine, Medicine, Indianapolis, United States of America, [5]Indiana University School of Medicine, Stark Neuroscience Research Institute, Indianapolis, United States of America

Aims: Late-onset Alzheimer's disease (LOAD) comprises more than 95% of all AD cases. Legacy transgenic, overexpression animal models do not effectively produce the heterogeneity observed clinically in LOAD patients and thus are not appropriate subjects for preclinical therapeutic development. We therefore generated and investigated novel LOAD mouse strains designed to better phenocopy the heterogeneity of human disease and reveal more appropriate molecular targets for treatment. Results from the Alzheimer's Disease Neuroimaging Initiative (ADNI) revealed that alterations in *MTHFR* expression produce changes in brain volume, white matter, and vascular inflammation. Understanding the effects of the *MTHFR*C677T* allele expression in mouse strains subjected to additional LOAD risk alleles will inform biomarker discovery and potential clinical therapeutics.
Methods: Mice expressing *Mthfr*C677T*, on a humanized *App*, *APOEe4*, and *Trem2*R47H* background, were assessed over multiple ages for indications of disease. Regular behavior measurements and biometric samples were collected longitudinally to 24 months. Upon endpoints blood and brain tissue was collected for transcriptomic, proteomics, and neuropathological, correlation and analyses.
Results: Initial studies in an aged mouse model with a LOAD-relevant genetic background showed that *Mthfr*C677T* produced a transcriptional signature in the brain more similar to those seen in human AD patients, supporting observations from public datasets. The enzymatic activity of MTHFR*C677T is known to be diminished, preventing homocysteine conversion, increasing blood homocysteine levels, and inducing vascular inflammation. Neuropathological and transcriptomic analysis of advanced age cohorts is underway along with more detailed, CNS-specific characterization of the many aspects of MTHFR function.
Conclusions: We observed strong correlations to human disease transcripts in AMP-AD expression modules with the expression of *Mthfr*C677T*. Here we show the evidence of emerging disease pathology in a novel LOAD2.*Mthfr*C677T* mouse strain.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0630 / #2396

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

UNTARGETED IMAGING MASS SPECTROMETRY REVEALS REGIONAL LIPID ACCRETION IN THE ALZHEIMER'S DISEASE MOUSE BRAIN: PIPELINE TO ANALYZE SPATIAL LIPIDOMICS DATA.

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Artur Lazarian[1], Nicholas Bartelo[2], Ana Paula Costa[1], William Dartora[1], Krista Wartchow[1], Richa Batra[2], Jan Krumsiek[2], Laura Beth Mcintire[1,3]
[1]Brain Health Imaging Institute, Weill Cornell Medicine, Radiology, New York, United States of America, [2]Institute for Computational Biomedicine, Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, New York, Physiology And Biophysics, New York, United States of America, [3]Columbia University Medical Center, Pathology And Cell Biology, New York, United States of America

Aims: Lipidomic data from autopsy brain, human plasma and animal models shows severe lipid dyshomeostasis in AD, thus, indicating a crucial role of the lipids in the development of Alzheimer's pathology. Previous studies have shown that the loss of polyunsaturated fatty acids among multiple phospholipid classes is common in AD affected human brain and mouse models.
Methods: We employ untargeted Desorption Electrospray Ionization (DESI) Imaging Mass Spectrometry to investigate spatial profiling of lipids between normal-aging and AD-affected mouse brains across various ages (6, 12 and 22 months old). Using PYTHON and R-studio, we developed a new pipeline to process spatially acquired data of several thousand precursor ions of lipids and to perform statistical analysis to determine the differential content of lipids among specific anatomical regions.
Results: By using Mass Spectrometry and applying appropriate lipid standards we show for the first time that specific lipid species including sphingomyelins, phospholipids and polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are highly enriched in the globus pallidus region of AD-affected mouse brains compared to wild type brain. This phenomenon is observed prior to amyloid plaque accumulation and behavioral deficits.
Conclusions: Untargeted DESI Imaging Mass Spectrometry facilitates spatial profiling of thousands of lipids in mouse brain. Our newly developed pipeline fosters comprehensive statistical analysis to compare specific regional lipid alterations and to discover lipids that are relevant to AD etiology and disease progression. The pipeline also facilitates distribution pattern recognition allowing spatial cluster analysis to identify lipids with similar regional distribution and changes due to genetic disposition and age. Ultimately, discovery of new differentially expressed lipids will lead to identification of new lipid-based biomarkers and mechanistic changes in lipid metabolism relevant to disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0631 / #1557

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

COMPUTATIONAL ANALYSIS OF SNRNA-SEQ DATA OF TBK1E696K MICE TO DISCOVER THE AGE-GENOTYPE IMPACT ON THE PROGRESSION OF AMYOTROPHIC LATERAL SCLEROSIS

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Babak Loghmani[1], Volker Ast[2], David Brenner[1,2], Rüstem Yilmaz[1], Angelika Duda[3], Rosanna Parlato[1], Jochen Weishaupt[1]
[1]Medical Faculty Mannheim, University Clinic Mannheim, Division Of Neurodegeneration, Mannheim, Germany, [2]Ulm University Medical Faculty, Neurology, Ulm, Germany, [3]University Medicine Mannheim, Clinical Chemistry, Mannheim, Germany

Aims: Mutations in the pleiotropic TANK1-binding kinase 1 (*TBK1*) are responsible for the onset of Amyotrophic Lateral Sclerosis (ALS), a lethal neurodegenerative disease. Specifically, the missense mutation p.E696K distinctly disrupts the TBK1 protein's interaction with the autophagy adaptor optineurin. We developed knock-in mice, referred to as *Tbk1*^{E696K}, which carry the p.E696K mutation. This mutation results in a hindrance of the autophagic process. In this study, we conducted a comprehensive computational analysis in two dimensions, namely age and genotype, using single-nuclei RNA sequencing, to understand the individual and combinatorial (age-associated) effect of the p.E696K homozygous mutation in the mouse spinal cord, mostly affected in ALS.
Methods: We compared the single-nuclei transcriptomics of wild-type and Tbk1^{E696K} knock-in mice in the spinal cord. The data were analysed at two levels: 1) single-nuclei and 2) pseudo-bulk. Moreover, multiple pathway analysis algorithms based on various databases were applied to identify the impact of the p.E696K mutation in specific cell-types at different ages (6 and 19 months), also corresponding to different disease stages.
Results: We found that age has a greater impact on the gene expression profile compared to genotype, and the effects caused by genotype (namely, by the p.E696K mutation), to some extent mimic the aging process. This finding is reflected for example by the number and the identity of differentially expressed genes, the dysregulated pathways, and cell type-specific dysregulated genes (e.g. in microglia)
Conclusions: The results suggested that the progression of TBK1-ALS has similarities with preponed or accelerated aging at the gene expression level, even at the early presymptomatic stages (6 months). Moreover, changes in cell-subtype identity can be used to dissect the hallmarks of the disease based on differentially expressed genes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0632 / #729

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

ASSOCIATION BETWEEN PLASMA PROTEOMICS AND DEMENTIA NEUROPATHOLOGY AT AUTOPSY

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Minerva Martinez-Castillo[1], Pamela Martino-Adami[2], Alberto Rábano[1], Alfredo Ramirez[2,3,4,5,6], Pascual Sanchez-Juan[1]
[1]Alzheimer's Centre Reina Sofia-CIEN Foundation-ISCIII, Cien Foundation, Madrid, Spain, [2]University Hospital Cologne, Psychiatry And Psychotherapy, Cologne, Germany, [3]German Center for Neurodegenerative Diseases (DZNE), Psychiatry, Bonn, Germany, [4]University of Cologne, Cluster Of Excellence Cellular Stress Responses In Aging-associated Diseases (cecad), Cologne, Germany, [5]Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, Psychiatry, San Antonio, United States of America, [6]University Hospital Bonn, Neurodegenerative Diseases And Geriatric Psychiatry, Bonn, Germany

Aims: Determine neuropathological correlates of ante-mortem plasma proteins in demented patients.
Methods: Plasma levels of ~2000 proteins from Centro Alzheimer-Fundación Reina Sofía ante-mortem samples (N=133) were quantified using Olink®Explore 3072 and passed the quality control. Patients were all demented (Alzheimer's disease [AD], N=103; vascular dementia, N=14; dementia with Lewy bodies, N=12; frontotemporal dementia, N=2; hippocampal sclerosis, N=1; tauopathy, N=1), had an average disease duration of 12 years, and were classified into the different AD neuropathologic change (ADNC) scores. Association between brain weight and plasma protein levels was evaluated using a linear model adjusted for age and sex, and correlation between brain weight and plasma protein levels in each ADNC score using correlational clustering. Protein–protein association networks were identified using STRING database.
Results: Linear regression analysis identified 290 proteins significantly associated with brain weight (corrected *p*-value, $q<0.05$). Next, correlation between significant protein levels with brain weight in each ADNC score group was calculated. Clustering of these correlation profiles showed that ADNC scores 1 (low-AD probability) and 3 (high-AD probability) were clustered together. To understand the similarity, proteins were classified considering the direction of their correlation coefficient in each ADNC score group. Group of 130 proteins was the only one where the direction of the relationship in ADNC score 2 was different from the others, it was selected for gene ontology enrichment analysis. Protein-protein network analysis revealed the top associated biological processes, including ESCRT-III complex disassembly ($q=2.3\text{x}10^{-3}$), and extracellular matrix assembly regulation ($q=0.02$).
Conclusions: Mixed forms of AD (ADNC score 2) may exhibit a different proteomic profile compared to non-AD dementias (ADNC score 1) and the purer forms of AD (ADNC score 3) that could be related to changes in biological processes involving the extracellular matrix.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0633 / #2178

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

FORMATION AND FUNCTION OF BETA-AMYLOID PEPTIDE ENDOGENOUS NANOPARTICLES

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Laura Beth Mcintire[1], Ana Paula Costa[1], Artur Lazarian[1], Krista Wartchow[1], William Dartora[1], Clay Bracken[2], Jason Mares[3], Tal Nuriel[4], Charles Karan[5], Sergey Pampou[5], Renu Nandakumar[6], Oliver Xu[6], Jui Changule[7], Oluwafunke Kolawole[8], Merav Antman-Passig[9], Richa Batra[10], Yujia Xu[7], Daniel Heller[9], Mony De Leon[1], Jan Krumsiek[10], Vilas Menon[3]
[1]Brain Health Imaging Institute, Weill Cornell Medicine, Radiology, New York, United States of America, [2]Weill Cornell, Biochemistry, New York, United States of America, [3]Columbia University, Neurology, New York, United States of America, [4]Columbia University Irvine Medical Center, Taub Institute, New York, United States of America, [5]Columbia University, Department Of Systems Biology, New York, United States of America, [6]Columbia University, Irving Institute Biomarkers Core, New York, United States of America, [7]Hunter College CUNY, Biochemistry, New York, United States of America, [8]City University New York, School Of Medicine, New York, United States of America, [9]Memorial Sloan Kettering Cancer Research, Molecular Pharmacology, New York, United States of America, [10]Institute for Computational Biomedicine, Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, New York, Physiology And Biophysics, New York, United States of America

Aims: Objective: Emerging studies from lipidomic and genetic data have repeatedly identified lipid metabolism as a major driver of etiology and progression of Alzheimer's disease. However, a system-wide understanding of the consequences of lipid dysregulation has not yet been addressed.
Methods: Using a candidate based genetic screen, we identified a network of genes involved in lipid metabolism which prevented synapse loss triggered by β-amyloid peptide (Aβ) suggesting coordination of lipid levels in response to Aβ challenge. We interrogated the disease associated changes in lipid metabolism from multiple data sets including the Religious Order Study, Memory Aging Project (ROS-MAP) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). Finally, using Nuclear Magnetic Resonance (NMR), circular dichroism and novel lipid binding assays, we identified specific lipid binding activity of Aβ.
Results: We found that deficits in acyl chain remodeling were able to model changes we found in lipidomic studies from human brain and endogenous nanoparticles (eNP) isolated from cerebral spinal fluid (CSF). Further, we found associations among characteristic clinical outcomes and fluid biomarkers with specific eNP identified by the Nightingale platform based on NMR detection of metabolites and apolipoproteins in ADNI. The composition of eNP is enriched in phospholipids containing polyunsaturated fatty acyl chains which we show bind Aβ directly and affect oxidation as well as aggregation of the peptide supporting a critical functional role.
Conclusions: We have identified acyl chain remodeling as a driver of lipid dyshomeostasis in AD progression. Further, we report specific functional consequences of Aβ binding to phospholipids harboring polyunsaturated acyl chains. Our studies support the specificity, necessity and sufficiency of polyunsaturated lipids for driving Aβ eNP formation and function.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0634 / #504

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

AN INTEGRATIVE MULTI-OMICS APPROACH REVEALS MOLECULAR SIGNATURES ASSOCIATED WITH DISTINCT AD RISK FACTORS IN MOUSE MODELS OF ALZHEIMER'S DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Ravi Shanker Pandey[1], Kevin Kotredes[2], Dylan Garceau[2], Duc Duong[3], Rima Kaddurah-Daouk[4], Nicholas Seyfried[3], Mike Sasner[2], Gareth Howell[2], Adrian Oblek[5], Bruce Lamb[5], Gregory Carter[2]
[1]THE JACKSON LABORATORY, For Genomics Medicine, FARMINGTON, United States of America, [2]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America, [3]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [4]Duke University, Psychiatry And Behavioral Sciences, Durham, United States of America, [5]Indiana University School of Medicine, Stark Neuroscience Research Institute, Indianapolis, United States of America

Aims: Alzheimer's disease (AD) is a complex, multifactorial pathology with high heterogeneity in biological alterations. Our understanding of cellular and molecular mechanisms from disease risk variants to various phenotypes is still limited. Therefore, it is required to integrate the information from multiple data modalities for thorough exploration of endophenotype networks, biological interactions related to disease and thus accelerate our understanding of heterogeneity in Alzheimer's disease.
Methods: We performed multi-level omics in a cohort of mouse models expressing humanized Abeta and two genetic risk factors (APOE4 and Trem2*R47H), termed as LOAD2, and mice harboring additional risk variants *Abca7*A1527G* and *Mthfr*677C>T* on to LOAD2 background at multiple ages for both sexes. Data from multiple omics platforms were integrated in an unbiased fashion, considering interaction between modalities using bioinformatics approaches. We also systematically aligned multimodal mouse data to relevant human studies cohort.
Results: Multi-omics integration identified major components of heterogeneity explaining the variance within the cohort and differentially associated with age, sex, and genotype. Enrichment analysis of genes and protein associated with these components were significantly enriched for multiple AD-related processes. Multi-omics profiling showed expression changes that are similar to those observed in human AD. In addition, we observed weak correspondence between change in protein and RNA expression in mouse models compared to controls, similar to recent results from the ROSMAP cohort, which reported weak correlation between protein and RNA expression.
Conclusions: We identified axes of variation within a cohort of LOAD mouse models using integrative multi-omics approach. Our analysis revealed interaction between distinct multi-omics molecular signatures associated with Alzheimer's disease. This study highlighted that assembling multi-omics measurements reveal interrelated pathway alterations in AD and the ability to identify biomarkers combinations that may inform clinical practice.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0635 / #2197

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

TITLE: ALZHEIMER DISEASE SUBTYPES BASED ON PLASMA LIPIDOMICS

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Camen Peña-Bautista[1], Lourdes Álvarez-Sánchez[1], Gemma Garcia-Lluch[1,2,3], Mar Peretó[1], Miguel Baquero[1], Consuelo Cháfer-Pericás[1]
[1]Instituto de Investigación Sanitaria La Fe, Grupo De Investigación En La Enfermedad De Alzheimer (ginea), Valencia, Spain, [2]Universidad Cardenal Herrera CEU, Pharmachology, Valencia, Spain, [3]Cátedra DeCo, Research, Valencia, Spain

Aims: Alzheimer disease (AD) is an heterogeneous and complex disease with different pathophysiological mechanisms involved, which could trigger in AD clinical subtypes. AD subtypes have been described according to atrophy patterns, CSF biomarkers, symptoms evolution. Regarding biochemical pathways, lipid metabolism plays an important role in AD, so the lipid levels have been evaluated as potential AD diagnosis biomarkers, and their levels could be studied to define AD subtypes. Therefore, the aim of this work is to describe AD subtypes according to the lipid profile in plasma samples from early AD patients and to evaluate the clinical significance of these subtypes.
Methods: Untargeted plasma lipidomic analysis was carried out in early AD patients (n = 31) diagnosed by CSF biomarkers (amyloid β42, total Tau, phosphorylated Tau). Then, an unsupervised cluster analysis was carried out to define early AD subgroups according to plasma lipid levels. After that, the clinical significance of each lipid profile subgroup was studied analysing differences for clinical variables (cognitive status, CSF biomarkers, medication, comorbidities, age, gender). In addition, a progression substudy (n=14) was carried out analysing the evolution in cognitive status in each subgroup.
Results: These AD patients were divided into 2 groups. Group 1 showed higher levels of plasma lipids and better cognitive status (neuropsychological tests RBANS.DM, CDR sum of boxes, and MMSE) than Group 2. However, not differences were found for other variables (age, gender, medication, comorbidities, cholesterol, triglycerides levels) between both groups. In addition, a substudy showed a trend to a slower decline along time in group 1.
Conclusions: Plasma lipid levels could differentiate two early AD subgroups, which showed different cognitive status and a trend to differential progression. However further research with a large cohort is required.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0636 / #2374

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

THE IPSC NEURODEGENERATIVE DISEASE INITIATIVE (INDI): GENERATING A HIGH-QUALITY ISOGENIC MUTANT IPSC REPOSITORY FOR STUDYING ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Daniel Ramos[1], Erika Lara[1], Andy Qi[1], Marianita Santiana[1], Ziyi Li[1,2], Luke Reilly[1], Caroline Pantazis[1], William Skarnes[3], Andrew Singleton[4,5], Mark Cookson[1,6], Michael Ward[1,7]
[1]NIH, Center For Alzheimer's And Related Dementias (card), Bethesda, United States of America, [2]Data Tecnica International, Data Science, Washington DC, United States of America, [3]The Jackson Laboratory for Genomic Medicine, The Jackson Laboratory For Genomic Medicine, Farmington, United States of America, [4]National Institute on Aging and National Institute of Neurological Disorders and Stroke, National Institutes of Health, Center For Alzheimer's And Related Dementias, Bethesda, United States of America, [5]National Institutes of Health, Molecular Genetics Unit, Laboratory Of Neurogenetics, Center For Alzheimer's And Related Dementias, Bethesda, United States of America, [6]NIH, Lab Of Neurogenetics, National Institute On Aging, Bethesda, United States of America, [7]NIH, National Institute Of Neurological Disorders And Stroke, Bethesda, United States of America

Aims: The growing scale of genetic studies has led to the identification of many genetic variants that contribute to risk for developing Alzheimer's Disease and Related Dementias (ADRDs), but how these variants contribute to disease risk remains poorly understood. The iPSC Neurodegenerative Disease Initiative (iNDI) is the largest-ever induced pluripotent stem cell (iPSC) genome engineering project, modeling over 100 ADRD mutations in high-quality isogenic human iPSCs. iNDI will generate foundational iPSC tools and datasets to study fundamental mechanisms of ADRDs and identify new therapeutic targets.
Methods: Phase 1: A parental iPSC line was selected based on growth characteristics, pluripotency, p53 pathway integrity, genetic risk, genomic integrity, and differentiation potential. All mutant lines are generated by the Jackson Laboratory (JAX) by CRISPR editing in the parental iPSC line. Phase 2: We characterize the downstream effects of ADRD mutations on iPSC-derived neuron biology using multi-omic readouts.
Results: To-date, iNDI has generated 107 cell lines modeling 37 ADRD-relevant mutations. 270 labs worldwide have requested iNDI lines, and 2 manuscripts utilizing iNDI cell lines have already been published. We recently completed pilot experiments demonstrating the iNDI phase 2 workflow, from highly paralleled iPSC thawing, culturing, expansion, and differentiation of a subset of iNDI mutant iPSC lines into cortical-like neurons. We now begin to explore multi-omic datasets of ADRD mutant iPSC-derived neurons to help understand proximate transcriptome and proteome phenotypes associated with ADRD mutations. We are now actively developing custom automated cell culture robotics for future large-scale experiments.
Conclusions: iNDI is the largest-ever iPSC genome engineering project and has distributed isogenic ADRD-relevant mutant iPSCs to labs worldwide. The resultant iPSC tools and datasets will be foundational for the study of ADRDs, and all datasets generated will be freely available.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0637 / #617

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

OLFACTORY STEM CELLS AS A NEW MODEL FOR INVESTIGATING POTENTIAL BIOMARKERS FOR ALZHEIMER'S DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Laura Rantanen[1], Maina Bitar[1], Riikka Lampinen[2], Alexandre Cristino[3], Harley Robinson[1], Katja Kanninen[2], Anthony White[1]
[1]QIMR Berghofer Medical Research Institute, Mental Health And Neuroscience, Herston, Australia, [2]University of Eastern Finland, A. I. Virtanen Institute For Molecular Sciences, Kuopio, Finland, [3]Griffith University, Griffith Institute For Drug Discovery, Nathan, Australia

Aims: Alzheimer's disease (AD) is a neurodegenerative disorder with an increasing incidence worldwide. There are currently no treatments to cure or effectively slow the progression of AD. To address this, patient-derived cell models of AD that co-relate with early clinical features observed in AD could be valuable to gain a better understanding of the disease and develop new treatments. Impaired olfaction is one of the earliest symptoms and a significant predictor of conversion to AD from mild cognitive impairment (MCI), a prodromal AD condition. Found deep within the naris, olfactory stem cells provide a window into the brain. Their inherent ability to form neuroglia makes these cells potentially an ideal model system to examine the early pathophysiological changes that take place in AD.
Methods: Human olfactory neurosphere-derived (ONS) cell lines were generated using olfactory mucosal biopsies from age-, gender- and ApoE genotype-matched cognitively healthy individuals (HC), patients with AD, and individuals with MCI (*n*=6 for each group). Omics analyses were performed to identify global gene and protein changes and associated pathways between HC, MCI and AD ONS cells, and to discover potential disease biomarkers.
Results: Transcriptomic results revealed several differentially expressed genes associated with cognitive changes, *AKAP6* being the most significantly altered. Proteomics analysis highlighted especially differentially expressed proteins, such as NDUFS4 and ENO1, and disease pathways associated with altered cell metabolism and mitochondrial function in AD ONS cells compared to MCI and HC.
Conclusions: This study demonstrated the potential of patient-derived ONS cells to provide a cell-based model for AD biomarker discovery. It revealed potential novel genes, proteins, and disease pathways that may have a role in AD, especially MCI to AD transition, and should be further examined.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0638 / #1428

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

SPATIOTEMPORAL ANALYSIS OF MIDBRAIN DOPAMINERGIC SUBPOPULATIONS IN AN AAV-MEDIATED ALPHA-SYNUCLEIN PARKINSON'S MOUSE MODEL

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Carmen-Jeanette Stepek[1], Ayse Ulusoy[2], Donato Di Monte[2], Jochen Prehn[1], Niamh Connolly[1]
[1]Royal College of Surgeons in Ireland, Physiology & Medical Physics, Dublin, Ireland, [2]German Center for Neurodegenerative Diseases, Ag Di Monte, Bonn, Germany

Aims: Pathological hallmarks of Parkinson's Disease (PD) are degeneration of dopaminergic neurons (DANs) in the substantia nigra (SN) and intraneuronal α-Synuclein inclusions known as Lewy bodies. DANs can be categorized into distinct subpopulations based on location, physiological functions and expression profiles. Over 60% of nigral DANs express Aldehyde Hydrogenase 1A1 (ALDH1A1). This subpopulation has been identified as selectively vulnerable in post-mortem PD tissue and is over-represented in pathways underpinning vulnerability in PD models. Other findings suggest more complex mechanisms of vulnerability that, during pathological processes, may include changes in neuronal phenotypic and expression profiles. In this study, distribution and transcriptome of midbrain ALDH1A1+ and ALDH1A1- DANs were elucidated in an animal model of α-Synuclein pathology.
Methods: Mice received intra-nigral injections of AAV-expressing human-α-Synuclein (SNCA) or GFP. Brain slices were collected 3- and 8-weeks post-injection. Neuroanatomical regions were delineated and DAN subtypes were identified using immunofluorescence. Spatially-resolved transcriptomics was performed on midbrain ALDH1A1+ and ALDH1A1- DANs using NanoString's GeoMx Digital Spatial Profiler. Bioinformatics [e.g., clustering, differential expression, enrichment analyses] was performed in R.
Results: Increased midbrain SNCA expression was accompanied by diffuse α-Synuclein pathology at both timepoints. Significant DAN loss was observed in the SN at 8 weeks but not in the ventral tegmental area (VTA). Cell counting did not detect overt differences in vulnerability between ALDH1A1+ and ALDH1A1- neurons. Differential expression analysis identified distinct transcriptomic signatures of ALDH1A1+/- subtypes at early and late timepoints and indicated that α-Synuclein pathology may reduce transcriptional differences over time. Enrichment analysis identified critical pathways associated with each subtype [e.g., synaptic transmission, calcium transport], underscoring the functional impact of α-Synuclein pathology.
Conclusions: Development of α-Synuclein pathology significantly affects expression profiles of midbrain dopaminergic subpopulations, likely bearing important functional consequences.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0639 / #1888

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

ASSOCIATION OF CSF PROTEOME WITH CSF P-TAU181 LEVELS AND OTHER BIOMARKERS OF ALZHEIMER'S DISEASE

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Min Qiao[1], Alexander Rookyard[2], Lipi Das[2], Marielba Zerlin-Esteves[1], Dolly Reyes-Dumeyer[3], Annie Lee[3], Rafael Lantigua[1], Martin Medrano[4], Diones Rivera[5], Lawrence Honig[1], Lewis Brown[2], Richard Mayeux[6], Badri Vardarajan[1,6]
[1]Columbia University, Department Of Neurology, New York, United States of America, [2]Columbia University, Department Of Biological Sciences, Quantitative Proteomics And Metabolomics Center, New York, United States of America, [3]Columbia University Irving Medical Center, The Gertrude H. Sergievsky Center, College Of Physicians And Surgeons, New York, United States of America, [4]Pontificia Universidad Catolica Madre y Maestra Santiago, School Of Medicine, Santiago, Dominican Republic, [5]CEDIMAT, Department Of Neurosurgery, Santo Domingo, Dominican Republic, [6]Columbia University Irving Medical Center, Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York, United States of America

Aims: We investigated the relationship between cerebrospinal fluid (CSF) proteome in Alzheimer's disease (AD) with clinical and biomarker-assisted diagnosis.
Methods: CSF was collected in 250 individuals of non-Hispanic white, African Americans, and Caribbean Hispanic individuals from Dominican Republic and New York City. CSF biomarkers of AD were measured including P-tau181, Aβ40, Aβ42, total-tau, neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP). CSF was depleted of abundant proteins followed by precipitation, cysteine reduction/alkylation, and proteolytic cleavage by trypsin. Peptides were measured using a Q Exactive HF mass spectrometer (Thermo Scientific). Association of individual and co-abundant modules of proteins were tested with the clinical diagnosis of AD, as well as biologically defined AD pathological process based on CSF P-tau181 and other biomarker levels.
Results: We detected 22,778 peptides in 865 protein groups (with greater than or equal to 2 peptides per protein), yielding an overall data completeness value of 97%. CSF levels of phospholipase D3 (PLD3, p=1.52E-07) and osteopontin (OSTP, p=2.16E-06) were increased and ceruloplasmin (CERU, p=6.88E-06) was decreased among individuals with high P-tau181 levels. These proteins were also associated with CSF Aβ42/Aβ40 ratio and total Tau levels but not with NfL. OSTP was also nominally associated with CSF levels of GFAP (p=4.6e-04). We did not identify any protein associations with clinical AD. Among proteins associated with P-tau181 levels, pathways related to axon development (p=1.39E-09), axonogenesis (p=5.31E-08) and regulation of axon regeneration (p=8.76E-06) were enriched. We are analyzing the CSF proteome in additional 250 participants for validation of identified proteins.
Conclusions: Unbiased profiling of circulating CSF proteins identified key proteins associated with β-amyloid and phosphorylated tau pathology. Biologically based diagnostic criteria may aid in the identification of unique pathogenic mechanisms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0640 / #2399

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

ALTERED LIPID METABOLISM AND ACYL CHAIN REMODELING IN ALZHEIMER'S DISEASE: SPATIAL INSIGHTSFROM A MOUSE MODEL

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Krista Wartchow[1], Ana Paula Costa[1], Artur Lazarian[1], William Dartora[2], Nicholas Bartelo[3], Jan Krumsiek[3], Vilas Menon[4], Jason Mares[5], Tal Nuriel[5], Laura Beth Mcintire[2,6]
[1]Brain Health Imaging Institute, Weill Cornell Medicine, Radiology, New York, United States of America, [2]Brain Health Imaging Institute, Department of Radiology, Weill Cornell Medicine, Radiology, New York, United States of America, [3]Institute for Computational Biomedicine, Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, New York, Physiology And Biophysics, New York, United States of America, [4]Columbia University Irving Medical Center, Center For Translational And Computational Neuroimmunology, Department Of Neurology And Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York, United States of America, [5]Columbia University, Neurology, New York, United States of America, [6]Columbia University Medical Center, Pathology And Cell Biology, New York, United States of America

Aims: Dysregulation of lipid homeostasis and the acyl chain remodeling pathway, along with depletion of specific lipid acyl species, are implicated in Alzheimer's Disease (AD) pathogenesis. We aimed to study the contribution of acyl chain remodeling pathways in the dysregulation of the lipidome over aging and in a mouse model of AD by integrating spatial lipidomic and coordinated spatial transcriptomic analyses.
Methods: Serial brain slices from a mouse model of AD were analyzed for lipid content using imaging mass spectrometry and for gene expression using RNAscope, and spatial gene expression. Wild type mice and those overexpressing amyloid precursor protein with the Swedish mutation (APPsw) were analyzed during aging at, 6, 12 and 22 months.
Results: We found regional changes in globus pallidus (GP) which showed an age-related increase in GFAP andACSL6 copy number. In the APPsw model, ACSL6 and GFAP copy number was elevated at 12 months, with a slight reduction at 22 months. The neuronal protein, NeuN decreased over time, with a more pronounced effect in the APPsw. Microglia, Iba-1 exhibited increased expression at 12 months and decreased at 22 months in APPsw. Spatial transcriptomics revealed differences in gene expression related to lipid metabolism. Imaging mass spectrometry detected regional lipid content differences in the GP, consistent with deficits in acyl chain remodeling in the AD model.
Conclusions: Dysregulation of lipid metabolism, including changes in the expression of enzymes involved in fatty acid metabolism such as ACSL6, has been linked to AD development. It is likely that astrogliosis in the GP area contributes to the observed lipid alterations detected through imaging mass spectrometry and spatial transcriptomics, revealing deficiencies in the Lands cycle acyl chain remodeling in lipid metabolism.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0641 / #1434

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

TMT PROTEOMIC ANALYSIS IDENTIFIES AMYLOID-BETA AND TAU PATHOLOGY-ASSOCIATED PEPTIDES ACROSS THE AD DISEASE CONTINUUM

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Sophia Weiner[1], Mathias Sauer[1], Andréa L. Benedet[1], Nicholas Ashton[1], Nesrine Rahmouni[2], Cécile Tissot[2], Joseph Therriault[2], Stijn Servaes[2], Jenna Stevenson[2], Pedro Rosa-Neto[3], Kaj Blennow[1], Henrik Zetterberg[1], Johan Gobom[1]
[1]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Göteborg, Sweden, [2]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [3]McGill Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada

Aims: Several molecular processes, such as posttranslational modifications (PTMs), contribute to the formation of the Alzheimer's disease (AD) hallmarks amyloid-beta (Aβ) plaques and tau neurofibrillary tangles. The aim of this explorative proteomic study was to identify novel peptides, including PTMs, in cerebrospinal fluid (CSF) associated with AD pathologies throughout the disease continuum.
Methods: We performed a cross-sectional TMT proteomic study of CSF samples from the Translational Biomarkers in Aging and Dementia (TRIAD) cohort (young adults (n=22), cognitively unimpaired (n=54), cognitively impaired (n=45), AD (n=19)); a cohort covering the AD continuum, highly profiled by clinical assessment, Aβ and tau positron emission tomography (PET), and fluid biomarkers. Exploiting the unbiased nature of MS-based proteomics, we performed all analyses on the peptide level. To determine pathology-associated peptides, we built linear regression models, performed correlation analyses, and assessed peptide abundances across the disease continuum.
Results: Preliminary results show a strong association between Aβ PET and, among others, peptides mapping to the following proteins: CORT (β_{std}=-0.52; p<0.001), SMOC1 (β_{std}=0.48; p<0.01), C3 (β_{std}=-0.33; p<0.01), and AQP4 (β_{std}=0.51; p<0.01), many of which have been shown to co-localize with Aβ plaques. In addition, we determined peptides stemming from the following proteins to be strongly related to tau pathology: 14-3-3 proteins YWHAZ (β_{std}=0.53; p<0.001), and YWHAE (β_{std}=0.51; p<0.001), as well as MDH1 (β_{std}=0.47; p<0.001), and OTUB1 (β_{std}=1.30; p<0.01). The 14-3-3 proteins displayed a stepwise increase in abundance across the AD continuum. Future analyses will elucidate disease associated PTMs and cleavage sites of the identified peptides.
Conclusions: Leveraging MS-based proteomics, we identified several peptides strongly associated with Aβ and tau pathology. Furthermore, we discovered diverging abundance patterns of these markers across the AD continuum, identifying both early- and late-stage CSF biomarker candidates.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0642 / #1817

Poster Topic: *Theme A: β-Amyloid Diseases / A06.e. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

BIOLOGICAL DOMAIN AND SUBDOMAIN MAPPING OF AD ENRICHED BIOLOGICAL PROCESSES

POSTERS: A06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Jesse Wiley[1], Gregory Cary[2], Sai Sruthi Amirtha Ganesh[1], Laura Heath[1], Abby Vander Linden[1], William Poehlman[1], Gregory Carter[3], Anna Greenwood[1]
[1]Sage Bionetworks, Sage Bionetworks, Seattle, United States of America, [2]Jackson Laboratories, Computational Neuroscience, Bar Harbor, United States of America, [3]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America

Aims: We performed gene set enrichment analysis (GSEA) on the Accelerating Medicine Project-Alzheimer's Disease (AMP-AD) transcriptomic and proteomic datasets within the Target Enablement to Accelerate Therapy Development for AD (TREAT-AD) bioinformatics pipeline. The enrichment is mapped onto the 19 biological domains and the subordinate subdomains to show disease specific process involvement in AD across parallel datasets.
Methods: The TREAT-AD informatics pipeline ingests large datasets and scores them based upon genetic, transcriptomic and proteomic AD risk association. The scored genes are aligned with their gene ontology terms. The biological domains describe 19 core areas of endophenotypic investigation in AD based upon systematic alignment of GO terms defining each domain. In order to more accurately and specifically identify disease processes within each biological domain, we developed risk-associated subdomains for each biological domain. The AMP-AD transcriptomic and proteomic data was aligned to both the biological domains and subdomains, with preliminary characterization of cell-type specificity mapping.
Results: The biological domain and subdomain enrichment across datasets demonstrated unique signatures of disease process. We were able to stratify previously observed signal in core down-regulated processes (Synapse and Mitochondria) and up-regulated processes (Immune Response, Structural Stabilization, and Lipid Metabolism) to more specific areas such as electron transport chain function and mitochondrial transport within the Mitochondria biological domain, core synaptic signaling and processing pathways in Synapse, and activation of innate immune response and adaptive immune response in the immune response biological domain.
Conclusions: The biological domain and subdomain mapping of AD-risk associated process may facilitate an open-source, open-science shareable resource for comparison of large datasets integrated into specific biological areas for identification of future therapeutic targets and hypotheses.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0643 / #986

Poster Topic: *Theme A: β-Amyloid Diseases / A06.f. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

ANALYTICAL VALIDATION OF BLOOD MITOCHONDRIAL METYLCYTOSINES FOR THE PROGNOSIS OF ALZHEIMER'S DISEASE DEMENTIA PROGRESSION AT MCI STAGE

POSTERS: A06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Paula Ferrer-Raventós[1], Beatriz Fontal[1], Pau Martí[2], Carla Trapero[3], Jose Luis Mosquera[2], Marta Blanch[1], Marta Barrachina[4]
[1]ADmit Therapeutics S.L., R&d Department, Esplugues de Llobregat, Spain, [2]ADmit Therapeutics S.L., Bioinformatics And Data Science Department, Esplugues de Llobregat, Spain, [3]ADmit Therapeutics S.L., Project Management, Esplugues de Llobregat, Spain, [4]ADmit Therapeutics S.L., Ceo, Esplugues de Llobregat, Spain

Aims: ADmit has developed a cutting-edge technology based on next-generation sequencing (NGS) analysis of mitochondrial DNA (mtDNA) epigenetic biomarkers present in the blood of patients with mild cognitive impairment (MCI). It provides a percentage of progression to Alzheimer's disease dementia (ADD) using a machine learning approach. The aim is to analyze the stability of mtDNA methylation: a) in blood stored at room temperature (RT), b) in different DNA freeze-thaw cycles, and c) in sample replicates.
Methods: Extracted DNA from whole blood recruited at Bellvitge University Hospital (Barcelona, Spain) was treated with bisulfite. Libraries were generated and sequenced by NGS using the MiSeq Illumina platform. a) From the blood of 5 patients, we extracted DNA immediately and stored other blood aliquots at RT for 2, 6, and 12 days prior to DNA extraction, b) we completed the following freeze-thaw cycles in DNA from 8 patients: 1, 3, 6 and 12 cycles, and c) we used DNA from 10 patients and replicate the bisulfite treatment 8 times.
Results: DNA methylation patterns in D-loop and ND1 mitochondrial regions are stable in the different conditions showing no significant statistical differences (FWER> 0.05) and no technical batches associated with systematic variation. We showed replicability in samples from the same patient. These results demonstrated the repeatability and reproducibility of our method within our facilities.
Conclusions: The storage conditions that samples may encounter during normal shipping and handling processes do not impact on mtDNA methylation. Therefore, our mtDNA mitochondrial approach is a feasible prognostic tool for the progression of ADD at the MCI stage.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0644 / #1840

Poster Topic: *Theme A: β-Amyloid Diseases / A06.f. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

FUNCTIONAL ANALYSES OF CPG-RELATED SINGLE NUCLEOTIDE POLYMORPHISMS IN ALZHEIMER'S DISEASE

POSTERS: A06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Yiyi Ma[1,2,3], Sanjeev Sariya[2,3,4], Dolly Reyes-Dumeyer[2,3,4], Rafael Lantigua[5], Martin Medrano[6], Diones Rivera[7,8], Ivonne Jiménez-Velázquez[9], Adam Brickman[2,3,4], Giuseppe Tosto[2,3,4], Badri Vardarajan[2,3,4], Richard Mayeux[2,3,4]
[1]Columbia University Irving Medical Center, Center For Translational And Computational Neuroimmunology, Department Of Neurology, New York, United States of America, [2]Vagelos College of Physicians and Surgeons, Columbia University, Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York, United States of America, [3]Columbia University, New York Presbyterian Hospital, Department Of Neurology, Vagelos College Of Physicians And Surgeons, New York, United States of America, [4]Vagelos College of Physicians and Surgeons, Columbia University, G.h. Sergievsky Center, New York, United States of America, [5]Columbia University Medical Center, Department Of Internal Medicine, New York, United States of America, [6]Pontificia Universidad Catolica Madre y Maestra, School Of Medicine, Santiago, Dominican Republic, [7]Universidad Pedro Henriquez Urena, School Of Medicine, Santo Domingo, Dominican Republic, [8]CEDIMAT, Plaza de la Salud, Department Of Neurosurgery, Santo Domingo, Dominican Republic, [9]Universidad de Puerto Rico, Medical Sciences Campus, Department Of Internal Medicine, San Juan, Puerto Rico

Aims: CpG-related single nucleotide polymorphisms (CGS) are special types of single nucleotide polymorphism (SNP) because they change the sequence of CpG dinucleotides, the targeted methylation sites. CGS might have special importance to Alzheimer's disease (AD) since both genetic variants and epigenetic features contribute to AD pathogenesis. We studied the effects of CpG variants in AD among a cohort of Caribbean Hispanics.
Methods: We annotated the CGS by checking the three base pairs flanking each SNP and derived the dosage of the CpG site-creating allele of multiple CGSs in each 1 Kb window across the genome. We conducted the genome-wide sliding window-based association analysis across 7,155 individuals, of which 3,194 (44.6%) were diagnosed as clinical AD. We used generalized linear mixed models (GLMMs) implemented in GMMAT with adjustments for age, sex, population structure, genomic relation matrix, and genotyping batches. For those genome-wide significant windows (P<5.0x10^{-8}), we conducted functional analyses using human brain DNA methylation and gene expression data in tissue from 116 Hispanic individuals.
Results: There were three independent genome-wide significant regions, which were located at *APOE* (Score=75.1, P=7.26x10^{-26}), *ADAM20* (Score=55.2, P=4.06x10^{-8}), between *VRTN* (Score=-19.6, P=1.47x10^{-8}) and *SYNDIG1L* (14q24) (Score=-37.7, P=2.25x10^{-9}), and *SPG7* (16q24.3) (Score=40.5, P=2.23x10^{-8}). Significant mQTL signals at *ADAM20* and *SPG7* were associated with reduced mRNA expression levels (P<0.05).
Conclusions: The CpG-related loci identified above in *APOE, ADAM20, VRTN-SYNDIGIL* and *SPG7* appear to act as functional hubs that could contribute to the effects of these genes in AD. *APOE, ADAM20,* and *SPG7* have been previously associated with AD in other populations, thus further investigation of CpG-related sites is warranted.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0645 / #2241

Poster Topic: *Theme A: β-Amyloid Diseases / A06.f. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

EPIGENOME-WIDE ANALYSIS REVEALS METHYLATION DIFFERENCES ASSOCIATED WITH APOE STATUS IN CELL-FREE DNA IN ALZHEIMER'S DISEASE

POSTERS: A06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Mónica Macías[1], Juan José Alba-Linares[2,3,4,5], Blanca Acha-Santamaria[1], Idoia Blanco-Luquin[1], Agustín Fernández Fernández[2,3,4,5], Miren Roldan[1], Amaya Urdánoz-Casado[1], Maitane Robles[1], Eneko Cabezon-Arteta[1], Javier Sánchez Ruiz De Gordoa[1,6], Jon Corroza[6], Elena Erro[1,6], Ivonne Jericó[6], Mario Fernández Fraga[2,3,4,5], Maite Mendioroz[1,6]
[1]Navarrabiomed, Hospital Universitario de Navarra-IdiSNA (Navarra Institute for Health Research), Universidad Pública de Navarra (UPNA), Neuroepigenetics Laboratory, Pamplona, Spain, [2]Nanomaterials and Nanotechnology Research Center (CINN-CSIC), Cancer Epigenetics And Nanomedicine Laboratory, El Entrego, Spain, [3]University of Oviedo, Health Research Institute Of Asturias (ispa-finba), Oviedo, Spain, [4]University of Oviedo, Institute Of Oncology Of Asturias (iuopa), Oviedo, Spain, [5]Carlos III Health Institute (ISCIII), Rare Diseases Ciber (ciberer), Madrid, Spain, [6]Hospital Universitario de Navarra-IdiSNA (Navarra Institute for Health Research), Neurology, Pamplona, Spain

Aims: Recent studies show that Alzheimer's disease (AD) patients harbor specific methylation marks in the brain. The main goal of the present study was to characterize circulating cell-free DNA (cfDNA) as a novel source of AD-specific epigenetic biomarkers to aid non-invasive diagnosis of AD by liquid biopsy procedures.
Methods: cfDNA was isolated from 2 mL plasma of 35 AD patients and 35 age- and gender-matched cognitively healthy controls by using QIAmp Circulating Nucleic Acid Kit (Qiagen) and bisulfited converted. Subsequently a genome-wide methylation analysis was executed using the Illumina Infinium® MethylationEPIC BeadChip microarray in the Illumina HiScan System (Illumina). Methylation data was fully preprocessed using the *minfi* package in R software. Differentially methylated regions (DMRs) between AD patients and controls were identified using linear regression models defined in *limma* package and *limma p*-values were fed in the *comb-p* function of the *EN*mix package. Bisulfite cloning sequencing was performed to validate methylation results obtained from the microarray.
Results: cfDNA was readily isolated from AD patients and controls. Differential analysis revealed 17 DMRs comparing AD *APOE* ε4 carriers and controls *APOE* ε4 non-carriers and 4 hypermethylated DMRs between AD *APOE* ε4 non-carriers and controls *APOE* ε4 non-carriers (Sidak-corrected $p<0.05$). Interestingly, several DMRs were annotated to AD-related genes. A DMR annotated to *HKR1* gene was further validated and DNA methylation levels were shown to be strongly increased in AD patients compared to controls (82 ± 10% vs 17 ± 11%; $p<0.001$).
Conclusions: These results suggest that liquid biopsy technique would provide access to AD-specific information in a non-invasive way. The availability of blood sampling makes the analysis of epigenetic alterations in cfDNA a promising source of biomarkers in AD during patients' lifetime.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0646 / #363

Poster Topic: *Theme A: β-Amyloid Diseases / A06.f. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

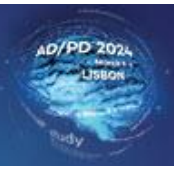
THE EPIGENETIC CODE OF ALZHEIMER'S DISEASE

POSTERS: A06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Alexi Nott, Philippa Wells, Kevin Ziegler
Imperial College London, Brain Sciences, London, United Kingdom

Aims: Interpreting Alzheimer's disease (AD) genetic risk variants is a major challenge because they are mostly located outside of genes and likely localise to gene regulatory regions called enhancers. Enhancers are sensitive to pathological changes and are dysregulated in the brains of AD patients. Recent studies have shown that AD-risk genes are expressed across vascular cell-types, as well as immune cells, however, epigenomic analysis of these rare cell-types is lacking. Our hypothesis goal is that the epigenetic landscape of vascular-associated cell-types in AD will define cell-type-specific disease-risk genes and will identify transcriptional regulators associated with pathology.
Methods: We have established florescence-activated nuclei sorting approaches to enrich nuclei from human vascular-associated cell-types (microglia, endothelial cells and pericytes), as well as neurons and oligodendrocytes. Acetylation of histone H3 Lysine 27 (H3K27ac) is located at active enhancers and is sensitive to changes in disease pathology. H3K27ac signal was assessed for our cell-type-enriched nuclei using chromatin immunoprecipitation and for rarer cell-types using single nuclei CUT&Tag.
Results: Epigenomic analysis of the neurovascular unit has identified a vascular-immune gene regulatory network. While AD genetics is predominantly associated with immune cells, we found that AD genetic risk is partially shared between immune and vascular cell-types and several loci are specific to the vasculature. Cell-type-specific epigenomic analysis in the AD brain has shown that gene regulatory regions are dysregulated across brain cell-types, in particular in glia and immune cell-types. AD-associated epigenomic changes mirror transcriptional changes and have now highlighted cell-type transcription factors that drive disease.
Conclusions: Collectively, these studies reveal cell-type-specific gene networks and transcription factors important for AD and highlight candidate targets that are dysregulated in disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0647 / #2117

Poster Topic: *Theme A: β-Amyloid Diseases / A06.f. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

DECIPHERING THE ROLE OF A NOVEL LONG NON-CODING RNA IN ASTROCYTE REACTIVITY AND ALZHEIMER'S DISEASE

POSTERS: A06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Sophie Schröder[1], Ulrike Fuchs[1], Dennis Krüger[1], Verena Gisa[1], André Fischer[1,2,3]
[1]German Center for Neurodegenerative Diseases (DZNE), Department For Epigenetics And Systems Medicine, Göttingen, Germany, [2]University Medical Center, Department Of Psychiatry And Psychotherapy, Göttingen, Germany, [3]University of Göttingen, Cluster Of Excellence "multiscale Bioimaging: From Molecular Machines To Networks Of Excitable Cells" (mbexc), Göttingen, Germany

Aims: Due to their diverse functions, long non-coding RNAs (lncRNAs) are emerging as important regulators of neuronal plasticity and have recently been linked to the onset and progression of neurodegenerative diseases such as Alzheimer's Disease. However, our knowledge about the role of tissue- and cell type-specific lncRNAs in the central nervous system is still limited. Therefore, the aim of this project was to identify astrocyte-specific lncRNAs in the human and mouse brain in the context of neurodegeneration and astrocyte reactivity and to characterize their function.
Methods: Single-nucleus total RNA sequencing data from brains of two non-demented humans were generated. From there, astrocyte-enriched lncRNAs were identified and their regulation in activated astrocytes and cognitive diseases was evaluated. The most intriguing candidate, here named AstroLNC, was then further characterized regarding its role in astrocytes.
Results: AstroLNC was found to be the most astrocyte-specific lncRNA in the human brain that has a mouse homologue. It was downregulated in reactive primary astrocytes and in Alzheimer's Disease. The knockdown of AstroLNC led to the acquisition of a pro-apoptotic and pro-inflammatory phenotype. At the same time, important astrocytic functions such as the uptake of glutamate and release of lactate were reduced, leading to the impaired support of primary neurons.
Conclusions: Astrocytes provide important metabolic support functions for neurons and can furthermore also tightly interact with synapses. The lncRNA AstroLNC is important for maintaining the expression levels of many synaptic genes and, at the same time, inhibiting the acquisition of a pro-apoptotic and pro-inflammatory phenotype. The downregulation of AstroLNC in activated astrocytes and in Alzheimer's Disease might contribute to disease progression and could be, due to its high cell-type specificity, an attractive drug target.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0648 / #2814

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

DEVELOPMENT OF CELL MODELS OF SPORADIC ALZHEIMER'S DISEASE BY CAPTURING PATIENT-DERIVED TRANSCRIPTOMIC FINGERPRINTS

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Alicia González Díaz[1], Andrea Possenti[1], Gustavo Antonio Urrutia[2], Benedetta Mannini[3], Michele Vendruscolo[1]
[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]WaveBreak Therapeutics, Cell Biology Platform, Cambridge, United Kingdom, [3]University of Florence, Department Of Experimental And Clinical Biomedical Sciences Mario Serio, Florence, Italy

Aims: While the aetiology of familiar Alzheimer´s Disease (fAD) is determined by genetic mutations in well-characterised genes, sporadic AD (sAD) arises from a complex interplay between genes and environment that remains poorly understood. This project rises from the hypothesis that early causative disease states, triggered by genetic and external factors, highly difficult to model, can be defined by transcriptomic fingerprints that functionally drive the cells into the disease phenotype. In this context, we aimed to integrate such fingerprints in human cells for the generation of sAD models.
Methods: We have developed a pipeline for the validation of early transcriptomic alterations identified from post-mortem patient samples which hold the potential to be causative of sAD. Bioinformatically-predicted candidates were analysed in human neuroblastoma SH-SY5Y cells to assess the effect of their knockdown (KD) on Aβ aggregation. Shortlisted candidate genes were then validated in iPSC-derived cortical neurons to study whether AD relevant phenotypes were triggered upon early expression perturbation.
Results: Our SH-SY5Y pre-screening assay identified 12 candidates which increased Aβ aggregation upon KD. FBXO2, a subunit of the ubiquitin protein ligase complex SCF, was chosen for further validation. The early downregulation of *FBXO2* in wild-type human cortical neurons triggered amyloidopathy, tauopathy and both functional and structural network impairment, hence enabling the generation of a comprehensive model of sporadic AD.
Conclusions: We report a neuronal model of sAD that recapitulates a set of key molecular AD hallmarks. We envision to expand our strategy towards the generation of panels of preclinical models that faithfully capture the molecular complexity of the full spectrum of AD patients, steering the drug discovery field towards personalised medicine.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0649 / #771

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

TRAUMATIC BRAIN INJURY EXACERBATES MEMORY IMPAIRMENTS AND AMYLOID PATHOLOGY IN THE 3XTG-AD MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Laura Abelleira Hervas, Hojun Kim, Magdalena Sastre
Imperial College, Brain Science, LONDON, United Kingdom

Aims: The cause of Alzheimer's disease (AD) remains unidentified, but it is likely the result of a combination of genetic and environmental factors. One significant risk factor for AD is traumatic brain injury (TBI). Several AD-associated pathological features, including Aβ deposition, elevated phosphorylated tau levels, acetylcholine deficits, blood-brain barrier disruption and memory decline have been detected in TBI-affected brains. The aim of this study was to investigate functional and pathological effects of a single closed head injury (CHI) in a mouse model of amyloid and tau pathology, the 3xTg-AD mouse, with the hypothesis that TBI may lead to memory impairments and in a raise on deposition of Aβ and tau phosphorylation, potentially exacerbating the progression to AD.
Methods: We induced a CHI in 6-month-old male and female 3xtg-AD mice using a 5mm flat steel tip electromagnetic impactor (Leica Impact One). The impact was aimed at bregma point (ML=0.0mm, AP=0.0mm), at a 4.0m/s with a 100ms dwell time and a 1mm impact. After a 28-day post-injury period, cognitive and locomotion functions were evaluated, and various inflammatory, neurodegenerative, and blood-brain barrier (BBB) markers were assessed using immunohistochemistry and immunofluorescence methodologies.
Results: Our findings reveal that CHI in 3xtg-AD mice leads to significant deficits in learning and memory when compared to sham animals by fear conditioning and novel object recognition tests. Additionally, we observed a 38% rise in intraneuronal amyloid beta (Aβ) accumulation and disruptions in the blood-brain barrier within the pericontusional cortex following CHI. In addition, we observed sexual dimorphisms in these effects.
Conclusions: In conclusion, our study demonstrates that the closed head injury model aggravates behavioural impairments and Aβ pathology in 3xtg-AD brain pathology 28 days after injury.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0650 / #598

Poster Topic: *Theme A: β-Amyloid Diseases / A06.f. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

INVESTIGATION OF THE CELL TYPE SPECIFIC PFC ENHANCER AND PROMOTER LANDSCAPE IN ALZHEIMER'S DISEASE

POSTERS: A06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Philippa Wells[1], Paulina Urbanavicicute[1], Reuben Yaa[1], Christian Nickl[2], Inge Holtman[3], Aydan Askarova[1], Sarah Marzi[1], Chris Glass[2], Alexi Nott[1]
[1]Imperial College London, Brain Sciences, London, United Kingdom, [2]UCSC, Dept. Of Cellular & Molecular Medicine, San Diego, United States of America, [3]University of Groningen, Department Of Biomedical Sciences Of Cells & Systems, Groningen, Netherlands

Aims: Alzheimer's disease is a complex progressive neurodegenerative disease, having major lifespan and societal implications in the context of the ageing worldwide population. Sporadic Alzheimer's disease is highly heritable (~70%) and it has been shown that the majority of risk loci in AD are located within non-coding regions and are likely to drive regulation of gene expression. Concurrently, differences in histone acetylation have been observed in the AD brain, likely secondary to genetic and non-genetic factors. There is a requirement to understand these processes in a cell-type specific manner.
Methods: We undertook a large-scale study to delineate the promoter and enhancer landscape in Alzheimer's disease (AD), using cell type enriched nuclei populations from post-mortem pre-frontal cortex (PFC). We investigated differentially acetylated regions as revealed by ChIPseq at (H3K27ac) within neurons, oligodendrocytes and microglia. We profiled differences in histone acetylation in AD compared to non-AD individuals, whilst controlling for potential biological and technical confounders and integrated profiles with genomic and chromatin conformation data.
Results: Differentially acetylated regions were identified within oligodendrocytes (2131 hyper-acetylated and 1310 hypo-acetylated), neurons (121 hyper and 148 hypo acetylated), and microglia (1511 hyper and 908 hypo acetylated) in AD cases versus control samples (EdgeR; $q < 0.05$). Functional investigation of the differentially acetylated regions via gene pathway analysis and motif analysis identifying putative transcription factors in AD demonstrated cell type specific roles in numerous disease pertinent processes including oxidative stress, immune response, excitotoxicity and circadian rhythm.
Conclusions: We have demonstrated cell type specific histone acetylation differences in the AD PFC, which are particularly evident within microglia and oligodendrocytes, giving much needed insight into mechanisms of disease in a cell type specific manner. Our work highlights mechanisms which may reflect useful therapeutic targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0651 / #497

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

MORPHOLOGICAL, BIOCHEMICAL AND RESPIRATORY EFFECTS OF DIFFERENTIATION ON SH-SY5Y CELLS

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Rachel Cruickshank, Lisa Chakrabarti, Kevin Gough
University of Nottingham, School Of Veterinary Medicine And Science, Loughborough, United Kingdom

Aims: In cellular models of Alzheimer's disease (AD), the neuroblastoma derived cell line SH-SY5Y is commonly used. Various methods exist to differentiate SH-SY5Y cells into a mature neuron-like phenotype. The main objective of this study is to assess the morphological, biochemical and respiratory changes of three SH-SY5Y differentiation protocols and evaluate their effectiveness as potential AD models.
Methods: Cells were differentiated according to previously described protocols using insulin like growth factor 1 (IGF-1), retinoic acid (RA), or RA combined with brain derived neurotrophic factor (BDNF). Immunocytochemistry was performed to assess morphological changes. Western blots were performed to assess protein level changes. High resolution respirometry was used to assess respiratory changes. Statistical analysis was performed with T-tests and ANOVA.
Results: Morphologically, ~90% of RA/BDNF and IGF-1 differentiated cells displayed neurites equal to or greater in length than the cell body, compared to 65% of RA differentiated cells and 25% of undifferentiated cells. RA and RA/BDNF differentiated cells had significantly higher levels of choline acetyl transferase and synaptophysin proteins than undifferentiated and IGF-1 differentiated cells. IGF-1 differentiated cells displayed significantly increased beta-III-tubulin protein levels compared to other cell types. Rotenone-induced inhibition of respiration was less pronounced in RA differentiated cells, suggesting that RA differentiation decreased the proportional contribution of complex I to respiration.
Conclusions: Morphologically, RA/BDNF and IGF-1 cells display a more mature neuronal phenotype than RA differentiated and undifferentiated cells. Biochemically, both RA and RA/BDNF differentiated cells display the same cholinergic phenotype, making them ideal for AD modelling. Mitochondrial dysfunction is an early hallmark of AD neurotoxicity, so an understanding of the way differentiation affects respiration is an important consideration in cellular modelling of AD. The novel respiratory differences presented provide insight into these developmental changes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0652 / #983

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

USING COMPLEX GENETICS IN MICE TO UNLOCK THE SECRETS OF RESILIENCE TO DEMENTIA

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Julia Rosander[1], Vivek Philip[2], Niran Hadad[2], Timothy Hohman[3], Vaibhav Janve[3], Yiyang Wu[3], Vilas Menon[4], Catherine Kaczorowski[1]
[1]The University of Michigan, Neurology, Ann Arbor, United States of America, [2]The Jackson Laboratory, Genetics, Bar Harbor, United States of America, [3]Vanderbilt University Medical Center, Vanderbilt Memory & Alzheimer's Center And Vanderbilt Genetics Institute, Nashville, United States of America, [4]Columbia University, Neurology, New York, United States of America

Aims: Cognitive resilience to AD is a phenomenon whereby and individual presents with normal cognitive function despite harboring familial Alzheimer's disease (FAD) mutations and corresponding brain neuropathologies. Determination of the underlying mechanisms of cognitive resilience to AD will likely offer novel disease modifying therapeutics for individuals at-risk for AD.
Methods: To determine transcriptional changes associated with resilience, we profiled the hippocampal transcriptome at the single cell level in top resilient and susceptible strains from the AD-BXD mouse reference panel, a genetically diverse mouse model of AD that better mimics human AD. Here, we used contextual fear memory paradigm to assess short-term memory function in AD-BXDs carrying the 5XFAD mutation. Resilience was defined based on age-related change in cognitive function relative to that of the entire AD-BXD population, where strains showing no or lower than average decline were considered resilient.
Results: We show that cognitive resilience is characterized by a transcriptional signature that diverges from that of susceptible strains in excitatory neurons of CA1, dentate gyrus and intratelencephalic neurons in layer 3 and 6 of the entorhinal cortex. We found that the transcriptional profile of resilient strains is enriched for regulation of transmembrane transport in presymptomatic stages that included a notable upregulation of Reln and Ntng2, whereas translation at the CA1 synapse corresponded to an upregulation of ribosomal genes in neurons from resilient AD mutation carrier mice.
Conclusions: Our findings suggest that resilience is conferred in memory-relevant regions through unique transcriptional changes in a cell-specific manner and provide a foundation for mechanistic studies required for resilience-based drug development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0653 / #1004

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

ABCA7 IS REQUIRED FOR MAINTAINING SYNAPTIC INTEGRITY AND ASTROGLIAL PROLIFERATION THROUGH UPREGULATED NEUROPEPTIDE Y ACTIVITY

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Huseyin Tayran[1], Prabesh Bhattarai[1,2], Elanur Yilmaz[1], Yuhao Min[3], Xue Wang[4], Özkan Is[5], Nastasia Nelson[1], Nada Kassara[1], Mehmet Cosacak[6], Ruya Dogru[1], Ronald Petersen[7], Kejal Kantarci[8], Joseph Reddy[4], Yiyi Ma[2], Min Qiao[9], Delaney Flaherty[1], Andrew Teich[2], Tamil Gunasekaran[10], Giuseppe Tosto[2], Badri Vardarajan[1], Nilüfer Ertekin-Taner[5,11], Richard Mayeux[1,2,10], Caghan Kizil[1,2]
[1]Columbia University Irving Medical Center, Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York, United States of America, [2]Columbia University Irving Medical Center, Department Of Neurology, New York, United States of America, [3]Mayo Clinc, Department Of Neuroscience, Jacksonville, United States of America, [4]Mayo Clinic, Department Of Quantitative Health Science, Jacksonville, United States of America, [5]Mayo Clinic, Department Of Neuroscience, Jacksonville, United States of America, [6]German Center for Neurodegenerative Diseases, Dzne, Dresden, Germany, [7]Mayo Clinic, Neurology, Rochester, United States of America, [8]Mayo Clinic, Radiology, Rochester, United States of America, [9]Columbia University Irving Medical Center, Neurology, New York, United States of America, [10]Columbia University Irving Medical Center, The Gertrude H. Sergievsky Center, College Of Physicians And Surgeons, New York, United States of America, [11]Mayo Clinic, Department Of Neurology, Jacksonville, United States of America

Aims: Genetic variations have emerged as crucial players in the etiology of Alzheimer's disease (AD), and they serve for a better understanding of the disease mechanisms; yet the specific roles of these genetic variants remain uncertain. Animal models with reminiscent disease pathology could uncover previously uncharacterized roles of these genes. Therefore, we generated zebrafish models for AD variants to analyze their function.
Methods: Using CRISPR/Cas9, we generated a knockout model for *abca7,* orthologous to human *ABCA7*. We performed single cell transcriptomics and analyzed the altered genes and molecular pathways in zebrafish. We leveraged data from multiethnic AD cohorts at Mayo Clinic and Columbia University, to perform genetic association studies, co-expression analyses, in silico interaction mapping, family based variant segregation analyses and epigenetic mQTL studies, and the functional and histological investigations in human and zebrafish.
Results: The *abca7*$^{+/-}$ zebrafish reduced astroglial proliferation, synaptic integrity, and microglial response after Aβ42 treatment. We found that the *abca7* loss-of-function (LOF) reduced neuropeptide Y (*npy*) expression as well as *bdnf* and *ngfr*. Human brain analysis showed reduced *NPY* in AD, regulatory interaction between *NPY* and *BDNF*, genetic variants in *NPY* associated with AD, and segregation of variants in *ABCA7*, *BDNF* and *NGFR* in families. *ABCA7* variants altered the epigenetic codes in *NPY*, *BDNF,* and *NGFR* promoter regions. Human results paralleled with zebrafish findings. NPY administration to zebrafish rescued the phenotypes in *abca7* knockout.
Conclusions: Our results demonstrate a previously unknown link between *ABCA7* and *NPY* in regulation of synaptic integrity and astroglial proliferation in AD. We show that zebrafish is a useful functional genomics model for investigating the roles of genetic variants found in humans.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0654 / #1227

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

TRANSCRIPTOMIC PROFILING IN MOUSE MODELS OF ALZHEIMER'S DISEASE REVEALS APOE GENOTYPE- AND SEX-DEPENDENT GLIAL CELL ALTERATIONS

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Yaqiao Li[1,2], Yanxia Hao[2], Carlota Serras[1], Seo Yeon Yoon[2], Brian Grone[2], Leonardo Ding[2], Jessica Blumenfeld[2], Tomiko Oskotsky[1], Yadong Huang[2,3], Marina Sirota[1]
[1]University of California, San Francisco, Bakar Computational Health Science Institute, San Francisco, United States of America, [2]Gladstone Institutes, Gladstone Institute Of Neurological Disease, San Francisco, United States of America, [3]University of California, San Francisco, Department Of Neurology, San Francisco, United States of America

Aims: This study aims to assess the complex interplay between age, sex, and APOE genotypes in regulating cell-type-specific transcriptional profiles in a mouse model of Alzheimer's Disease (AD).
Methods: Hippocampal samples of a sex-balanced cohort of APOE3-KI and APOE4-KI mice at 6, 12, and 18 months of age were collected for single-nuclei RNA-sequencing (snRNA-seq). Quality assurance, count normalization, clustering, cell type identification, and differentially expressed gene (DEG) analysis were performed using the Seurat package in RStudio.
Results: The snRNA-seq dataset comprises 527,395 cells covering 27,153 genes. 35 cell clusters were identified, representing six major brain cell types: astrocytes, microglia, oligodendrocytes, oligodendrocyte precursor cells (OPCs), and excitatory and inhibitory neurons. We found that sex significantly influenced cell fraction variance in astrocyte and inhibitory neuron clusters, while APOE genotype and its interaction with age significantly impacted cell fraction variability in the OPC cluster. Analyzing sex and age-stratified DEGs and enriched pathways in APOE4-KI versus APOE3-KI microglia and astrocytes revealed age-dependent inverse effects in males and females dependent on APOE genotypes. At 12 months, proliferation-related genes were upregulated in APOE4-KI males and downregulated in females. At 18 months, synaptic activity and neurogenesis-related genes were downregulated in APOE4-KI males but upregulated in females. Furthermore, males exhibited consistent gene regulation by APOE genotypes across cell types, while females displayed a greater prevalence of opposing DEG regulations. Lastly, cell-cell communication analysis with CellChat revealed sex-biased communication from astrocytes to inhibitory neurons, with an age-dependent augmentation.
Conclusions: There is a clear interplay between age, APOE genotype, and sex in mouse models of AD, with strong sex-biased effects in microglia and astrocytes. This suggests that targeting sex-specific glial cell dysfunction could be a valuable precision medicine approach.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0655 / #1899

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

PRIMARY CILIA DYSREGULATION IN ALZHEIMER'S DISEASE

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Emiko Miller[1], Peter Bambakidis[2], Edwin Vázquez-Rosa[3], Zea Bud[4], Youngmin Yu[3], Yeo Jung Koh[5], Salvatore Caradonna[3], Preethy Sridharan[6], Coral Cintrón-Pérez[7], Kathryn Franke[8], Sarah Barker[5], Andrew Pieper[7]
[1]Case Western Reserve University School of Medicine, Department Of Neurosciences, Cleveland, United States of America, [2]St.Olaf College, Department Of Chemistry, Northfield, United States of America, [3]Case Western Reserve University, Psychiatry, Cleveland, United States of America, [4]Case Western Reserve University, Frances Payne Bolton School Of Nursing, Cleveland, United States of America, [5]Case Western Reserve University, Pathology, Cleveland, United States of America, [6]Case Western Reserve University, Neuroscience, Cleveland, United States of America, [7]University Hospitals Cleveland Medical Center, Harrington Discovery Institute, Cleveland, United States of America, [8]Louis Stokes VA Medical Center, Geriatric Psychiatry, Cleveland, United States of America

Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that lacks any kind of effective treatment options. A critical barrier to overcome right now is understanding disease pathogenesis to identify new neurotherapeutic opportunities. AD is canonically characterized by the buildup of amyloid plaques and tau tangles, which is thought to lead to neurodegeneration and progressive loss of cognitive function. Although there has been a concerted effort to investigate these pathological mechanisms, we still lack therapeutic success. Therefore, we aim to identify new targets through the primary cilium, which is a widely overlooked neuronal signaling hub that might offer insights into the pathophysiology of AD.
Methods: To help investigate the etiology of neurodegeneration in AD, we conducted unbiased analysis of differentially expressed genes (DEGs) in postmortem brains from AD subjects, compared to age-matched non-AD control subjects. Differentially expressed genes related to the primary cilia were further investigated in pre-symptomatic and post-symptomatic 5xFAD mice, an amyloid-driven mouse model of AD that carries five human mutations in the amyloid precursor protein and presenilin 1 genes.
Results: This effort revealed a unexpectedly high number of DEGs that were related to the neuronal primary cilia, an organelle that has received very little attention in the field of AD. Gene ontology analysis revealed dysregulation of cilium biogenes and degredation. Notably, we found significant downregulation of that primary cilia specific adenylate cyclase 3 (AC3) in both 5xFAD mice and humans with AD.
Conclusions: In conclusion, our research has unveiled a novel perspective on AD by bringing the neuronal primary cilia to the forefront of investigation. These findings position the primary cilia as a previously unrecognized locus of injury in AD pathology which could serve as new neurotherapeutic targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0656 / #919

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

UNDERSTANDING THE MOLECULAR MECHANISMS THAT DRIVE NEURONAL LOSS IN PARKINSON'S DISEASE

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Joe Park, Wayne Carter
University of Nottingham, Medical School, nottingham, United Kingdom

Aims: While Parkinsons disease (PD) proteomic changes have been established in the context of Lewy body and α-synuclein aggregates this study aimed to investigate further changes in Protein I-isoaspartyl methyltransferase (PIMT) and Microtubule Associated Protein 2 (MAP2) . With the changes in expression of these proteins in different regions of the PD brain being less understood.
Methods: A cohort of 10 PD and 10 control (CO) age and sex matched post-mortem samples were used with samples from the prefrontal cortex (PFC) , hippocampus and corpus callosum (CC) . These underwent protein assays, SDS-PAGE and western immunoblotting for PIMT and MAP2 detection for each brain region. The proteins were detected and quantified using imageLab6.0 before being normalised to the housekeeping protein Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and total lane protein (TLP). A Mann-Whitney U test was used to calculate statistical significance.
Results: MAP2 expression increased by a statistically significant 650% (p-value = 0.0052 normalised to TLP) in the PFC. While PIMT expression decreased by a statistically significant 42% (p-value = 0.0040 normalised to TLP) in the same brain region when comparing PD to CO samples. For the hippocampus and CC no statistically significant results were achieved. It is worth noting this data is preliminary and these protein changes may also be validated using an alternative method such as immunohistochemistry .
Conclusions: These results show the potential importance of normal regulation of MAP2 and PIMT in preventing neurodegeneration in the PD brain. These insights provide basis for the potential future use of MAP2 and PIMT as biomarkers. Additionally, the proposed mechanisms by which cytosolic dopamine (DA) affects PIMT and post translational modifications affect MAP2 may provide possible mechanisms to utilise for therapeutic benefit.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0657 / #1308

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

A COMPARATIVE ANALYSIS OF IPSC-DERIVED NEURAL PROGENITOR CELLS AND ADULT HUMAN NEURAL STEM/PROGENITOR CELLS

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Yu-Mi Shim[1,2,3], Sooyeon Yoo[1,2], Kwanghoon Lee[1,2], Seoug-Ik Kim[1,2,3], Jae-Kyung Won[1,2], Sung-Hye Park[1,2,3]
[1]Seoul National University Hospital, Dementia Brain Bank, Seoul, Korea, Republic of, [2]Seoul National University Hospital, Pathology, Seoul, Korea, Republic of, [3]Seoul National University, Pathology, Seoul, Korea, Republic of

Aims: Neuroscience increasingly uses iPSC-derived NPCs and aNSPCs for brain research, offering new perspectives but presenting developmental challenges. Our study aims to compare these cell types, clarifying their properties and applications to aid in selecting the right model for specialized neuroscience investigations.
Methods: aNSPCs were sourced from epilepsy patients' ependymal layer near the hippocampus and postmortem SVZ samples. iPSCs were cultured, induced to form EBs, then underwent neural induction via dual SMAD inhibition. RNA sequencing was performed on various SNUH samples using the Illumina platform (TruSeq)
Results: Bulk RNA sequencing revealed that samples within similar groups had nearly identical gene expression patterns, as depicted in an MDS plot. Notably, iNPC and aNSPC samples closely clustered, suggesting shared neurodevelopmental and functional attributes. However, differences exist. While both cell types show similar developmental potential, ICC analysis indicates that aNSPCs are more mature than iNPCs. This is evident from aNSPCs expressing CD133, PAX6, and NESTIN. In contrast, iNPCs also express SOX2, a neural stem cell marker. Neither cell type expressed common neuronal markers like OCT4, NANOG, MAP2, NeuN, GFAP, or OLIG2.
Conclusions: Our study compares iPSC-derived neural progenitor cells (iNPCs) and adult human neural stem/progenitor cells (aNSPCs) using RNA sequencing and ICC experimentation. Results show shared neurodevelopmental attributes between these cell types, but also differences in maturity and developmental markers. This ongoing study plans to include additional iNPC samples for further analysis. The insights gained can potentially guide future research into therapeutic applications of these cells in neurodegenerative disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0658 / #2105

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

DOPAMINE STIMULATES L-LACTATE PRODUCTION IN SINGLE PRIMARY ASTROCYTES

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Keita Sugiyama[1], Anemari Harvot[1,2], Nina Vardjan[1,2], Robert Zorec[1,2]
[1]Laboratory of Neuroendocrinology - Molecular Cell Physiology, Institute of Pathophysiology, Faculty Of Medicine, Ljubljana, Slovenia, [2]Laboratory of Cell Engineering, Celica Biomedical, Ljubljana, Slovenia

Aims: Dopaminergic signaling is associated with various neurodegenerative diseases, including Alzheimer's and Parkinson's disease, and has garnered attention as a potential target for astrocytes. However, the regulatory role of dopamine in astroglial metabolism, especially L-lactate production is poorly understood. Previous research shows that astroglial aerobic glycolysis with the end product L-lactate is regulated by both Ca^{2+} and cAMP signaling influenced by noradrenaline binding to adrenergic receptors. In this research, we, therefore, investigated the effect of dopamine on astroglial aerobic glycolysis.
Methods: Primary astrocyte cultures were derived from the cortex of 2–3-day-old Wistar rats, and we used the inverted fluorescence microscope system (Colibri, Zeiss) to employ the fluorescence resonance energy transfer (FRET) technique. To evaluate the response of astrocytes to dopamine at the single-cell level, astrocytes were transfected with the FRET cAMP nanosensor (Epac1-camps) and the FRET L-lactate nanosensor (Laconic). Using agonists and antagonists, we targeted the D1 receptors but also β-adrenergic receptors, monitoring the concentrations of intracellular cAMP ($[cAMP]_i$) and L-lactate ($[lac]_i$).
Results: Dopamine induced a dose-dependent increase in $[cAMP]_i$ largely via D1 receptor activation, which was confirmed by a D1 receptor agonist (SKF81297) and inhibited by a D1 receptor antagonist (SCH23390). When dopamine was applied in the presence of a β-adrenergic receptor antagonist (Propranolol), the increase in $[cAMP]_i$ was partially inhibited. Moreover, dopamine application increased $[lac]_i$ in astrocytes.
Conclusions: Our results suggest that (i) dopamine modulates $[cAMP]_i$ via not only the D1 receptors but also possibly through the β-adrenergic receptors, and that (ii) dopamine facilitates aerobic glycolysis via these receptors. Future work will delve into the dopamine-induced dynamics of intracellular glucose and Ca^{2+} in astrocytes to further elucidate the regulatory role of dopamine in astroglial metabolism.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0659 / #2594

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

EXCITATORY AND INHIBITORY NEURONS PRODUCE DISTINCT AMYLOID STRUCTURES IN MOUSE MODELS OF APP OVEREXPRESSION

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Gabriella Perez, Rong Zhao, Danish Uddin, Joanna Jankowsky
Baylor College of Medicine, Neuroscience, Houston, United States of America

Aims: We investigated how the cellular localization of pathogenic amyloid precursor protein (APP) might influence amyloid accumulation in the brain. Our primary objective was to understand how different neuronal subtypes contribute to the heterogeneity of amyloid beta (Aβ) plaque development.
Methods: We generated transgenic mouse models to overexpress APP either in excitatory neurons using the CaMKII promoter, or in inhibitory neurons using the GAD2 promoter. We immunostained brain sections from each model to measure Aβ plaque load, identify fibrillar plaques using thioflavin-S, evaluate microglial activation around plaques using Iba1, and detect dystrophic neurites using LAMP-1. We also measured Aβ40 and Aβ42 levels from the cortices of these models using the Luminex platform.
Results: We found significant differences in Aβ aggregation patterns between the two models. Plaque formation appeared earlier in the CaMKII-APP model than in the GAD2-APP model, beginning at 3 and 18 months respectively. The GAD2-APP model exhibited primarily diffuse Aβ deposits and lacked fibrillar plaques throughout the cortex, while the CaMKII-APP mice displayed extensive fibrillar deposits. Microglial activation and dystrophic neurites were prominent around plaques in the CaMKII-APP mice, but these responses were absent in the cortex of GAD2-APP animals. Remarkably, although both models expressed the same APPswe/ind transgene, GAD2-APP mice deposited a much greater level of Aβ42 relative to 40 than CaMKII-APP mice.
Conclusions: Our findings suggest that distinct neuronal subtypes process APP in distinct ways to produce different Aβ structures. This diversity of Aβ aggregation may contribute to the heterogeneity observed in Alzheimer's disease pathology, clinical presentation, and disease progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0660 / #1240

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

AGE- AND SEX-DEPENDENT CHANGES IN SLEEP AND NESTING BEHAVIOR IN AN ALZHEIMER'S DISEASE MOUSE MODEL, APP-SAA KNOCK-IN MICE

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Marilyn Duncan[1], Haleigh Whitlock[1], Jayden Alcorn[1], Will Briones[1], Michael Murphy[2], Sridhar Sunderam[3], Bruce O'Hara[4], Adam Bachstetter[1]
[1]University of Kentucky Medical School, Dept. Of Neuroscience, Lexington, United States of America, [2]University of Kentucky Medical School, Dept. Of Biochemistry, Lexington, United States of America, [3]University of Kentucky College of Engineering, Dept. Of Biomedical Engineering, Lexington, United States of America, [4]University of Kentucky College of Arts and Sciences, Dept. Of Biology, Lexington, United States of America

Aims: Aims: To investigate if the APP^{SAA} knock-in mouse model of Alzheimer's disease exhibits age- and sex-dependent changes in sleep and nesting, an activity of daily living that enhances sleep.
Methods: Methods: Using a longitudinal design, sleep and nesting were monitored in male and female APP^{SAA} and wild-type (WT) mice (N=8/genotype/sex) from 4-17 months of age, because previous studies indicate that APP^{SAA} mice exhibit amyloidosis and running behavior alterations during this age range. Every 2-3 months, the mice were transferred to individual cages for piezoelectric sleep recording for one week. Each cage contained cotton squares, allowing construction of nests that were scored on a 5-point scale (5=best nest). Sleep percentages during the light, dark, and 24-hour periods were assessed with SPSS 28.0, using 2-way ANOVA to test for the main effects of sex and genotype. Kruskal Wallis was used to asses nesting scores.
Results: Results: At all ages tested, female mice of both genotypes slept less than male mice. APPSAA mice showed significantly less daytime and total sleep percentages than WT mice at 15 and 17 months. Nesting scores were not significantly affected by sex but decreased as the mice aged (P<.001), with APPSAA mice showing lower scores at 15 and 17 months.
Conclusions: Conclusions: Female sex deleteriously affects sleep in the APPSAA mice, as previously observed in other AD mouse models. At older ages, the APPSAA mice exhibit a loss of daytime (rest phase) sleep, mimicking the condition in AD patients. Nesting, a mouse activity of daily living, also declines with age, more prominently in the APPSAA than WT mice. In summary, APPSAA mice exhibit age-related behavioral changes that are similar to those observed in AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0661 / #1011

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

COMBINED REDUCTION OF AMYLOID-BETA AND TAU PRODUCTION RESCUES NEURONAL CIRCUIT DYSFUNCTION IN A MOUSE MODEL OF ALZHEIMER'S DISEASE.

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Robert Ellingford[1], Samuel Harris[1], Rikesh Rajani[1], Lindsay Welikovitch[2], Eric Jacobi[3], Sonia Ruggieri[3], Rhiannon Laban[1], Amanda Heslegrave[1], Dervis Salih[1], Umran Yaman[1], Henrik Zetterberg[1], Jakob Von Engelhardt[3], Bradley Hyman[2], Marc Aurel Busche[4]
[1]UK Dementia Research Institute, University College London, London, United Kingdom, [2]Harvard Medical School, Massachusetts Alzheimer's Disease Research Center, Charlestown, United States of America, [3]Institute of Pathophysiology, Johannes Gutenberg University, Focus Program Translational Neuroscience, University Medical Center, Mainz, Germany, [4]University College London, Uk Dementia Research Institute At Ucl, London, United Kingdom

Aims: The memory deficits and cognitive decline associated with Alzheimer's Disease (AD) become evident when both amyloid-beta and tau pathology are widespread across cortical-hippocampal circuits. However, the causes of dysfunction within these circuits in AD, and whether this dysfunction is reversible, remains unknown. We aimed to assess the impact of amyloid-beta and tau accumulation upon the function of cortical-hippocampal circuits and determine whether any associated deficits can be rescued following reduced expression of these proteins.
Methods: We used two-photon calcium imaging and multi-region Neuropixels electrophysiology to record neuronal activity within cortical-hippocampal circuits of the APP/PS1xTg410 mouse model of AD, before and after treatments to suppress amyloid-beta and/or tau production. We employed additional immunohistochemistry, blood plasma analysis and nucleated patch electrophysiology to assess the effect of treatment on AD biomarkers and investigate the mechanisms underlying treatment effects.
Results: Accumulation of amyloid-beta and tau caused a strong reduction in neuronal firing across cortical-hippocampal circuits. Importantly, combined reduction of both pathogenic proteins was sufficient to reinstate normal activity patterns while reducing individually proteins had no impact on neuronal dysfunction. Combination treatment prevented the accumulation of soluble AD-associated biomarkers but had no impact on the density of neuropathological plaques and tangles in cortical tissue. Finally, restoration of neuronal activity was concurrent with increased density and function of NMDA receptors.
Conclusions: Our data suggest both amyloid-beta and tau elicit effects via NMDA receptors that act to suppress neuronal activity. These effects are likely mediated by soluble forms of both proteins. Crucially, our data suggest that at advanced stages of AD, where both amyloid-beta and tau pathology are widespread, therapeutic strategies repressing both proteins simultaneously may provide greater clinical benefits to cognitive function in patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0662 / #2054

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

BRAIN AREAS LIPIDOMICS IN FEMALE TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Laura Ferré González[1], Ángel Balaguer[2], Marta Roca[3], Artemis Ftara[4], Ana Lloret[4], Consuelo Cháfer-Pericás[1]
[1]Instituto de investigación La Fe, Grupo De Investigación En Enfermedad De Alzheimer, Valencia, Spain, [2]University of Valencia, Faculty Of Mathematics, Valencia, Spain, [3]Instituto de investigación La Fe, Analytical Unit, Valencia, Spain, [4]University of Valencia, Physiology, Valencia, Spain

Aims: Lipids are the major component of the brain with important structural and functional properties. Lipid disruption could play a relevant role in Alzheimer's disease (AD), as recent research pointed out. Therefore, a comprehensive analysis of brain lipid composition would improve the pathogenesis knowledge. Some brain lipidomic studies showed significant differences compared to controls, but few studies have focused in different brain areas related to AD. Furthermore, AD is more prevalent in females, but there is a lack of studies focusing on this sex. Therefore, the aim of this work is to perform a lipidomic study in selected brain areas (cerebellum, amygdala, hippocampus, cortex) from wild-type (WT, n=10) and APPswe/PS1dE9 transgenic (AD, n=10) female mice of 5 months of age, as model of early AD, to identify alterations in lipid composition.
Methods: A lipidomic mass spectrometry-based method was optimized and applied for brain tissue.
Results: As result, several lipid variables were detected in the positive ionisation mode (n=252) and in the negative ionisation mode (n=196). Of these, some lipids showed statistically significant differences between mice groups in cerebellum (n=68), amygdala (n=49), hippocampus (n=48) and cortex (n=22). In addition, some lipids (n=15) from the glycerolipid, phospholipid and sphingolipid families were statistically significant in several brain areas simultaneously between WT and AD mice.
Conclusions: A selection of lipid variables was made to develop a multivariate approach to assess their discriminant potential, showing high diagnostic indexes, especially in cerebellum and amygdala (sensitivity 70 – 100%, sensibility 80 – 100%).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0663 / #420

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

A NOVEL 3D IMAGING PIPELINE FOR ANALYZING EFFICACY OF THERAPEUTIC COMPOUNDS ON AMYLOID-BETA PATHOLOGY IN PRECLINICAL ALZHEIMER'S DISEASE ANIMAL MODELS

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Gianna Ferron[1], Stefan Linehan[1], Tim Ragan[1], Kevin Elk[2], Dylan Garceau[2], Mike Sasner[2]
[1]TissueVision Inc., Imaging, Newton, United States of America, [2]The Jackson Laboratory, Model-ad Center, Bar Harbor, United States of America

Aims: Standard laboratory approaches assessing amyloid-beta (Aβ) lack the ability to provide region-specific quantitation with high-throughput whole-organ imaging and often require destructive homogenization of tissue. We developed a novel Serial Two-Photon Plus (STP^2) pipeline to quantify Aβ plaque progression as a function of brain region, resulting in indexed brain sections for secondary analysis using MALDI HiPLEX-IHC with imaging mass spectrometry (IMS).
Methods: 5XFAD (JAX #8730) and APP SAA (JAX #34711) mouse brains labeled with methoxy-X04 were serially imaged and sectioned on the STP^2 platform. Resulting datasets were registered to the Allen Mouse Brain Common Coordinate Framework (CCFv3) and region-specific plaque analysis was conducted. Using MALDI HiPLEX-IHC staining, fourteen (14) protein signatures were imaged on select sections and aligned to the corresponding STP^2 sections using a registration pipeline. The intensity of each signal was assessed quantitatively for all processed 2D sections and summarized across major 3D brain regions in the Allen CCFv3.
Results: The analysis of plaque distribution revealed distinct spatial-temporal changes across the whole-brain datasets. STP^2 imaging and CCFv3 mapping allowed for targeted evaluation of Aβ plaques and a comparison of regional changes occurring with age or treatment. Using data from 4 time points, we can observe a progressive increase in plaque accumulation in regions such as the hippocampal formation, thalamus, and cortical subplate, providing a baseline for targeted additional analysis and comparison to treated brains.
Conclusions: This novel technology has great promise for both quantifying the spatial-temporal Aβ plaque efficacy of AD animal models and producing translatable preclinical AD data for drug discovery. The high sensitivity and precision of the STP^2 platform and high multiplexity of MALDI HiPLEX-IHC secondary analysis provides data-rich results to assess the difficult research questions surrounding AD disease progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0664 / #817

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

UNC5C T835M MUTATION-MEDIATED NEURODEGENERATION IN LATE-ONSET ALZHEIMER'S DISEASE IN A NOVEL MOUSE MODEL

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Devi Krishna Priya Karunakaran[1], Makenna Ley[1], Joanna Guo[1], Mai Khatri[1], Katherine Sadleir[1], Jelena Popovic[1], Arun Upadhyay[1], Ryan Watts[2], Jasvinder Atwal[3], Daniele Procissi[4], Jeffrey Savas[1], Robert Vassar[1]
[1]Feinberg School of Medicine, Northwestern University, Neurology, Chicago, United States of America, [2]Denali Therapeutics Inc.,, Neuroscience, South Sanfrancisco, United States of America, [3]Genentech Inc., Neuroscience, South San Francisco, United States of America, [4]Northwestern University, Center For Preclinical Imaging Core Facility, Chicago, United States of America

Aims: Recently, a rare autosomal dominant coding mutation, T835M, was discovered in the Un-coordinated 5c (UNC5C) netrin receptor gene that segregated with late-onset AD (LOAD). T835M alters a conserved amino acid in the hinge region of the Unc5c death domain, suggesting the mutation may increase apoptosis. Indeed, in primary hippocampal neurons, overexpression of T835M increased cell death in response to neurotoxic stimuli including beta-amyloid (Aβ) suggesting a mechanism by which T835M may confer increased risk of LOAD, however the molecular mechanism of T835M-mediated cell death has not yet been explored. Understanding the molecular mechanism of cell death in regions susceptible to neurodegeneration such as hippocampus could shed light on the players and pathways involved in cell death in AD pathogenesis.
Methods: We generated a mouse knock-in (KI) model of Unc5c T835M Mutation and employed biochemical and histological analyses to understand the molecular mechanism of T835M-mediated pathogenesis in late onset Alzheimer's disease.
Results: We show that homozygous KI mice have significantly reduced hippocampal volume, increased ventricular volume, dendritic disorganization (CA1 region) and reduced Unc5c protein level by 12-18 months of age. Further, we show that the neuronal cell death is observed in the KI mice by 12 months of age by TUNEL analysis and activated Caspase 3/7 activity assay. KI mice also show morphological changes in the astrocytes with reduced GFAP levels and significantly increased activation of microglia. Proteomics analysis of hippocampal samples corroborate the biochemical and histological results which showed upregulation of oxidative stress and downregulation of chaperone proteins at 18 months.
Conclusions: Overall, these results suggest that T835M mutation causes neurodegeneration by creating an oxidative stress environment leading to synaptic degeneration and weakened astrocytes, thereby leading to neuronal cell death via apoptosis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0665 / #1523

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

ANALYSIS OF MOTOR FINE FUNCTION IN THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Ioanna Kousiappa[1], Stylianos Valiantis[1], Nikolas Perentos[2], Savvas Papacostas[1], Avgis Hadjipapas[3], Andreas Koupparis[1]
[1]Cyprus Institute of Neurology and Genetics, Neurobiology, Nicosia, Cyprus, [2]University of Nicosia, School Of Veterinary Medicine, Engomi, Cyprus, [3]University of Nicosia, Medical School, Nicosia, Cyprus

Aims: Alzheimer's disease (AD) is characterized by deficits in memory, cognition and motor function that are proportional to the disease's progression. AD mouse models have shown similar motor difficulties based on motor behavioral tests. The main objective of this project was to investigate the fine motor skills of the 5xFAD Alzheimer's mouse model.
Methods: 3- and 9-month-old transgenic 5xFAD mice were compared to their wild-type (WT) littermates with three motor behavioral assays (n=48 mice). Rotarod test was used to assess the motor coordination. Balance beam test was conducted at three different beams (15, 10 and 6 mm-width) to evaluate the fine motor coordination and balance, while single-pellet reaching test was performed to assess the fine skilled limb movement.
Results: Findings showed a motor deficit of 9M 5xFAD mice in the rotarod test, since they fell at lower rotation speed compared to 9M WT mice. Results from the balance beam test exhibited that 9M 5XFAD mice traverse each beam at significantly greater time and slower speed. A motor performance scoring of the data revealed that 9M 5xFAD mice was the most affected group with a significant impairment at 6 mm with increased presence of dragging and foot slips. Single-pellet reaching test revealed an impairment in fine limb movement mostly in 9M 5xFAD mice, since 3M, 9M WT and 3M 5xFAD mice achieved significantly higher success rate and speed compared to 9M 5xFAD mice to reach successfully the food.
Conclusions: This research provided the first concrete proof of fine motor deterioration in 9M 5xFAD mice. Collectively, older transgenic mice presented the most impaired performance at each behavioral assay, proposing that advanced AD-related pathology may has a role to play in motor function, especially in skilled movements.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0666 / #778

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

PF-04691502, A PI3K/MTOR DUAL INHIBITOR, IMPROVES LEARNING DEFICITS IN APP/PS1 MICE

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Marika Lanza, Giovanna Casili, Rossella Basilotta, Alberto Repici, Salvatore Oddo, Salvatore Cuzzocrea, Emanuela Esposito
University of Messina, Chibiofaram, Messina, Italy

Aims: Aging is the greatest risk factor for several neurodegenerative disorders, including Alzheimer's disease (AD). Overwhelming evidence indicates that reducing mTOR signaling improves health span and lifespan in a multitude of organisms. PI3K is a key regulator of mTOR activity; the PI3K/mTOR signaling pathway regulates several key biological mechanisms related to cell development, cell survival, protein synthesis, autophagy, metabolism, and learning and memory. To this end, up-regulation of the PI3K/mTOR signaling contributes to AD neuropathology and causes neurodegeneration and learning and memory deficits. In this study, we sought to determine the molecular correlates of memory deficits in APP/PS1 mice, a widely used animal model AD.
Methods: 18-month-old APP/PS1 and WT mice were dosed orally with 1 mg/Kg PF-04691502, an ATP-competitive PI3K/mTOR dual inhibitor, for 12 weeks. At the end of the treatment, we assessed changes in spatial learning and memory using the Morris water maze. We then processed their brains for neuropathological and biochemical assessment of amyloid-β (Aβ).
Results: We found that PF-04691502 improved learning and memory in APP/PS1 mice. Currently, we are processing the tissue to assess potential changes in brain Aβ deposits and soluble and insoluble Aβ levels. We will also assess the effects of reducing PIK3/mTOR signaling on inflammation.
Conclusions: These results provide preclinical data indicating that PF-04691502 may be a valid therapeutic approach for AD and other neurodegenerative disorders associated with aging and mTOR hyperactivity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0667 / #1104

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

CEREBRAL PERFUSION AND METABOLISM ACROSS THE LIFESPAN OF THE NOVEL HUMAN AMYLOID BETA KNOCK-IN MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Andre Obenaus[1], Amandine Jullienne[1], Charles Burton[2], Scott Persohn[2], Rojina Pad[1], Ayati Mishra[1], Tia Ketsan[1], Aditya Singh[1], Paul Territo[3]
[1]University of California Irvine, Pediatrics, Irvine, United States of America, [2]Indiana University School of Medicine, Stark Neuroscience, Indianapolis, United States of America, [3]Indiana University School of Medicine, Medicine, Indianapolis, United States of America

Aims: To elucidate the role of genetics, age and environmental risk factors on Alzheimer's disease (AD), the human amyloid beta knock-in (hAβKI) was developed and deeply phenotyped by MODEL-AD for cerebral perfusion and metabolism.
Methods: hAβKI mice were imaged at 6-24mo (n=6/sex/age/genotype) via dynamic contrast-enhanced MRI at 9.4T, while 18F-FDG was acquired via Siemens Inveon PET/CT. Using established protocols, images were processed, registered, segmented, and quantified for cerebral blood flow (CBF) and volume (CBV), glycolytic metabolism, connectomics, and neurovascular uncoupling.
Results: Hippocampal CBF was elevated in 24mo-old males hAβKI ($p=0.024$), while females exhibited reduced CBF ($p=0.018$) relative to WT controls. CBV was significantly decreased in the male temporal lobes ($p=0.048$), but not in females ($p=0.59$) compared to WT. Hippocampal 18F-FDG was decreased in hAβKI males ($p=0.042$) but not females compared to WT mice. In contrast, male hAβKI mice showed reduced hippocampal 18F-FDG compared to hAβKI females ($p=0.02$). In the entorhinal cortex, only female hAβKI mice showed elevated 18F-FDG uptake ($p=0.039$) compared to WT. PET connectomics revealed significant ($p<0.05$) alterations in 5 of 7 functional modules between female hAβKI and WT controls. At 12 mo, axial cortical vascular density was reduced in hAβKI compared to WT mice (53.08 vs. 59.6%), but similar amongst sexes. Further analyses for regional neurovascular uncoupling are underway.
Conclusions: These data suggest sex-dependent regional differences in CBF and CBV of hAβKI compared to WT mice. Glycolytic uptake across most brain regions were divergent, with females increasing while males decreased. Moreover, hAβKI mice show phenotypic changes in regions known to be vulnerable in AD and are consistent with neurovascular uncoupling and network reorganization observed with sex and age in the clinic.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0668 / #183

Poster Topic: *Theme A: β-Amyloid Diseases / A06.g. Cell, Molecular and Systems Biology: Other*

INVESTIGATION OF ESTRADIOL TREATMENT EFFECTS IN ALZHEIMER'S DISEASE USING THE IN VITRO NEURAL MODELS DERIVED FROM HUMAN IPSC

POSTERS: A06.G. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Sopak Supakul[1], Chisato Oyama[2], Yuki Hatakeyama[1], Sumihiro Maeda[1], Hideyuki Okano[1]
[1]Keio University School of Medicine, Physiology, Tokyo, Japan, [2]Waseda University, Department Of Electrical Engineering And Bioscience, Tokyo, Japan

Aims: 17β-Estradiol (E2) was previously demonstrated to have neurotherapeutic effects on animal models of Alzheimer's disease (AD). However, the clinical trials on E2 replacement therapy for preventing AD onset yielded inconsistent results. Therefore, it is necessary to clarify the therapeutic effects of E2 on human cells. This study explored the therapeutic effects of E2 on the in vitro model from human iPSCs.
Methods: A systematic review and meta-analysis using a random-effects model of the previously reported AD clinical trials was conducted to summarize the effects of E2 replacement therapy on AD prevention. Then, the iPSCs from the donors of the 2 healthy control lines, 2 familial AD lines (APP V717L and APP KM670/671NL), and 3 sporadic AD lines (APOE e3/e3, APOE e3/e4, and APOE e3/e3) were induced into neurons. In addition to the mono-culture model of the neurons, we examined the effects of E2 on the co-culture model of the iPSC-derived neurons and astrocytes.
Results: The meta-analysis concluded that E2 replacement therapy reduced the risk of AD onset (OR, 0.69; 95% confidence interval [CI], 0.53–0.91; I^2 = 82%). Neural models from the AD iPSC lines demonstrated an elevation in secreted Aβ levels and astrogliosis-like phenotype compared to the control lines. E2 treatment to the neurons increased neuronal activity and promoted neurite complexity. Furthermore, E2 treatment to the co-culture model ameliorated the astrogliosis-like phenotype. However, contrary to the previous reports, E2 treatment did not alter the levels of Aβ secretion and pTau accumulation.
Conclusions: E2 treatment to the human cellular model did not affect Aβ secretion and pTau accumulation, but promoted neuronal plasticity and mitigated the astrogliosis-like phenotype. This study demonstrated the molecular effects of E2 on neuronal plasticity and AD pathogenesis utilizing human iPSCs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0669 / #2329

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

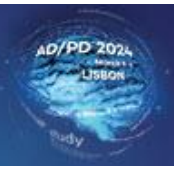
INTEGRATING GENOMIC AND ENVIRONMENTAL FACTORS FOR THE DEVELOPMENT OF PRECLINICAL MODELS OF LATE-ONSET ALZHEIMER'S DISEASE

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Adrian Oblak[1], Mike Sasner[2], Kevin Kotredes[2], Ravi Shanker Pandey[3], Alaina Reagan[2], Katherine Haynes[4], Claudia Rangel-Barajas[1], Stacey Sukoff Rizzo[4], Gregory Carter[2], Bruce Lamb[1], Gareth Howell[2]
[1]Indiana University School of Medicine, Stark Neuroscience, Indianapolis, United States of America, [2]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America, [3]THE JACKSON LABORATORY, For Genomics Medicine, FARMINGTON, United States of America, [4]University of Pittsburgh, Medicine, Pittsburgh, United States of America

Aims: The IU/JAX/PITT MODEL-AD Center's primary focus is to characterize mouse models that express significant genetic risk factors, namely the APOE4 allele of apolipoprotein E and the R47H allele of triggering receptor expressed on myeloid cells (Trem2*R47H).
Methods: To achieve this, we established the LOAD2 strain, which was double homozygous for humanized amyloid-beta, APOE4 and Trem2R47H on the C57BL6J (B6) genetic background. We employed a comprehensive phenotyping approach, which included in vivo imaging, multi-omics analysis, and immunofluorescence. Furthermore, we explored the impact of a high fat/high sugar diet (HFD) on the alignment of mouse models with human LOAD.
Results: Findings indicate that, when compared to LOAD2 mice fed a regular diet, LOAD2 mice on an HFD exhibit increased levels of insoluble Aβ, cortical neuronal cell loss, elevated levels of neurofilament light chain (NfL) in both the plasma and brain. Intriguingly, gene expression profiles and proteomic signatures of aged LOAD2+HFD mice aligned with 'omics signatures of AD patients in the absence of core neuritic plaques, which were not detected up to 24 months of age. Additionally, positron emission tomography and computed tomography (PET/CT) scans using 64Cu-PTSM and 18F-FDG reveal more pronounced disruptions in blood flow and glucose uptake in LOAD2 HFD mice.
Conclusions: Mice with genetic risk for LOAD coupled with environmental risk factors demonstrate aging-dependent changes in line with a spectrum and trajectory of features of clinical LOAD. From a precision medicine approach, our Preclinical Testing Core is prioritizing LOAD2+HFD mice as an important model system for evaluating the therapeutic potential of non-amyloid targeting therapeutics as well as for prophylactic interventions initiated prior to significant amyloid accumulation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0670 / #868

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

DEVELOPMENT OF A NOVEL ALZHEIMER'S DISEASE MOUSE MODEL BASED ON CHRONIC PLASMALOGEN DEFICIENCY IN ADULTHOOD

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Shawn Ritchie[1], Tara Smith[1], Kaeli Knudsen[2]
[1]Med-Life Discoveries LP, Therapeutics, SASKATOON, Canada, [2]Med-Life Discoveries LP, Therapeutics, Saskatoon, Canada

Aims: Plasmalogens are vinyl-ether-containing membrane phospholipids involved in many functions, particularly neurotransmission. Plasmalogen deficiency has been associated with Alzheimer's disease (AD), leading to the hypothesis it underlies the disease process. However, the lack of an animal model displaying a chronic plasmalogen deficiency beginning in adulthood has made it impossible to understand the effects of the deficiency in brain structure and function as it relates to AD. We therefore developed and characterized a novel plasmalogen-deficient knockout mouse model of AD containing a conditional *Gnpat* deletion that can be induced postnatally.
Methods: We introduced loxP sites flanking exon 4 of *Gnpat,* a plasmalogen biosynthetic gene. Upon tamoxifen administration, a recombination and deletion of the region occurs, resulting in loss of plasmalogen biosynthesis. Following tamoxifen treatment, the animals were characterized by functional assessments (open field, sleep monitoring, and nerve conduction), neuroimaging (anatomical MRI and mass spectrometry imaging (MSI), and for neuroinflammatory markers (NfL).
Results: Within one month of tamoxifen treatment in adult *Gnpat* cKO animals, there was a clear reduction in plasmalogen levels in serum and multiple tissues including brain. Activity levels, sleep architecture, nerve conduction, and NfL levels were all altered in deficient animals. Brain and white matter volumes were reduced, which correlated with reduced brain plasmalogen levels as detected by MSI. Preliminary results following treatment with PPI-1011, an oral plasmalogen therapeutic precursor, showed normalization of brain structure and lipid composition.
Conclusions: Our *Gnpat* conditional mouse model confirms for the first time that plasmalogen reductions in adulthood, comparable to the chronic situation observed in individuals with AD, are sufficient to impair function, alter sleep architecture, increase neuroinflammatory markers and reduce brain volumes. This model therefore represents a critical tool in the evaluation of future plasmalogen-targeted therapeutics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0671 / #2230

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

MECHANISMS UNDERLYING REDUCTIONS OF SEROTONERGIC AXON PROJECTIONS TO THE CORTEX IN APP KNOCK-IN MOUSE MODEL OF AB PATHOLOGY

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Yasufumi Sakakibara[1], Yu Hirota[1,2], Kyoko Ibaraki[1], Kimi Takei[1], Risa Nishijima[1], Michiko Sekiya[1,3], Koichi Iijima[1,3]
[1]National Center for Geriatrics and Gerontology, Department Of Neurogenetics, Obu City, Aichi, Japan, [2]Japan Society for the Promotion of Science, Jsps Research Fellow, Tokyo, Japan, [3]Nagoya City University, Graduate School Of Pharmaceutical Sciences, Nagoya, Aichi, Japan

Aims: Dorsal raphe nucleus (DRN) is a nucleus containing the cell bodies of serotonergic neurons in the brainstem and is one of the earliest regions affected by Alzheimer's disease (AD). Defects in serotoninergic system is thought to be related to cognitive declines and behavioral and psychiatric problems in the early stage of AD and has been a drug target to improve clinical symptoms. However, mechanisms underlying degeneration of serotonergic system in AD remain elusive. In this study, we analyzed structural changes of serotonergic system upon accumulation of amyloid-β (Aβ) pathology in cortical areas using *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ knock-in mice.
Methods: We compared the density of serotonin (5-HT)-positive axons in the cortex and the number of serotonergic neurons in the DRN between *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ and wild-type (WT) C57BL/6J mice at 6 and 24 months of age. We also asked whether tau pathologywas formed in the serotonergic axons and in the DRN in *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice.
Results: Immunohistochemical analyses revealed that *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice exhibited age-dependent decreases in the density of 5-HT-positive axons in the cortex compared to WT mice. In contrast, *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice did not display loss of 5-HT-positive neurons in the DRN even at 24 months of age. Furthermore, phosphorylated tau was not accumulated in either the nerve terminals or the cell bodies of DRN neurons in the brains of *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ mice.
Conclusions: This study demonstrates that cortical Aβ pathology reduces the density of serotonergic axons independent of neuron loss and tau pathology in the DRN. These results also suggest that age-dependent accumulation of Aβ in the cortex chronically damages serotonergic axons during the preclinical period, which may lead to death of DRN neurons accumulated tau during aging in AD pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0672 / #1178

Poster Topic: *Theme A: β-Amyloid Diseases / A07.b. Animal Models: Primates, naturally occuring models and brain organoids*

PROTEOMIC ANALYSIS OF PATIENT HIPPOCAMPAL BRAIN CELLS REVEALS EARLY CELLULAR DYSFUNCTION AND PROGRESSION OF ALZHEIMER'S DISEASE PATHOGENESIS

POSTERS: A07.B. ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS

Yuriy Pomeshchik[1], Erika Velasquez[1], Jeovanis Gil[2], Oxana Klementieva[3], Ritha Gidlöf[4], Marie Sydoff[4], Silvia Bagnoli[5], Benedetta Nacmias[5], Sandro Sorbi[5], Gunilla Westergren-Thorsson[6], Gunnar Gouras[3], Melinda Rezeli[7], Laurent Roybon[8]
[1]Lund University, Experimental Medical Science, Lund, Sweden, [2]Lund University, Biomedical Engineering, Lund, Sweden, [3]Faculty of Medicine, Lund University, Experimental Medical Science, Lund, Sweden, [4]Lund University, Bioimaging Centre, Lund, Sweden, [5]University of Florence, Department Of Neuroscience, Psychology, Drug Research And Child Health, Firenze, Italy, [6]Lund University, Experimental Medical Science, lund, Sweden, [7]Lund University, Swedish National Infrastructure For Biological Mass Spectrometry, Lund, Sweden, [8]Van Andel Institute, Neurodegenerative Science, Grand Rapids, United States of America

Aims: The hippocampus is a primary region affected in Alzheimer's disease (AD). Because AD postmortem brain tissue is not available prior to symptomatic stage, we lack understanding of early cellular pathogenic mechanisms.
Methods: To address this issue, we examined the cellular origin and progression of AD pathogenesis by comparing proteomic changes in patient-based model systems including iPSC-derived brain cells transplanted into the mouse brain hippocampus.
Results: Proteomic analysis of the graft enabled the identification of pathways and network dysfunction in AD patient brain cells, associated with increased levels of Aβ-42 and β-sheet structures. Interestingly, the host cells surrounding the AD graft also presented alterations in cellular biological pathways. Furthermore, proteomic analysis across human iPSC-based models and human post-mortem hippocampal tissue projected longitudinal cellular changes indicative of early to end stage AD cellular pathogenesis.
Conclusions: Our data showcase patient-based models to study the cell autonomous origin and progression of AD pathogenesis

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0673 / #607

Poster Topic: *Theme A: β-Amyloid Diseases / A07.b. Animal Models: Primates, naturally occuring models and brain organoids*

DEVELOPMENT OF HUMANIZED MODELS TO STUDY PROGRESSION OF ALZHEIMER'S DISEASE

POSTERS: A07.B. ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS

Yuriy Pomeshchik[1,2,3], Erika Velasquez[1,2,3], Jeovanis Gil[4], Oxana Klementieva[3], Isak Martinsson[1,3], Silvia Bagnoli[5,6], Benedetta Nacmias[5,6], Sandro Sorbi[5,6], Gunnar Gouras[1,3], Melinda Rezeli[4,7], Laurent Roybon[1,2,3,8]
[1]Lund University, Strategic Research Area Multipark, Lund, Sweden, [2]Lund University, Lund Stem Cell Center, Lund, Sweden, [3]Faculty of Medicine, Lund University, Experimental Medical Science, Lund, Sweden, [4]Lund University, Biomedical Engineering, Lund, Sweden, [5]University of Florence, Department Of Neuroscience, Psychology, Drug Research And Child Health, Firenze, Italy, [6]Neurophysiopathology, Irccs Fondazione Don Carlo Gnocchi, Florence, Italy, [7]Lund University, Swedish National Infrastructure For Biological Mass Spectrometry, Lund, Sweden, [8]Van Andel Institute, Neurodegenerative Science, Grand Rapids, United States of America

Aims: Our understanding of early pathogenic processes within the hippocampus, a primary brain region severely impacted in Alzheimer's disease (AD), is hampered by the unavailability of pre-symptomatic postmortem brain tissue. Our goal was to develop advanced iPSC-based models closely mimicking human AD pathology and emphasize the utility of patient-based models, such as humanized chimeric mice, for understanding the cell-autonomous origin and progression of AD.
Methods: We developed a chemical approach to rapidly generate adherent hippocampal neurons (HNs) and free-floating hippocampal spheroids from human iPSCs. To model AD pathology in vivo, we created humanized chimeric mice by transplanting iPSC-derived brain cells into the mouse hippocampus. We employed Western blotting, immunocytochemistry, qRT-PCR, MSD multi-array, synchrotron-based FTIR, and shotgun proteomics to phenotype these AD models and compared them with postmortem AD human brain tissue.
Results: HNs derived from AD patients revealed complex cellular dysfunctions resembling prodromal pathology in vitro. When grafted into immunodeficient mice, patient HNs integrated into the host environment, creating an in vivo model mimicking patient brain parenchyma, with the advantage of being vascularized. At six months, this novel patient iPSC-based AD model displayed significant alterations in the human proteome, detected with LC-MS/MS, and signs of incipient protein aggregation measured by FTIR microspectroscopy. Importantly, these changes occurred before amyloid plaque formation but with elevated Aβ-42 levels, confirming the model's fidelity to prodromal AD pathology.
Conclusions: Our models offer a valuable platform for studying early pathogenic hippocampal changes in AD patients, providing insights into mechanisms and potential therapeutic targets for early-stage AD. Developing patient-based models provides a robust approach to investigate the cell-autonomous origin and progression of AD pathogenesis across its various stages.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0674 / #1844

Poster Topic: *Theme A: β-Amyloid Diseases / A07.b. Animal Models: Primates, naturally occuring models and brain organoids*

GENOMIC ANALYSIS OF FIBROBLASTS FROM MARMOSETS CARRYING EARLY-ONSET ALZHEIMER'S DISEASE MUTATIONS IN PSEN1

POSTERS: A07.B. ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS

Gregory Carter[1], Annat Haber[1], Duc Duong[2], Nicholas Seyfried[3], Takeshi Murai[4], Laura Schultz[4], Hasi Huhe[4], Sang Ho Choi[4], Julia Kofler[5], David Schaeffer[4], Stephanie Hachem[4], Jung Eun Park[4], Gregg Homanics[4], Stacey Sukoff Rizzo[6], Afonso Silva[4]
[1]THE JACKSON LABORATORY, The Jackson Laboratory, Bar Harbor, United States of America, [2]Emory University School of Medicine, Center For Neurological Disorder, Atlanta, United States of America, [3]Emory University School of Medicine, Department Of Biochemistry, Atlanta, United States of America, [4]University of Pittsburgh, Neurobiology, Pittsburgh, United States of America, [5]University of Pittsburgh, Pathology, Pittsburgh, United States of America, [6]University of Pittsburgh, Medicine, Pittsburgh, United States of America

Aims: We present genetic, genomics, and proteomic analysis of fibroblast lines derived from a colony of marmosets genetically engineered with familial variants in PSEN1.
Methods: We performed whole-genome sequencing on 50 individuals, including eight mutant carriers. We validated the presence of the PSEN1 mutations and assessed variation at multiple other Alzheimer's disease loci. Fibroblast cultures were obtained from 12 animals and assayed using a Nanostring AD gene expression panel and label-free proteomics. This allowed us to quantify 800 transcripts and 2165 proteins per sample.
Results: We detected differential gene expression for genes enriched in neuron development and amyloid-beta regulation, providing strong evidence for the functional relevance of the engineered variants. We quantitatively compared changes in marmoset PSEN1 fibroblasts to similar molecular measures in postmortem brain tissue and induced pluripotent stem cells (iPSCs) from human AD studies. Both gene and protein expression changes in the undifferentiated fibroblasts correlated with changes in iPSCs from human AD carriers reprogrammed into neuronal lineages.
Conclusions: These findings demonstrate that disease-relevant pathways and processes are altered in fibroblasts from mutant marmosets, provide a roadmap for more advanced molecular studies of AD in aging marmosets and marmoset-derived cell models, and outline a strategy to align marmoset models with human disease to facilitate robust translation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0675 / #1755

Poster Topic: *Theme A: β-Amyloid Diseases / A07.a. Animal Models: Transgenic rodents*

TRANSGENIC INHERITANCE PATTERN MODULATES PLAQUE BURDEN IN THE 5XFAD MOUSE MODEL

POSTERS: A07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Andrew Octavian Sasmita[1], Constanze Depp[1], Taisiia Nazarenko[1], Lena Spieth[2], Stefan Berghoff[2], Klaus-Armin Nave[1]
[1]Max Planck Institute for Multidisciplinary Sciences, City Campus, Neurogenetics, Göttingen, Germany, [2]Technical University Munich, Institute Of Neuronal Cell Biology, Munich, Germany

Aims: The 5xFAD mouse model is one of the most commonly used mouse models of amyloidosis or more specifically, Alzheimer's disease (AD). Sex dimorphism has been reported in many transgenic AD mouse models, but even after stratification of mouse cohorts by sex, the variability of amyloid burden remain staggeringly high. As this line is bred heterozygously, here, we present a jarring relationship between the parental source of the transgene and the amyloid burden that ensued.
Methods: We performed *in toto* amyloid plaque staining with the Congo red dye and imaged whole hemispheres via light sheet microscopy. We grouped our gender-matched data based on whether the mice inherited their transgene paternally or maternally.
Results: Mice that inherit their transgenes paternally develop a much higher amyloid burden, especially within cortical regions where amyloid plaque numbers are twice as many. We further stratified our data based on the parental and grandparental source of the transgene. We saw even more clustering of our data when taking the grandparental origin into account, albeit not as strongly as the direct parental source. This suggests that this transgenic inheritance pattern persists through generations of breeding, highlighting the importance of mouse pedigree in 5xFAD mouse, or perhaps, transgenic mouse research in general. As mice that inherit the transgene would naturally be gestated within 5xFAD mothers, we analyzed offspring of heterozygous breeding pairs. The amyloid burden of the heteroyzgous offspring still clustered into two separate populations, suggesting that it is unlikely that the distinct amyloid plaque populations are the result of maternal immune priming.
Conclusions: We provided a novel outlook on the relationship between the 5xFAD transgenic source and amyloid plaque burden *in vivo. W*e believe that epigenetic analysis of these mice would remain valuable.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0676 / #2430

Poster Topic: *Theme A: β-Amyloid Diseases / A07.b. Animal Models: Primates, naturally occuring models and brain organoids*

EFFECT OF CALCINEURIN/NFAT INHIBITORS ON COGNITION IN A CANINE MODEL OF ALZHEIMER DISEASE

POSTERS: A07.B. ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS

Lorena Sordo[1], Margo Ubele[2], Kathy Boaz[2], Jennifer Mefford[3], Erin Jones[3], Katie Mccarty[3], Jeffrey Smiley[3], Stasia Bembenek Bailey[3], Jessica Perpich[3], Beverly Meacham[4], David Powell[4], Frederick Bresch[3], Michael Phelan[1], Jessica Noche[5], Craig Stark[5], László Puskás[6], Christopher Norris[3], Elizabeth Head[1]
[1]University of California Irvine, Pathology And Laboratory Medicine, Irvine, United States of America, [2]Sanders Brown Center on Aging, University of Kentucky, Pharmacology And Nutritional Sciences, Kentucky, United States of America, [3]University of Kentucky, Division Of Laboratory Animal Resources, Kentucky, United States of America, [4]University of Kentucky, Magnetic Resonance Imaging And Spectroscopy Center, Kentucky, United States of America, [5]University of California Irvine, Neurobiology And Behavior, Irvine, United States of America, [6]Aperus Pharma, Aperus Pharma, Szeged, Hungary

Aims: Calcineurin/NFAT signaling increases in Alzheimer disease (AD) and is associated with neurodegeneration, neuroinflammation, amyloid-β (Aβ) production, and cognitive decline. In AD rodent models, calcineurin/NFAT (CN/NFAT) inhibitors improved cognition and ameliorated neuroinflammation and synapse dysfunction, suggesting that CN/NFAT inhibitors (e.g., tacrolimus and Q134R) are attractive potential therapeutics to improve/prevent AD-associated cognitive impairments. We hypothesized that chronic low-dose administration of tacrolimus and Q134R will delay cognitive decline over time in middle-aged beagles, a model of human brain aging and AD.
Methods: We evaluated cognitive outcomes in 37 middle-aged beagles at baseline and during follow-up (years 1-3), including spatial learning [landmark-discrimination (1, 2 and 4cm)], visual discrimination learning, reversal learning (executive function), and spatial working memory (20-, 70-, and 110-second delays). Dogs were ranked for cognition at baseline and randomized into treatment groups: Control/Placebo (n=12), Q134R (n=12), and tacrolimus (n=13).
Results: Accuracy at all landmark-discrimination distances declined 20% faster in control dogs, relative to tacrolimus, and 15% faster than Q134R dogs, at the most difficult distance of 4cm. Accuracy on spatial working memory task declined 21% faster/year among controls than tacrolimus (years 2&3); and 18% faster than Q134R dogs (year 1). Furthermore, performance on visual discrimination and reversal tasks declined with age; however, no treatment effect was found in these tasks.
Conclusions: We found that both tacrolimus and Q134R showed beneficial preventative effects on age-related decline in spatial functions and memory, but not on associative learning nor executive function in a canine model of AD, suggesting that CN/NFAT inhibitors have the potential to reduce or delay cognitive impairment in AD

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0677 / #1013

Poster Topic: *Theme A: β-Amyloid Diseases / A07.c. Animal Models: Non-mamalian models, Other*

GENERATION OF A NON-FAMILIAL/ ENVIRONMENTAL MOUSE MODEL FOR ALZHEIMER'S DISEASE AND ITS USE FOR THERAPY DEVELOPMENT

POSTERS: A07.C. ANIMAL MODELS: NON-MAMALIAN MODELS, OTHER

Sahar Sweetat[1], Moti Ben Shabat[1], Paschalis Theotokis[2], Nir Suissa[1], Eleni Karafoulidou[2], Michal Lichtenstein[3], Olga Touloumi[2], Rami Abu-Fene[4], Ann Saada[5], Haya Lorberboum-Galski[3], Amit Lotan[6], Nikolaos Grigoriadis[2], Hanna Rosenmann[1]
[1]Hadassah Hebrew University Medical Center, Neurology, Jerusalem, Israel, [2]AHEPA University Hospital, Aristotle University of Thessaloniki, Neurology, Thessaloniki, Greece, [3]IMRIC, Hebrew University, Biochemistry And Molecular Biology, Jerusalem, Israel, [4]Hadassah Hebrew University Medical Center, Internal Medicine, Jerusalem, Israel, [5]Hadassah Hebrew University Medical Center, Genetics And Metabolic Diseases, Jerusalem, Israel, [6]Hadassah Hebrew University Medical Center, Psychiatry, Jerusalem, Israel

Aims: While vast majority of AD patients are non-familial, the animal models of AD in common use for studying disease pathogenesis and therapy development - are mostly of a genetic form (transgenic mice). We aimed to develop a non-familial, environmental model for AD, and use it for further studying our new developed therapies.
Methods: To generate an environmental model for dementia/AD, naïve female mice went through ovariectomy (to accelerate aging/ menopause) and fed with high fat-sugar-salt diet - for exposing them to factors associated with increased risk the development of dementia/AD. Sham operated mice fed with standard diet served as normal controls. Behavioral-, biochemical- and histological-studies, as well as blood pressure tests, were performed. In addition, we tested the response of this newly generated dementia/AD model to our newly developed Mitochondrial Transfer Therapy.
Results: The ovariectomized mice fed with high fat-sugar-salt diet showed increased blood pressure, glucose, insulin and lipids in the serum, with impaired cognitive performance in the Y-maze and NOR maze, accompanied with the presence of robust brain pathology of amyloid and tau tangle pathology, gliosis, and reduced blood vessel density. Preliminary results showed that treating this newly developed environmental model for dementia/AD with Mitochondrial Transfer – resulted in reduced amyloid plaques, tau pathology, gliosis and increased blood vessel density in hippocampus, with better cognitive performance in Y-maze.
Conclusions: Ovariectomized mice fed with high fat-sugar-salt diet showed dementia/AD characteristics, providing us an authentic environmental model for AD to represent a high portion of the AD patients. This newly developed AD model showed responsiveness to our newly developed therapeutic approach of Mitochondrial Transfer Therapy for AD, and further supports its value.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0678 / #1133

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

CONTRIBUTION OF THE MITOCHONDRIAL COMPLEX I INHIBITOR ANNONACIN TO THE ALPHA-SYNUCLEIN/TAU CO-PATHOLOGY IN CARIBBEAN ATYPICAL PARKINSONISM

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Patrick Pierre Michel[1], Florencia González-Lizárraga[2], Susana Boluda[3], José Ruis Hidalgo[4], Cesar L Avila[2], Benjamin Socias[2], Rosana Chehin[2], Rita Raisman-Vozari[1], Annie Lannuzel[5]
[1]Paris Brain Institute-ICM, Inserm Cnrs Hôpital De La Pitié Salpêtrière, Sorbonne Université, Paris, France, [2]IMMCA, Conicet-unt-siprosa, Tucumán, Argentina, [3]Hôpital de La Pitié-Salpêtrière, Department Of Neuropathology, Paris, France, [4]Instituto de Química Orgánica, Unt-fbqf-argentina, Tucumán, Argentina, [5]University Hospital of Guadeloupe, Neurology, Cic 1424, Pointe-à-Pitre, France

Aims: High consumption of Annonacae plant products containing the mitochondrial toxin annonacin has been previously recognized as a risk factor for atypical degenerative parkinsonism in the French Caribbean islands. Our objectives were to further characterize protein amyloid aggregation in this disorder, and determine to what extent annonacin could contribute to this pathogenic process.
Methods: We performed post-mortem histopathological analysis of brain samples from 8 patients, and more specifically assessed the distribution and burden of a-Synuclein (aS) and tau lesions. We also studied the impact of annonacin on a-Syn and tau aggregation using Thioflavin-T (ThT) fluorescent assays with corresponding recombinant human proteins as substrate.
Results: Caribbean atypical parkinsonism (CAP) represents a group of patients with heterogeneous clinical and histopathogical features. A tau/αS co-pathology, with a predominance of either aS or tau lesions, is observed in the majority (5/8) of cases. Annonacin amplifies aS aggregation, and leads to the formation of new fibrillary species having the capacity to seed tau aggregation.
Conclusions: We suggest that annonacin may contribute to degenerative Caribbean parkinsonism by modulating the production of tau and αS pathogenic protein assemblies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0679 / #1014

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

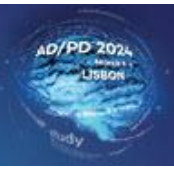
EFFECTS OF P301L-TAU ON POST-TRANSLATIONAL MODIFICATIONS OF MICROTUBULES IN HUMAN IPSC-DERIVED CORTICAL NEURONS AND TAU TRANSGENIC MICE

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Mhd Aghyad Al Kabbani[1], Hans Zempel[2], Christoph Köhler[3]
[1]University Hospital of Cologne, Institute Of Human Genetics, Köln, Germany, [2]University Hospital of Cologne, Center For Molecular Medicine Cologne, Institute Of Human Genetics, Köln, Germany, [3]University of Cologne, Center Anatomy Ii, Medical Faculty, Cologne, Germany

Aims: TAU is a microtubule-associated-protein that promotes microtubule assembly and stability in the axon. TAU is missorted and aggregated in an array of diseases known as tauopathies. Microtubules are essential for neuronal function and are regulated via a complex set of post-translational modifications (PTMs), changes in which affect microtubule stability and dynamics, microtubule interaction with other proteins/cellular structures, and mediate recruitment of microtubule-severing enzymes. Impairment of microtubule dynamics cause neuronal dysfunction and may cause cognitive impairment in human disease. We therefore studied the effects of a disease-causing mutation of TAU (P301L) on the levels and localization of microtubule PTMs indicative of microtubule stability and dynamics.
Methods: To investigate TAU localization, phosphorylation, and effects on tubulin PTMs, we expressed wild-type or P301L-TAU in human *MAPT*-KO induced pluripotent stem cell-derived neurons (iNs) and studied TAU in neurons in the hippocampus of mice transgenic for human P301L-TAU (pR5-mice) via immunostaining and western blotting.
Results: iNs expressing P301L-TAU showed increased TAU phosphorylation at the AT8, but not the p-Ser-262 epitope, increased acetylation and polyglutamylation, but unchanged tyrosination of microtubules compared to endogenous TAU-expressing neurons. P301L-TAU expression was insufficient to trigger TAU mislocalization or aggregation in iNs. Hippocampal neurons in pR5-mice similarly exhibited tauopathy-typical AT8-phosphorylation, decreased acetylation and increased polyglutamylation levels of their microtubules compared to non-transgenic littermates, but also TAU missorting apparent by increased somatodendritic presence of TAU assessed with a total TAU antibody.
Conclusions: In sum, P301L mutant TAU results in changes of microtubule PTMs, suggestive of impairment of microtubule stability. This is accompanied by missorting and aggregation in mice but not in human neurons. Microtubule PTM/impairment may be of key importance in tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0680 / #2219

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

APP AND TAU PROTEINS ARE DIFFERENTIALLY REGULATED BY VCP INTERACTORS

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Catherine Baud[1], Raphaelle Caillierez[2], Hanane Abouelfarah[2], Adriana Figueroa Garcia[2], Luc Buee[2], Patricia Melnyk[1], Nicolas Sergeant[2]
[1]University of Lille INSERM UMR S-1172, Brain Biology And Chemistry, Lille Neurosciences & Cognition, Lille, France, [2]University of Lille INSERM UMR S-1172, Alzheimer & Tauopathies, Lille Neurosciences And Cognition Center, Lille, France

Aims: Alzheimer's disease (AD) is the most prevalent form of dementia with aging. However there is still no cure. The neuropathological hallmarks of AD are ß-amyloid deposits, derived from cleavages of the amyloid-ß precursor protein (APP) and neurofibrillary degeneration or tangles (NTFs) resulting from the intraneuronal aggregation of the microtubule-associated protein Tau, hyper– and abnormally phosphorylated. A hypothetical mechanism to explain these lesions can arise from the deregulation of protein homeostasis and degradation systems like the unfolded-protein response (UPR), autophagy-lysosome pathway and clearance of protein aggregates at the crossroad of which is the valosin-containing protein VCP/p97. VCP/p97 is a homohexameric AAA-ATPase which, together with its numerous adaptors, recognizes ubiquitylated proteins to address them for degradation by the proteasome or autophagy. Its dysfunctions have been associated with neurodegenerative diseases including inclusion body myopathy with Paget's disease frontotemporal dementia and amyotrophic lateral sclerosis (IBMPFD). Moreover, lower VCP expression levels are observed in AD brains, and there is a growing body of evidence for a link between Tau seeding, aggregation propagation, phosphorylation and VCP in literature. However, the precise mechanism by which VCP/p97 could regulate Tau phosphorylation and aggregation remains poorly understood as well as its contribution to APP metabolism.
Methods: To further decipher the potential mechanism, VCP interactome was achieved by mass spectrometry following immunoisolation from cells treated or not with NMS-873, the most potent and specific VCP pharmacological inhibitor.
Results: We showed that VCP inhibition or silencing increases Abeta production, while repressing Tau aggregation. Bioinformatic analyses determined potent APP or Tau metabolism regulators and will be presented.
Conclusions: Our results suggest that VCP contributes to regulate Tau phosphorylation and APP metabolism, which could represent an attractive therapeutic target for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0681 / #1658

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

AGGREGATE-SPECIFIC SINGLE-MOLECULE PROFILING REVEALS HETEROGENEOUS LANDSCAPE OF TAU AGGREGATES IN DISEASE

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Dorothea Böken, Dezerae Cox, Melanie Burke, David Klenerman
University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom

Aims: Hyperphosphorylation and aggregation of the microtubule binding protein tau play a key role in the development of Alzheimer's disease. While the structure of the filamentous aggregates formed in humans has recently been determined to atomic resolution, there is far less information available about the smaller aggregate precursors, thought to be the most neurotoxic. To address this gap, we have developed a single-molecule pull-down (SiMPull) able to detect tau aggregates in clinically relevant human samples, including human brain homogenate and serum.
Methods: This method enables the detection and characterization of individual tau aggregates, as opposed to averaged features obtained from traditional bulk techniques. By adapting the assay to simultaneously detect multiple features in individual aggregates, we were also able to derive compositional profiles for pathological modifications present in individual aggregates, including phosphorylation at different sites and ubiquitination.
Results: We report the number, size and shape of individual aggregates measured via super-resolution microscopy, revealing disease-specific differences in tau aggregate morphology. We further demonstrate that over 80% of tau aggregates in Alzheimer's disease brains had multiple pathological phosphorylation markers (AT8 and T181) simultaneously, compared to only 5% in healthy samples.
Conclusions: Together, tau SiMPull identified distinct subpopulations of large, modified tau aggregates that were invisible to traditional methodologies. These morphological and compositional differences distinguish samples taken from disease cohorts, offering to illuminate underlying disease mechanisms, sand providing a foundation for novel diagnostic strategies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0682 / #2452

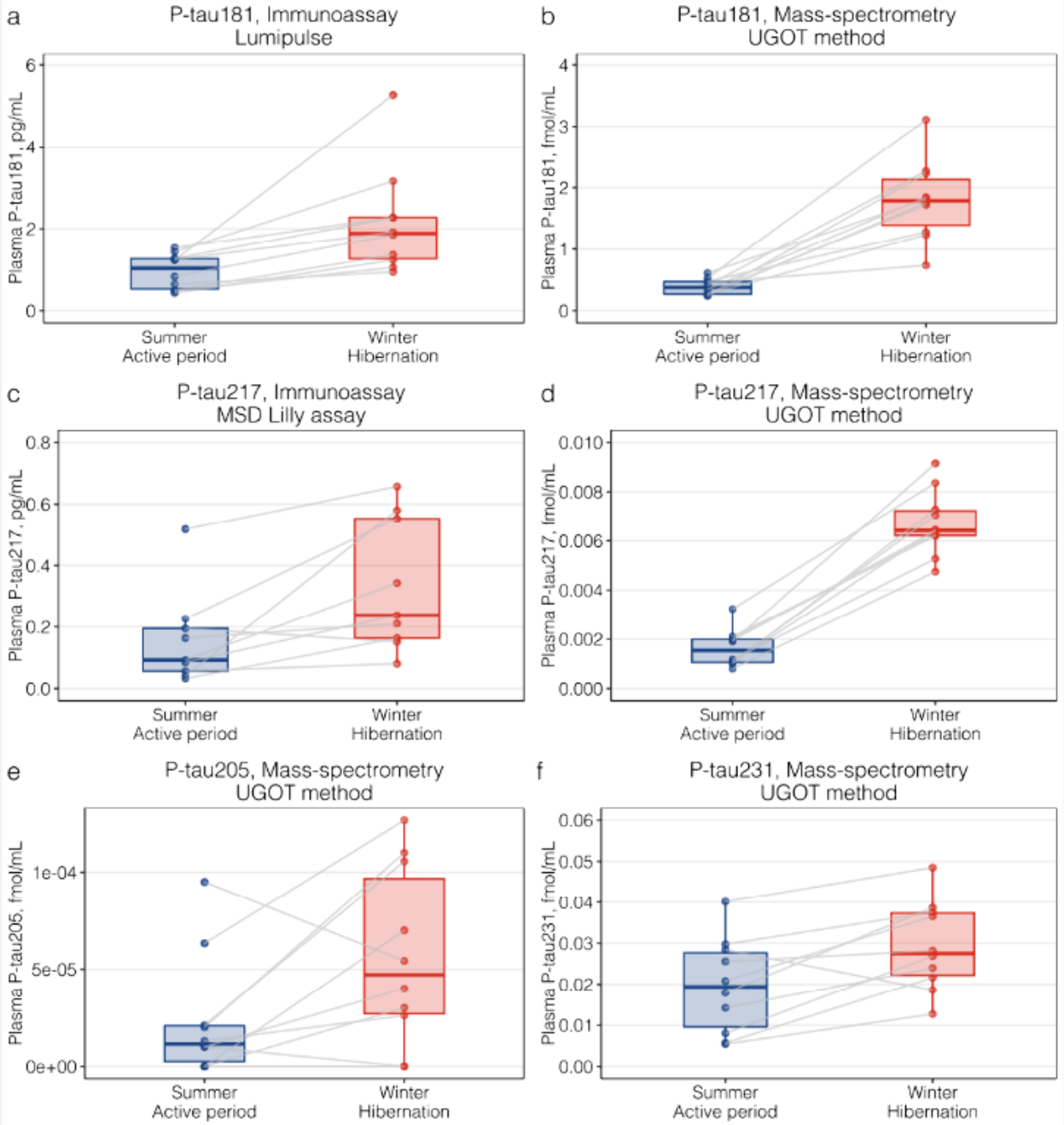
Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

PLASMA BIOMARKERS DETECT HIBERNATION-LINKED REVERSIBLE TAU HYPERPHOSPHORYLATION IN BROWN BEARS

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Wagner Brum[1], Laia Montoliu-Gaya[1], Shorena Janelidze[2], Juan Lantero-Rodriguez[1], Eduardo R Zimmer[3], Henrik Zetterberg[1], Oskar Hansson[2], Nicholas Ashton[1], Ole Fröbert[4], Kaj Blennow[1]
[1]Department of Psychiatry and Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden, [2]Lund University, Department Of Clinical Sciences, Lund, Sweden, [3]Department of Pharmacology, Graduate Program in Biological Sciences: Biochemistry (PPGBioq) and Phamarcology and Therapeutics (PPGFT), Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil, [4]Örebro University, Cardiology Department, Örebro, Sweden

Aims: Tau hyperphosphorylation is one of the key pathological hallmarks of several neurodegenerative diseases, including Alzheimer's disease (AD). While tauopathies have been largely studied in transgenic animals and diseased humans, physiological models of tau hyperphosphorylation remain under-explored. Hibernation-linked tau hyperphosphorylation has been reported in neuropathological studies on various mammal hibernating species, always marked by full de-phosphorylation upon awakening, without signs of insoluble tau deposits. We aimed to evaluate whether these hibernation-linked tau hyperphosphorylation abnormalities could be detected *in vivo* using plasma phosphorylated tau (p-tau) biomarkers.
Methods: Paired plasma samples were collected from free-ranging brown bears (*Ursus arctos*; n=10), during their active state (summer) and hibernation (winter), and human-bear tau sequence homology was evaluated to determine whether currently available tau assays were suitable. With immunoassays (IA), we measured p-tau181$_{IA}$ (Lumipulse, Fujirebio assay) and p-tau217 (MSD; Lilly assay). With a novel validated in-house mass spectrometry (MS; UGOT) assay for simultaneous quantification of tau species in the plasma, we measured p-tau181, p-tau199, p-tau202, p-tau205, p-tau217$_{MS}$, p-tau231. Non-parametric paired tests were used for season comparisons, and percentage change from summer was computed.
Results: During hibernation, significant increases were observed for p-tau181 (IA: +128%, p=0.013; MS: +411%, p<0.0001), p-tau205 (+169%, p=0.012) and p-tau217 (IA: +269%, p=0.047; MS: +371%, p<0.0001) (Figure 1), while no changes were observed for p-tau199 (p=0.49), p-tau202 (p=0.52) and p-tau231 (p=0.12).



Conclusions: We report *in vivo* evidence supporting the previously described hibernation-linked reversible tau hyperphosphorylation process in hibernating brown bears. During hibernation, these p-tau blood biomarkers are changed in the same direction as in AD, but under a physiological phenomenon marked by several adaptive changes, including lowering of neuronal activity. Further translational studies of this phenomenon may provide insights into novel anti-tau treatment strategies in humans.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0683 / #1136

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

EXPLORING EARLY EXTRACELLULAR DISEASE MECHANISMS: CROSS-INTERACTIONS BETWEEN TAU AND AMYLOID BETA IN ALZHEIMER'S DISEASE

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Daniela Freitas, Guilherme Moreira, António Figueira, Cláudio Gomes
Faculdade de Ciências da Universidade de Lisboa, Bioisi - Biosystems & Integrative Sciences Institute, Lisboa, Portugal

Aims: Since the underlying mechanisms of early Alzheimer's Disease are not well understood, we aimed to explore plausible extracellular cross-interactions between Tau and Amyloid beta (Abeta) that could condition disease development, as well as the effect of the early-stage chaperone S100B in this context.
Methods: The effect of Abeta on Tau was assessed following the aggregation of a fixed concentration of the Tau AD core (TADC, $Tau_{306-378}$) by monitoring X-34 fluorescence intensity in the presence of Abeta42 monomers under cofactor-free conditions. To study the effect of Tau over Abeta, the *in vitro* aggregation of a fixed concentration of Abeta42 monomers in the presence of increasing proportions of TADC and Tau-K18 ($Tau_{244-372}$) was monitored by ThT fluorescence. Finally, the influence of S100B on TADC aggregation, with and without heparin, was similarly evaluated with the fragment alone and in the presence of Abeta42 monomers. The toxicity of end-point species was assessed by liposome leakage assays.
Results: TADC aggregation was accelerated in the presence of Abeta42 in a concentration-dependent manner, and the end-point species present were fully toxic for liposomes. On the contrary, Abeta42 aggregation was inhibited by both TADC and K18. S100B had a dual-behavior on TADC aggregation, accelerating it at substoichiometric proportions and fully inhibiting it at equimolar proportions, though this inhibition was not complete when heparin was present. Finally, under mixed conditions with Abeta42, the inhibitory effect of S100B over TADC aggregation was lost.
Conclusions: Tau and Abeta have opposite effects on each other's *in vitro* aggregation. S100B, while able to inhibit TADC aggregation and toxicity, showed a concentration-dependent dual-behavior, accelerating its aggregation at lower proportions. These results highlight the complex interplay of events in early-disease scenarios in Alzheimer's Disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0684 / #764

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

HS3ST2 EXPRESSION INDUCES THE CELL AUTONOMOUS AGGREGATION OF TAU

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Minh Bao Huynh[1], Nicolas Reberque[1], Heloise Merrick[1], Wilton Gomez-Henao[1], Estelle Jospin[1], Denis Biard[2], Dulce Papy-Garcia[1]
[1]University Paris-Est Créteil (UPEC), Gly-crret Research Unit, Faculty Of Science And Technology, Creteil, France, [2]CEA, Institut de Biologie François Jacob (IBFJ), Université Paris-Saclay, Laboratoire Sepia, Fontenay-aux-Roses, France

Aims: Heparan sulfates have long been known to intracellularly accumulate in Alzheimer's disease neurons, where they colocalize with neurofibrillary tangles made of abnormally phosphorylated and aggregated tau protein. However, the reasons and consequences of the heparan sulfates accumulation in the Alzheimer's cells are not yet well understood. Previously, we showed that the neural heparan sulfate 3-*O*-sulfotransferase HS3ST2 is critical for the abnormal phosphorylation of tau in Alzheimer's disease-related tauopathy. Using cell models of tauopathy we showed that intracellular 3-*O*-sulfatated heparan sulfates (3S-HS) interact with tau inducing its abnormal phosphorylation. However, it is unknown whether HS3ST2 expression induces the intracellular aggregation of tau in cells. In this work we aim to investigate whether 3S-HS by HS3ST2 can promote the spontaneous sef-agregation of tau in cells.
Methods: Here, by using replicative pEBV plasmids, we engineered HEK293 cells to stably express HS3ST2 together with human tau carrying or not the P301S mutation.
Results: We show that HS3ST2 gain of function induces the cell autonomous aggregation of tau not only in cells expressing tauP301S, but also in cells expressing the wild type tau. Our engineered cells mimicked both the HS intracellular accumulation observed in neurons of Alzheimer's disease and the tau aggregation characteristic of tauopathy development and evolution.
Conclusions: These results give evidence that the neural HS3ST2 plays a critical role in the cell autonomous self-aggregation of tau.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0685 / #845

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

DISCOVERY OF SMALL RNA SPECIES UNDERLYING TAU AGGREGATION AND PATHOLOGY

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Ami Kobayashi[1], Anna Krichevsky[2]
[1]Brigham and Women's Hospital, Harvard Medical School, Neurology, Boston, United States of America, [2]Brigham and Women's Hospital, Neurology, Boston, United States of America

Aims: Several reports and our new data suggest specific small RNA (sRNA) transcripts as the major tau binding partners that may facilitate its aggregation in Alzheimer's diseases and other tauopathies. Distinct classes of sRNA, including snoRNA and tRNA, have been proposed as the primary candidates. Our data suggest that persistent neuronal stress implicated in tauopathies leads to tRNA cleavage and accumulation of specific tRNA-derived fragments (tRFs) in neurons. Despite the established role of tRFs as factors triggering stress granule formation in stress response in various proliferative cells, their neuronal functions are unknown. The goal of our work is to identify endogenous sRNA species contributing to tau pathology and neurodegeneration.
Methods: To discover specific RNA transcripts enriched in tau complexes and aggregates, we optimized Cross-Linking and ImmunoPrecipitation (CLIP) technique coupled with the minimally biased small RNA detection for an array of anti-Tau antibodies. In addition, we developed *in situ* imaging technology (small RNA FISH) to monitor sRNA localization in pathological tau aggregates in rodent and human neurons and brain tissues.
Results: We observed an accumulation of specific tRFs in human Alzheimer's disease brains and the Tau P301S mouse model. Using several models of long-lasting neuronal stress that employ low subtoxic doses of glutamate, H2O2, or Aβ, we identified specific tRFs most strongly accumulating in these conditions in Tau WT and mutant cells. Our data further suggest some of these tRFs as selective and physiological tau-binders.
Conclusions: While we continue to investigate and validate the specificity of tau-tRF interactions, our current study suggests new molecular targets and biomarkers for therapeutic interventions, contributing to our understanding of the complexity and etiology of tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0686 / #440

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

UNCOVERING ELEVATED TAU TPP MOTIF PHOSPHORYLATION IN THE BRAIN OF ALZHEIMER'S DISEASE PATIENTS

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Lei Liu[1], Jean-Pierre Bellier[1], Yuqi Cai[1], Sarah Alam[1], Thorsten Wiederhold[2], Arica Aiello[2], Jonathan Vogelgsang[3], Sabina Berretta[3], Jasmeer Chhatwal[1], Dennis Selkoe[1]
[1]Brigham and Women's Hospital, Neurology, Cambridge, United States of America, [2]Cell Signaling Technology, Inc., R&d, Danvers, United States of America, [3]McLean Hospital, Harvard Brain Tissue Resource Center, Belmont, United States of America

Aims: A wide array of post-translational modifications of the tau protein occur in Alzheimer's disease (AD) and are critical to pathogenesis and biomarker development. Several promising tau markers, especially pT181, pT217 and pT231, rely on increased phosphorylation within a common molecular motif - threonine-proline-proline (TPP). Here, we use novel assays to examine systematically the extent to which phosphorylation of the pTPP molecular motif occurs in AD brain and how its differential phosphorylation patterns can be tied to disease staging and progression.
Methods: We validated several new and existing antibodies against pT217 and pT231, pT175, and pT181, then combined immunohistochemistry (IHC) and sensitive immunoassays (ELISA) to broadly examine the phosphorylation of the tau TPP motif across many AD brains.
Results: We find that the pTPP tau burden, as examined by IHC and ELISA, correlates to Braak stages across all TPP sites examined. Moreover, we observed significant regional variability across four TPP motif phosphorylation sites in multiple brains of sporadic, late-onset AD patients.
Conclusions: We conclude that the elevation of TPP tau phosphorylation in AD brains correlates to disease progression. The regional variability of pTPP tau suggests that examining different phosphorylation sites may be needed to assess tau pathology comprehensively.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0687 / #1964

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

LEVERAGING CELL-TYPE-SPECIFIC PATHOGENIC TAU REACTIVITY PATHWAYS TO UNCOVER AMYLOID TOXICITY MODIFIERS

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Roman Praschberger, Jeevanjot Singh, Patrik Verstreken
VIB-KU Leuven, Vib-ku Leuven Center For Brain And Disease Research, Leuven, Belgium

Aims: Tauopathies are characterized by certain neuronal subtypes being more affected than others, giving rise to the disease-defining symptoms. Since tau is expressed brain-wide without an obvious correlation with neuronal vulnerability, we hypothesized that different neurons are differentially susceptible to pathogenic tau toxicity and therefore contributing to the observed selective neuronal vulnerability. We have experimentally confirmed this with brain-wide single-cell RNA-seq across >200 unique neuron types of *Drosophila* models of tauopathy. Here, we investigate whether and how different neurons react differentially to pathogenic tau and assess if these pathways contribute to neuronal vulnerability/resilience to tau.
Methods: We compare differentially expressed genes and pathways in different neuronal subtypes in *Drosophila* models of tauopathy and relate these changes to Alzheimer's disease brains. We also perform scRNA-seq on non-aggregating tau flies harboring a PHF6 deletion in order to extract pathways specific to aggregation toxicity. Finally, we integrate these data and perform an unbiased experimental modifier screen based on the top differentially expressed genes.
Results: While we detect shared deregulations across cell-types – mainly in ribosomal and mitochondrial pathways - we also detect abundant transcriptional changes that are specific to certain neuron types. This underlines the values of single-cell studies to understand tau-induced reactivity pathways, which is further underlined by the observation that at the bulk analysis level we detect several-fold fewer transcriptional changes, potentially due to a dilution effect via unaffected cell-types. This suggests that different neurons react differently to pathogenic tau. Several of the deregulated genes were also potent tau toxicity modifier, indicating causality.
Conclusions: Single-cell RNA-seq derived pathways of tau reactivity might be useful to understand toxicity pathways.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0688 / #701

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

NEURONAL MECP2 PHOSPHORYLATION PRECEDES TAUOPATHY IN HIPPOCAMPUS AND MIDDLE TEMPORAL GYRUS OF SPORADIC ALZHEIMER'S DISEASE

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Qing-Rong Liu[1], Mark Horowitz[2], Qin Yao[2], Min Zhu[2], Qinghua Chen[2], Josephine Egan[2], Christopher Ramsden[2]
[1]National Institute on Aging (NIA/NIH), Lab Of Clinical Investigation, Baltimore, United States of America, [2]National Institute on Aging (NIA/NIH), Laboratory Of Clinical Investigation, Baltimore, United States of America

Aims: MECP2, an epigenetic transcription repressor, participates in neuron dendritic arborization and its phosphorylation regulates synaptic plasticity. Although MECP2 dysfunction has been implicated in Rett syndrome, its potential role in sporadic Alzheimer's disease (sAD) is largely unknown. We sought to determine whether MECP2-pS423 (pMECP2) can be detected in autopsied human hippocampus and middle temporal gyrus prior to Tau-hyperphosphorylation and whether its expression was increased in mild cognitive impairment (MCI) and sAD cases.
Methods: We developed and validated a rabbit anti-pMECP2 specific polyclonal antibody and carried out immunohistochemistry (IHC) on rapidly-autopsied postmortem hippocampus, entorhinal cortex (ErC), and middle temporal gyrus (MTG) specimens from 30 cases spanning the clinicopathological spectrum of sAD. We used HALO 3.3 to quantify the positive signals.
Results: pMECP2 expression increased in hippocampus, ErC, and MTG throughout the sAD spectrum with minimal, moderate, and strong expression in Controls, MCI, sAD cases, respectively. pMECP2 was primarily localized to soma and to a lesser extent within neurites emanating from affected neurons. Prominent pMECP2 expression was observed in neuron populations that are known to be selectively vulnerable to Tau-related neurodegeneration, including ErC layer II neurons and CA1 pyramidal neurons. pMECP2 expression was significantly correlated with pTau expression in each annotated region. In the hippocampus of Braak stage I-II controls, IHC revealed a small number of pMECP2-positive neurons in a similar distribution as observed for pTau. Multiplex-immunofluorescence revealed prominent cellular colocalization of pMECP2 and pTau. However, in some pyramidal neurons, pMECP2 expression was observed in the soma while AT8 positive pTau was confined to the neuropil thread, suggesting that cytoplasmic translocation of pMECP2 from nuclei may precede neurofibrillary tangle formation.
Conclusions: pMECP2 is elevated in sAD brain and correlates with pTau-associated neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0689 / #324

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

NUCLEAR ALTERATIONS AND TOXIC TAU CONFORMERS DEPOSITION IN NEURONS, ASTROCYTES AND MICROGLIA OF ALZHEIMER'S DISEASE, PROGRESSIVE SUPRANUCLEAR PALSY, AND DEMENTIA WITH LEWY BODY

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Lajja Majmundar[1], Rakez Kayed[2], Mauro Montalbano[2]
[1]University of Texas Medical Branch, John Sealy School Of Medicine, Galveston, United States of America, [2]University of Texas Medical Branch, Department Of Neurology, Galveston, United States of America

Aims: Tauopathies consist of age-associated neurodegenerative diseases (NDDs) characterized by pathological tau aggregation which leads to progressive neuronal dysfunction and death. Microglia and astrocytes have been described in several NDDs as playing important roles in synaptic spreading of toxic tau. In this study, human brain slices from age-matched non-demented (Control), Alzheimer's Disease (AD), Progressive Supranuclear Palsy (PSP), and Dementia with Lewy Body (DLB) cases were used to explore neuronal and glial nuclear alterations and investigate cell-specific deposition of toxic tau species.
Methods: Systematic macroscopic-histological examination of toxic tau aggregates in cortical human brains, by combinations of immunofluorescence staining were investigated for their association with specific cell types. Moreover, we investigated the nuclear density and chromatin condensation markers in these tissues. The Pearson's colocalization coefficient (PCC) for the different staining combinations were measured and presented as an averaged coefficient of determination, R^2.
Results: In the totality of cortical nuclei, a significantly greater nuclear area and chromatin condensation was seen in AD, and a reduction in nuclear density and chromatin condensation was seen in DLB and PSP. These observations showed that each disease presents varying nuclear phenotypes. Moreover, colocalization of toxic tau conformers showed a positive correlation mainly in neurons, indicating a large deposition of toxic tau in this cell type. A positive correlation in astrocytes was observed for distinct aggregates of neurotoxic phenotypes but not neuroprotective phenotypes. Microglia cells showed positive co-localization with both in varying degrees. In this study, we observed that each disease presents a specific nuclear signature and cell-type specific tau deposition.
Conclusions: This greater understanding of tau aggregation shows a cell-type tropism of toxic tau species and can give greater insight into appropriate more personalized therapeutic frameworks.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0690 / #2355

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

EXPLORING NEUROTOXIC EFFECTS OF EXTRACELLULAR TAU FIBRILS ON IPSC-DERIVED RETINAL NEURONS

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Lorenza Mautone[1], Ylenia Gigante[2], Silvia Ghirga[3], Lorenzo Barolo[4], Paola Baiocco[4], Alberto Boffi[5], Silvia Di Angelantonio[4]
[1]CLN2S-IIT (Italian Institute of technology), Iit (italian Institute Of Technology) Rome, Viale regina Elena, Italy, [2]Italian Institute of Technology - IIT- Rome, Italian Institute Of Technology - Iit- Rome, Viale Regina Elena, Italy, [3]D-TAILS, D-tails, Roma, Italy, [4]SAPIENZA UNIVERSITY OF ROME, Department Of Physiology And Pharmacology "v.erspamer", ROME, Italy, [5]SAPIENZA UNIVERSITY OF ROME, Department Of Biochemicalsciences "alessandro Rossi Farnelli", ROME, Italy

Aims: Tau fibrils, abnormal aggregates of the tau protein associated with neurodegenerative diseases, disrupt neuronal function and are primarily linked to brain pathology. However, evidence suggests their presence in the retina, sparking interest in their potential as a model for studying neurodegeneration and as a biomarker for disease diagnosis and progression. This study explores their presence in the retina, proposing it as a model for neurodegeneration research and a potential biomarker for disease. We focused on tau fragment K18, a truncated tau form with high binding and aggregation properties.
Methods: Fibrillation of this fragment was induced with heparin to generate oligomers or medium-length fibrils. Retinal neurons were differentiated from human iPSCs to study the impact of extracellular tau oligomers and fibrils in a controlled environment. Assessing tau seed uptake and concentration, we performed tau k18 seeding and collected samples after 1 and 15 days for immunofluorescence analysis.
Results: showed an increased Cleaved-casp3 positive nuclei in our cultures treated for 15-days, and an alteration in cytoskeleton markers suggested a correlation between tau fibrils exposure and cellular damage. Neurotoxicity effect of tau seeds was also confirmed by live/dead assay.
Conclusions: We concluded that tau fibrils induced cellular stress, disrupted neuronal function, and caused cell death in iPSC-derived retinal neurons. In summary, tau fibrils in the retina represent a burgeoning area of research with potential implications for understanding neurodegenerative diseases. They offer insights into disease mechanisms, diagnostic possibilities, and therapeutic monitoring. The in vitro models developed serve as a valuable tool for investigating the consequences of tau pathology on retinal cells, providing a foundation for exploring interventions to protect retinal health.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0691 / #719

Poster Topic: *Theme A: β-Amyloid Diseases / A07.c. Animal Models: Non-mamalian models, Other*

DIECKOL AS A NOVEL NEUROPROTECTIVE CANDIDATE WITH COGNITION IMPROVEMENT AND MULTIFACETED MECHANISMS IN ALZHEIMER'S DISEASE MOUSE MODEL

POSTERS: A07.C. ANIMAL MODELS: NON-MAMALIAN MODELS, OTHER

Kumju Youn[1,2], Jeong-Hyun Yoon[3], Mira Jun[1,2,3]
[1]Dong-A University, Center For Food & Bio Innovation, Busan, Korea, Republic of, [2]Dong-A University, Department Of Food Science And Nutrition, Busan, Korea, Republic of, [3]The graduate School of Dong-A University, Department Of Health Sciences, Busan, Korea, Republic of

Aims: Alzheimer's disease (AD) is an age-related neurodegenerative disorder associated with memory and cognitive deficits. Both amyloid β (Aβ) deposition and inflammatory response occur in the early course of AD, but the progression of cognitive impairment and its relationship with Aβ and neuroinflammation have not been fully understood. Dieckol is a phenolic compound from brown algae and has been reported to possess several health benefits. In particular, our previous studies have shown that the compound exerts the neuroprotective effects by inhibiting amyloidogenesis, oxidative stress and inflammatory responses against Aβ injury in cellular system. The aim of the present study was to demonstrate the cognitive improvement effect of dieckol *via* multiple mechanisms in AD mouse model.
Methods: Human $A\beta_{1-42}$ peptide was injected into the hippocampal CA1 region of mouse brains, followed by administration of dieckol (100 mg/kg/day) for 3 weeks, and histological changes and neuroprotective effect of dieckol were evaluated.
Results: Immunostaining showed that Aβ injection dramatically increased Aβ plaques compared to the vehicle injection, while administration of dieckol after Aβinjection decreased Aβ burden through Akt/GSK-3β/Nrf2 regulated amyloidogenic pathway. Dieckol suppressed neuroinflammatory responses in the Aβ group as evidenced by lower tissue levels of IL-1β, GFAP, and iNOS, except for COX-2. Moreover, the compound inhibited both nuclear translocation of NF-kB p65 subunit and IkBα phosphorylation, which significantly attenuated Aβ-mediated cognitive and memory dysfunction.
Conclusions: Overall, the present study provided a novel insight into feasibility of developing the compound as a neuroprotective agent for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0692 / #195

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

PPIA BINDS TAU AND SLOWS AGGREGATION IN VITRO INDEPENDENT OF ISOMERASE ACTIVITY

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Ayde Mendoza-Oliva[1], Bryan Ryder[1], Charles White[2], Valerie Perez[1], Lukasz Joachimiak[1], Marc Diamond[1]
[1]University of Texas Southwestern Medical Center, Center For Alzheimer's And Neurodegenerative Diseases, Dallas, United States of America, [2]University of Texas Southwestern Medical Center, Department Of Pathology, Dallas, United States of America

Aims: Based on evidence linking proline isomerization with tau pathology and since we found association of peptidyl-prolyl isomerase A (PPIA) with tau in Alzheimer's brain, we tested whether PPIA's cis-trans proline isomerase activity modifies tau aggregation *in vitro* and in cells.
Methods: PPIA-tau binding in human brain and in cells was determined using a pull-down assay. Recombinant human PPIA and tau were used for *in vitro* experimentation. The binding affinity was determined using microscale thermophoresis. The effect of PPIA isomerase activity on tau aggregation was analyzed by dynamic light scattering. The PPIA-tau interaction sites were mapped using crosslinking-mass spectrometry and the binding mode was determined by protein modeling. To test PPIA's effect in a cell model of tau aggregation its expression was genetically modified either by overexpression or CRISPR/Cas9 knockout.
Results: PPIA co-purifies with tau in human tauopathy brains. The conformational state of tau is not determinant for its interaction. PPIA affinity for tau is comparable to that shown with other proline isomerases. Proteomics experiments show in molecular detail that PPIA binds tau through its proline-rich domain (PRD). *In vitro,* PPIA delays tau aggregation kinetics independently of its proline isomerase activity. However, in cells, we did not detect any change in tau aggregation when PPIA proline isomerase activity was genetically abolished or when its levels of expression were increased.
Conclusions: PPIA directly binds tau through its PRD. *In vitro*, PPIA's effect on tau aggregation may arise from a function unrelated to its isomerase activity. Since there are multiple aspects of cellular proteostasis that involve PPIA, its role on tau maybe be dependent on cellular state or on the existence of more actors that regulate the PPIA-tau interaction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0693 / #2438

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

IN VIVO IMAGING OF AXONAL TRANSPORT REVEALS EARLY PATHOLOGICAL CHANGES INDUCED BY TAU MUTATIONS AND THEIR REVERSIBILITY

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Edoardo Moretto[1,2], Chiara Panzi[1], Skye Stuart[1], Anna Masato[1], Samantha De La-Rocque[1], Emily Huff[1], Ian White[3], Jemima Burden[3], Giampietro Schiavo[1,4,5]
[1]UCL, Uk Dri, London, United Kingdom, [2]CNR, Institute Of Neuroscience, Vedano al Lambro (MB), Italy, [3]UCL, Mrc Laboratory For Molecular Cell Biology, London, United Kingdom, [4]UCL, Department Of Neuromuscular Diseases, London, United Kingdom, [5]UCL, Queen Square Motor Neuron Disease Centre, London, United Kingdom

Aims: Tau is a protein abundantly expressed in neurons where it modulates the stability of axonal microtubules, thus contributing to the regulation of axonal transport of several organelles. Tau aggregates in a group of neurodegenerative diseases named tauopathies, which include frontotemporal dementia (FTD) and Alzheimer's disease. Our work aimed at studying axonal transport defects induced by tau pathology, both in cultured neurons and *in vivo* in the mouse brain. We also tested the reversibility of these deficits via pharmacological inhibition of the MAPK p38.
Methods: We investigated cultured mouse neurons and tauopathy mouse models *in vivo*, using immunoistochemistry, live imaging and in vivo two photon microscopy.
Results: We found that human tau showed regions of higher density along axons, reminiscent of tau envelopes, a microtubule-bound multimeric state of tau, distinct from pathological aggregates. FTD-linked mutations, known to increase pathological phosphorylation and aggregation of tau, induces larger envelopes, an effect that is reversed by inhibition of p38 MAPK, known to phosphorylate tau at multiple sites. Functionally, axonal transport of BDNF-containing secretory granules is affected by mutant tau envelopes as observed both *in vitro* and *in vivo* by using a new assay based on two-photon microscopy on tauopathy mouse models. Interestingly, this impairment occurred very early on, before overt tau aggregation. Inhibition of p38 MAPK was able to partially rescue the defects in axonal transport both *in vitro* and *in vivo*.
Conclusions: Our data suggests that tau envelopes size regulates axonal transport, an effect dependent on tau phosphorylation. Inefficient organelles transport may have severe consequences on the activity and plasticity of neuronal circuits. The evidence that reducing tau phosphorylation by inhibiting p38 MAPK potentiated axonal transport points towards inhibition of p38 MAPK as a promising therapeutic strategy in tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0694 / #634

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

ENHANCING LATERAL RESOLUTION USING SUPER-RESOLUTION MICROSCOPY TO UNRAVEL SYNAPTIC TAU PATHOLOGY.

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Érika Sánchez-Aced[1,2], Borja Moya-Llamas[1], Soraya Torres[1,2], Joaquim Aumatell Escabias[1], Martí Colom-Cadena[3], Jordi Pegueroles[1], Natalia Valle-Tamayo[1,2], Alba Cervantes González[1,2], Esther Álvarez-Sánchez[1], Sara Serrano-Requena[1], Laia Lidón[1,2], Laura Molina-Porcel[4,5], Iban Aldecoa[4,6], Raquel Sánchez-Valle[4,5], Oriol Dols-Icardo[1,2], Olivia Belbin[1,2], Juan Fortea[1,2], Tara Spires-Jones[3], Sònia Sirisi[1,2], Sílvia Pujals[7], Alberto Lleó[1,2]
[1]Memory Unit, Sant Pau Biomedical Research Institute, Neurology Department, Hospital De La Santa Creu I Sant Pau, Universitat Autònoma De Barcelona, Barcelona, Spain, [2]Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas, Ciberned, Madrid, Spain, [3]Centre for Discovery Brain Sciences, UK Dementia Research Institute, The University Of Edinburgh, Edinburgh, United Kingdom, [4]Neurological Tissue Bank of the Biobanc-Hospital Clinic-IDIBAPS, Institut D'investigacions Biomèdiques August Pi I Sunyer, Barcelona, Spain, [5]Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic De Barcelona, Idibaps, Barcelona, Spain, [6]Biomedical Diagnostic Center, Hospital Clinic of Barcelona, University of Barcelona, Department Of Pathology, Barcelona, Spain, [7]Institute for Advanced Chemistry of Catalonia (IQAC-CSIC), Department Of Biological Chemistry, Barcelona, Spain

Aims: Synaptic loss is a pathological hallmark in Alzheimer's disease (AD) that correlates with cognitive decline. However, the investigation in human brain is limited by the lack of adequate tools to resolved these small structures. Our primary objective was to combine array tomography (AT) with direct stochastic optical reconstruction microscopy (dSTORM) to achieve an enhanced lateral resolution optimal to resolve synaptic terminals in human postmortem brain and study synaptic tau pathology in AD.
Methods: We used AT samples obtained from controls and sporadic AD patients(n=3) from our AT cohort to study the lateral resolution achieved with the combination of AT+dSTORM. We measured the distance between the pre and post-synaptic markers. We also utilized 2 µm-thick paraffin (FFPE) samples from SAD patients(n=2) to visualize hyperphosphorylated tau using AT8 antibody. This marker was used for resolution comparison in confocal and STORM imaging.
Results: The combination of AT+dSTORM provides a significant improvement in lateral resolution compared to AT alone with conventional microscopy. This combination allowed to visualize the nanoscale architecture of individual synapses, including the synaptic cleft. The median distance between SYPH and PSD95 was 0.064µm±0.061, without overlap at distances of up to 0.008µm. We observed a significant improvement in lateral resolution using FFPE samples with dSTORM compared with confocal microscopy. However the AT+STORM combination offered the best results for visualizing aggregates at the
synapse.

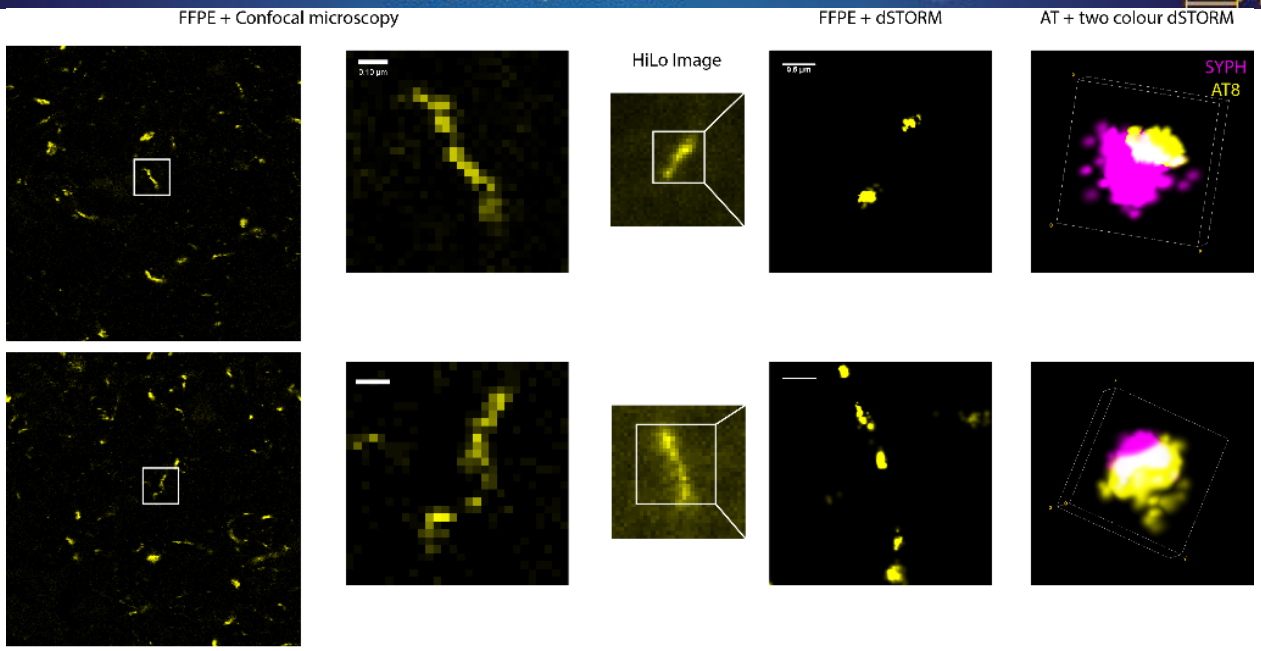


Figure 1. Comparison of Lateral Resolution obtained using confocal microscopy (left) and dSTORM (right).

Conclusions: Our findings highlight the potential of the combination of AT+dSTORM as an optimal condition to visualise tau aggregates at the synapse and to precisely resolve pre- and post-synapse structures in human brain. This innovative approach improves the understanding of synaptic pathology in neurodegenerative diseases, that could facilitate more targeted therapeutic interventions and a deeper understanding of the mechanisms underlying cognitive impairment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0695 / #1739

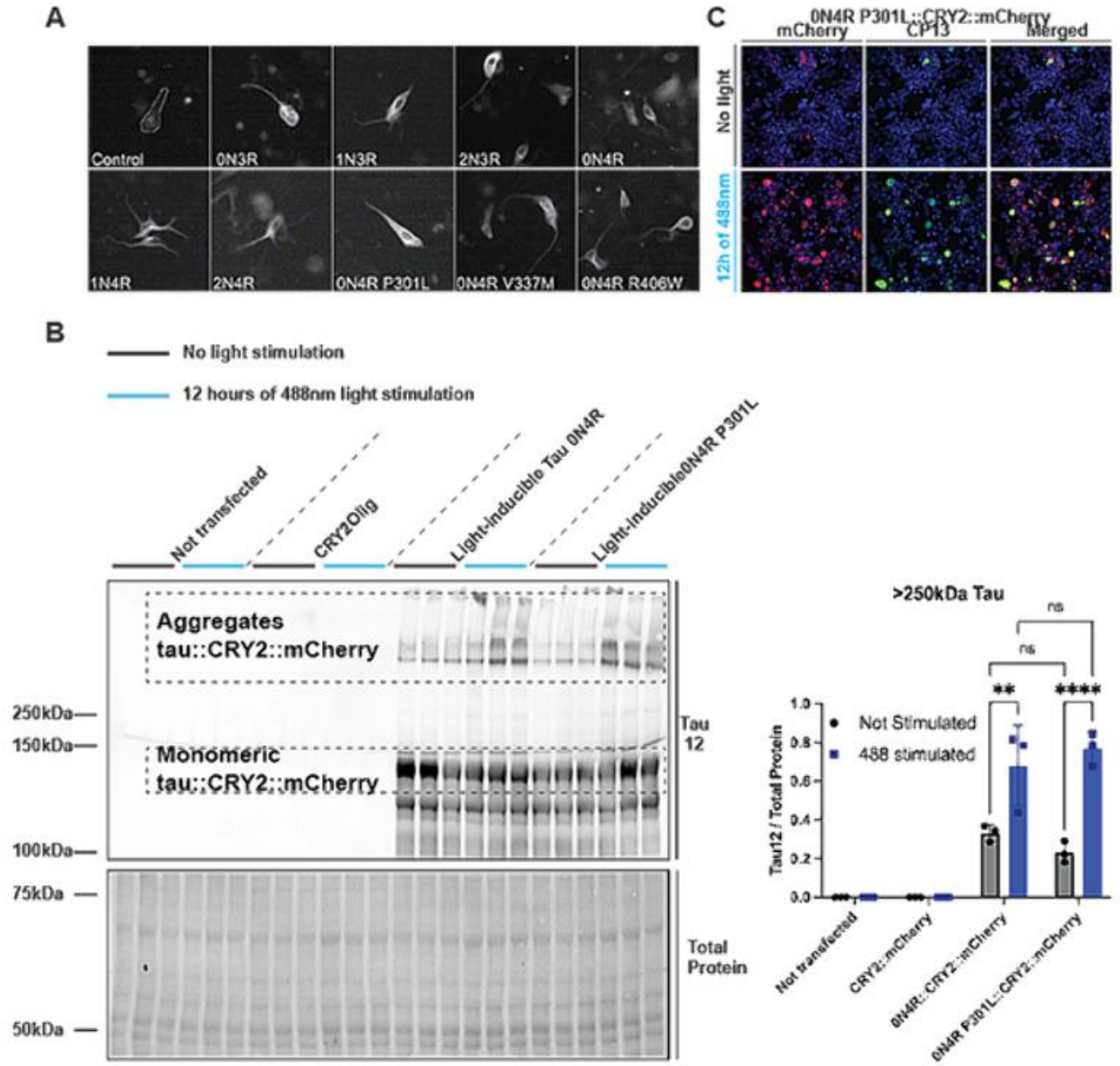
Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

MODELING TAU AGGREGATION THROUGH OPTOGENETICS

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Marcos Schaan Profes, Lyucheng Zou, Kurt Farrell, John Crary
Icahn School of Medicine at Mount Sinai, Department Of Pathology, Friedman Brain Institute, Ronald M. Loeb Center For Alzheimer's Disease, New York, United States of America

Aims: Tauopathies comprise a broad category of diseases associated with cognitive impairment. The molecular underpinnings of neurofibrillary neurodegeneration remain poorly understood and there is a paucity of robust cellular models for mechanistic studies and drug development. Hence, there is a critical need for new tau aggregation models and for further research to better understand the molecular basis of tauopathies. **OBJECTIVE:** To develop an optogenetics-based cellular model suitable for high-throughput analysis to aid in mechanistic studies of tau mediated cell death.
Methods: We engineered a panel of light-activated CRY2-tau constructs that enables assessment of tau aggregation kinetics and allows to focus on specific tau proteoforms to address questions on tau proteostasis, and associated pathway alterations with precise spatiotemporal control. This panel includes all CNS tau isoforms and a spectrum of mutations as well as mCherry for live cell imaging. This is a departure from the variable tau models available that rely on non-physiological modifiers of tau structure or the utilization of fibrils taken from diseased brains. Cell lines were transfected and assayed following light activation using immunoblotting and live imaging.
Results: Overexpression of CRY2-tau constructs showed stable inclusions after light stimulation, which were absent or markedly diminished in controls (Fig 1). Immunoblotting confirmed the presence of high molecular weight tau aggregates following stimulation. Inclusions were immunopositive for phospho-tau by immunocytochemistry and
immunoblot.



Conclusions: These data demonstrate that this system is capable of generating pathology-relevant tau species and has potential to reveal mechanistic insights into neurofibrillary degeneration. The precise spatiotemporal resolution of the system represents a potentially useful platform for drug screening.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0696 / #1381

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

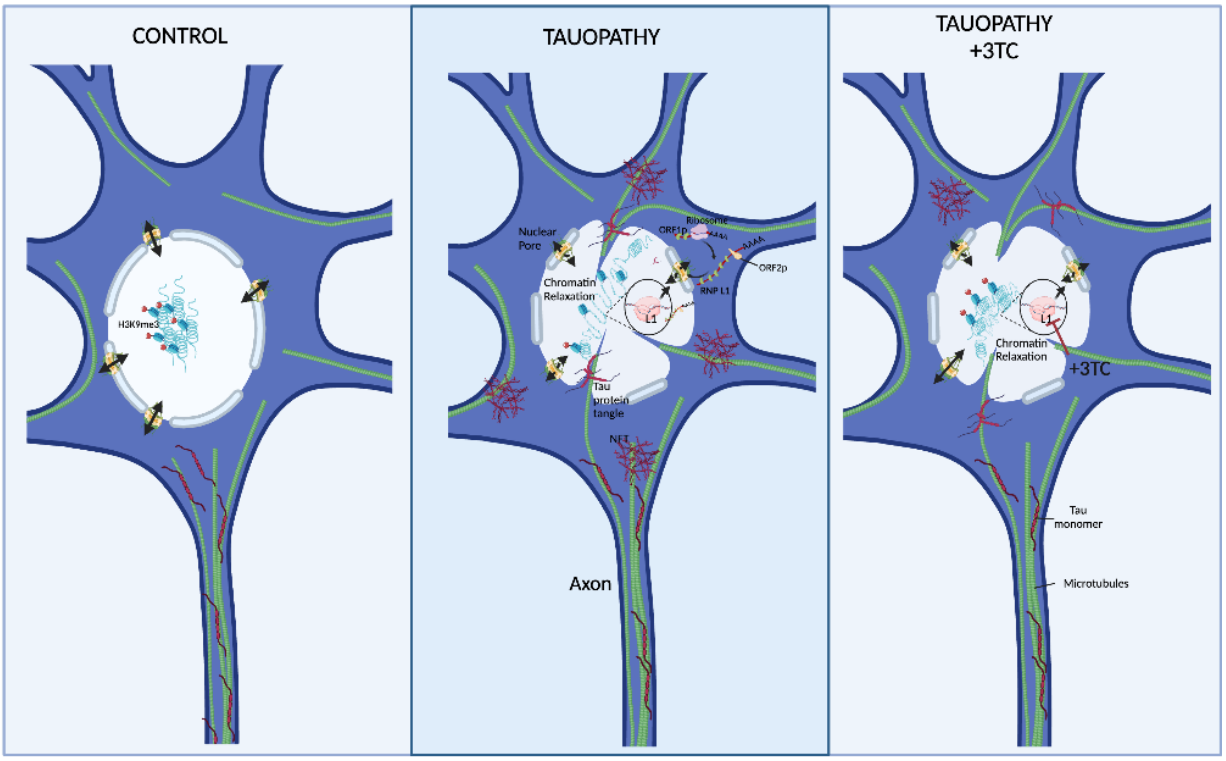
TACKLING TAUOPATHIES: LAMIVUDINE'S PROMISE IN NEURODEGENERATIVE THERAPY

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Laura Vallés Saiz, Jesús Ávila, Félix Hernández
Centro de Biología Molecular Severo Ochoa, Molecular Neuropathology, Madrid, Spain

Aims: 1. Investigate the potential protective effects of the reverse transcriptase inhibitor lamivudine (3TC) in a P301S mouse model of Alzheimer's disease based on the overexpression of tau protein associated with FTDP-17 tauopathy. 2. Assess the relationship between dysregulation of transposable elements and neurodegenerative disorders, specifically abnormal tau accumulation.
Methods: Lamivudine was administered to P301S mice via drinking water. These mice were subjected to the Rotarod test to evaluate motor deficits and the Y-maze test to assess short-term memory. Various immunofluorescence assays were conducted for histopathological evaluation. Experiments in HeLa cells were conducted to assess retrotransposition both with and without tau and lamivudine
Results: Lamivudine treatment showed a 30% increase in survival and improvements in behavior, such as a decrease in motor deficits and enhancement of short-term memory. Additionally, treated mice exhibited significant beneficial effects at the histopathological level, including a reduction in abnormal tau phosphorylation, decreased brain inflammation, decreased neuronal death, and attenuation of hippocampal atrophy in lamivudine-treated mice. Finally, we demonstrated in vitro that there was an increased insertion of LINE-1 in HeLa cells when tau was co-expressed, compared to cells without tau, and lamivudine could inhibit this process.
Conclusions: The data from this study suggest that the progression of tauopathies can be attenuated by the administration of lamivudine when symptoms of neuropathology first appear. This suggests a potential therapeutic approach to mitigate the effects of neurodegenerative disorders associated with dysregulated transposable elements and tau protein abnormalities. A connection exists between tau protein and LINE-1 retrotransposition, with higher retrotransposition in the presence of tau, and lamivudine reduces this

activity.


CONTROL
TAUOPATHY
TAUOPATHY
+3TC
H3K9me3
Nuclear
Pore
Chromatin
Relaxation
ORF1p
Ribosome
AAAA
ORF2p
RNP L1
L1
Tau
protein
tangle
NFT
Axon
Chromatin
Relaxation
+3TC
Tau
monomer
Microtubules

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0697 / #1466

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

COGNITIVE DECLINE AND TAU-ASSOCIATED PATHOLOGY WORSEN AFTER LATE-LIFE DEPRESSION IN P301S MICE

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Laura Vegas-Gomez[1], Cristina Gutierrez-Sastre[1], Maria Angeles Arredondo-Alcala[1], Antonia Gutierrez[1,2], Ines Moreno-Gonzalez[1,2,3]
[1]Universidad de Málaga, Departamento De Biologia Celular, Genética Y Fisiologia, Malaga, Spain, [2]Centro de Investigacion Biomedica en Red Sobre Enfermedades Neurodegenerativas, Ciberned, madrid, Spain, [3]The University of Texas Health Science Center at Houston, 3 Department Of Neurology, Houston, United States of America

Aims: Clinical studies suggest that depression could be considered an important risk factor for the future development of cognitive impairment and Alzheimer's disease (AD). In fact, there is a strong association between late-life depression and AD. The age of AD onset has been shown to be accelerated in patients with mild cognitive impairment (MCI) with a history of depression, and women appear to be particularly more vulnerable to this condition. In addition, individuals with MCI who present depressive symptoms have an elevated burden of amyloid-beta (Aβ), the main toxic protein associated with Alzheimer's pathology, and a higher risk of developing AD compared to non-depressed MCI patients. Although it has been described that some transgenic models of AD can develop signs like depression in advanced stages, the induction of Alzheimer's pathology due to a depressive process has not been studied under experimental conditions to emulate late-life depression as a risk factor for AD.
Methods: The objective of this study is to determine, by inducing unpredictable mild chronic stress (CUMS) in tau transgenic P301S mice, whether depression is a cause, rather than a consequence, of AD development.
Results: The results of our study indicate that the induction of CUMS in transgenic animals induces phenotypic changes related to a depressive state. Behavioral and histological studies suggest that depression-like induction can worse AD pathology.
Conclusions: The findings generated in this project could provide evidence of depression as a risk factor for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0698 / #417

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

TAU CLUSTERING ON THE NEURONAL PLASMA MEMBRANE IS IMPEDED BY NA+/K+-ATPASE DERIVED PEPTIDE

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Xiaojie Yu[1], Soki Bradel Ngonza-Nito[2], Ronald Melki[2], Antoine Triller[1]
[1]Institut de Biologie de l'ENS(IBENS), Cellular Biology Of The Synapse, Paris, France, [2]Institut Francois Jacob (MIRCen), Cea And Laboratory Of Neurodegenerative Diseases, Fontenay-Aux-Roses cedex, France

Aims: Abnormal accumulation of tau aggregates in the brain is a hallmark of tauopathies. Both monomer and fibril tau are detected in the extracellular environment and internalized by neurons in either free form or inside vesicles. However, whether monomer tau accumulates on the plasma membrane before internalization remains unclear. In this study, we will dissect the diffusion properties of both monomer and fibril tau on the plasma membrane.
Methods: Purified monomer and fibril tau were applied to primary neuronal culture and organotypic slice culture to mimic the pathologic environment. We adopted multiple single-molecule imaging approaches including single-molecule localization microscopy and quantum dots single particle tracking together with confocal imaging to quantitively analysis the clustering and dissociation process of monomer and fibril tau on the neuonal plasma membrane.
Results: Similar to fibril tau, monomer tau forms clusters on the plasma membrane following a time- and concentration-dependent manner. Monomer tau is involved in fibril tau clustering to enhance cluster stabilization and result in dynamic structures on the plasma membrane. Additionally, we describe the different diffusion properties of monomer and fibril tau on the plasma membrane suggesting their different binding partners on the membrane. Meanwhile, based on our previous work, we designed and verified a small peptide derived from Na^+/K^+-ATPase which alters tau clustering process and can be used as a potential therapeutic tool to postpone disease progression.
Conclusions: Monomer tau accumulates to clusters on the plasma membrane and is involved in fibril tau clustering to stabilize its structures, which suggests that monomer tau also plays an important role on tau spreading in tauopathies. The designed short peptide from Na^+/K^+-ATPase alters tau clustering process suggesting a new therapeutic method to postpone disease progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0699 / #2799

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

HUMAN IPSC 4R TAUOPATHY MODEL UNCOVERS MODIFIERS OF TAU PROPAGATION

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Celeste Parra Bravo[1], Alice Giani[1], Jesus Madero Perez[1], Zeping Zhao[1], Avi Samelson[2], Man Ying Wong[1], Alessandro Evangelisti[1], Li Fan[1], Tatyana Pozner[1], Maria Mercedes[1], Pearly Ye[1], Tark Patel[3], Allan Yarahmady[3], Gillian Carling[1], Virginia Lee[4], Manu Sharma[1], Sue-Ann Mok[3], Wenjie Luo[1], Mingrui Zhao[1], Martin Kampmann[2], Shiaoching Gong[1], Li Gan[1]
[1]Weill Cornell Medicine, Appel Alzheimer's Disease Research Institute, New York, United States of America, [2]University of California, San Francisco, Institute For Neurodegenerative Diseases, Department Of Biochemistry And Biophysics, San Francisco, United States of America, [3]University of Alberta, Department Of Biochemistry, Alberta, Canada, [4]Center for Neurodegenerative Disease Research, Institute on Aging, University of Pennsylvania School of Medicine, Department Of Pathology And Laboratory Medicine, Philadelphia, United States of America

Aims: Tauopathies are age-associated neurodegenerative diseases whose mechanistic underpinnings remain elusive, partially due to lack of appropriate human models. Current human induced pluripotent stem cell (hiPSC)-derived neurons express very low levels of 4-repeat (4R)-tau isoforms that are normally expressed in adult brain. Here, aimed to create new iPSC lines that expressed 4R-tau and 4R-tau carrying the P301S *MAPT* mutation when differentiated into neurons, to characterize and dissect the molecular mechanisms of underlying 4R-tauopathy in human neurons.
Methods: We employed the use of CRISPR editing to engineer the iPSC lines, and used molecular biology techniques, bulk and single-cell RNA sequencing, and immunostaining to characterize the lines. We found endogenous tau aggregation in the exclusively 4R-P301S neurons seeded with K18-PL tau seeds. With this, we utilized electrophysiology, transmission electron microscopy, and CRISPRi functional genomic screening to understand the pathways and factors driving tau inclusion formation.
Results: We found 4R-P301S neurons display progressive Tau inclusions upon seeding with Tau fibrils and recapitulate features of tauopathy phenotypes, including shared transcriptomic signatures, autophagic body accumulation, and impaired neuronal activity. A CRISPRi screen of genes associated with Tau pathobiology identified over 500 genetic modifiers of Tau-seeding-induced Tau propagation, including retromer VPS29 and the UFMylation cascade as top modifiers. In AD brains, the UFMylation cascade is altered in neurofibrillary-tangle-bearing neurons. Inhibiting the UFMylation cascade suppressed seeding-induced Tau propagation.
Conclusions: We characterized the 4R and 4R-P301S neuronal cell lines and identified novel genetic modifiers of 4R-tau inclusions, and thus, this model provides a powerful platform to identify novel therapeutic strategies for 4R tauopathy in human neurons.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0700 / #1613

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

STUDYING TAU-INDUCED NEURON-ASTROCYTE SIGNALLING

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Ambika Mahajan[1], Kevin Batenburg[1], Wiep Scheper[1,2]
[1]Amsterdam UMC, Human Genetics, Amsterdam, Netherlands, [2]Centre for Neurogenomics and Cognitive Research, Functional Genomics, Amsterdam, Netherlands

Aims: Tau pathology is strongly associated with neurodegeneration in numerous diseases including Alzheimer's Disease and Fronto-Temporal Dementia. Aggregation of tau disrupts cellular homeostasis and leads to activation of proteostatic stress responses in the neurons, sustained activation of which is toxic. Recent research from our lab has shown that progressive intraneuronal tau aggregation activates the integrated stress response (ISR) and increases reactive oxygen species (ROS) in astrocytes (Batenburg et al., 2022). In this study, we aim to elucidate the mechanism underlying the tau-induced cell non-autonomous response in astrocytes by determining the mode of transfer and the effect of ISR activation on astrocyte function.
Methods: Utilising our extensively validated seed-independent approach to induce tau aggregation (Batenburg et al., 2022; Jorge-Oliva et al., 2022, 2023), we employ direct and sandwich co-culture and monoculture models of human iPSC-derived neurons and human foetal astrocytes and mouse primary neurons and astrocytes to study neuron-astrocyte signalling and astrocyte function. High-content microscopy and confocal microscopy are utilised to determine cell type-specific ISR activation. Molecular and pharmacological interventions are employed to elucidate pathways involved in neuron-glia signalling and its downstream effects.
Results: Our data indicate that extracellular tau is not involved in tau-induced cell non-autonomous ISR activation in astrocytes. We are currently investigating the mode of transfer of the stress response through the transferring of conditioned media, and direct and sandwich co-cultures. Furthermore, we are studying the effects of activation of the ISR on astrocytic physiology.
Conclusions: Identification of the mechanism underlying the astrocytic non-autonomous response will provide insight into the role of astrocytes in tau-induced neurodegeneration. Knowledge of the molecular mechanism involved in tau-induced neuron-glia signalling will potentially provide novel therapeutic targets for neurodegenerative tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0701 / #333

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

TAU PATHOLOGY IN HUB REGIONS IS ASSOCIATED WITH HIGHER CONVERSION TO ALZHEIMER'S DISEASE

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Fardin Nabizadeh
Iran University of Medical Science, Tehran, Iran, School Of Medicine, Tehran, Iran

Aims: Previous studies showed that tau pathology spreads trans-synaptically across interconnected neurons. However, it is not clear whether the individuals who convert to Alzheimer's disease (AD) have higher tau pathology in globally connected hubs. We aimed to perform a study by combining resting-state fMRI and longitudinal tau-PET to investigate the association between tau pathology in globally connected hub regions and conversion to AD.
Methods: The data of 110 patients with mild cognitive impairment (MCI) was obtained from ADNI. Tau-hub ratio was calculated which represents the pattern of tau pathology considering the functional connectivity of each region to other regions.
Results: Our analysis showed that the tau-hub ratio was significantly higher among MCI patients who converts to AD over the follow-up (p:0.002). Moreover, there was a strong correlation between the tau-hub ratio and disease progression in MCI patients ($p<0.001$, r:0.453).
Conclusions: Our findings suggest that the tau pathology in globally connected hub regions may accelerate tau spreading through connected regions, AD progression, and conversion rate to AD.

P0702 / #334

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

REMOTE AND LOCAL EFFECT OF AB ON TAU SPREADING THROUGH FUNCTIONAL CONNECTIONS

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Fardin Nabizadeh
Iran University of Medical Science, Tehran, Iran, School Of Medicine, Tehran, Iran

Aims: Alzheimer's disease (AD) is characterized by the accumulation of Amyloid-beta (Aβ) plaques initiated approximately two decades before the symptom onset followed by buildup and spreading of neurofibrillary tau aggregates. Although it has been suggested that the Aβ amplifies tau spreading the observed spatial disparity called it into question. Yet it is unclear how neocortical Aβ remotely affects early pathological tau, triggering it to leave the early formation area, and how Aβ facilitates tau aggregate spreading throughout cortical regions. I aimed to investigate how Aβ can facilitate tau spreading through neuronal connections in the AD pathological process by combining fMRI normative connectomes and longitudinal in vivo molecular imaging data.
Methods: In total, the imaging data of 317 participants including, 173 Aβ-negative non-demented and 144 Aβ-positive non-demented participants have entered the study from ADNI. Furthermore, normative resting-state fMRI connectomes were used to model tau spreading through functional connections.
Results: It was observed that the Aβ in regions with the highest deposition (Aβ epicenter) is remotely associated with connectivity-based spreading of tau pathology. Moreover, Aβ in regions that exhibit the highest tau pathology (tau epicenter) is associated with increased connectivity-based tau spreading to non-epicenter regions.
Conclusions: The findings provide a further explanation for a long-standing question of how Aβ can affect tau aggregate spreading through neuronal connections despite spatial incongruity. The results suggest that Aβ pathology can remotely and locally facilitate connectivity-based spreading of tau aggregates.

P0703 / #1697

Poster Topic: *Theme B: Taupathies / B01.a. Disease Mechanisms, Pathophysiology: Tau aggregation, phophorylation, acetylation & modifications*

MAPPING OF POSTTRANSLATIONAL MODIFICATIONS OF NEURONAL MICROTUBULES AS MARKERS OF STABILITY DURING HIBERNATION IN HAMSTERS

POSTERS: B01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS

Julia Ziegert, Moana Künemuth, Max Holzer, Isabel Hilbrich, Jens Stieler, Markus Morawski, Thomas Arendt
Paul Flechsig Institut, Ag Holzer, Leipzig, Germany

Aims: Abnormal phosphorylation and subcellular translocation of tau protein are hallmarks of a variety of neurological disorders, including Alzheimer's disease (AD). Recently we described the reversible formation of highly phosphorylated tau protein in hibernating hamsters. Despite the extreme conditions during torpor, inducing highly phosphorylated tau protein and the cold-induced instability of microtubules, neuronal processes and associated memory contents remain largely intact upon arousal, necessitating compensation for cold-induced changes. We aim to analyse posttranslational modifications of microtubules during torpor in comparison to euthermic brain reagions in hamsters.
Methods: Posttranslational tubulin modifications such as polyglutamylation, Δ2-tubulin, Δ3-tubulin, tyrosination, detyrosination and acetylation were quantified in relation to total tubulin in brain areas of cerebellum, hippocampus, neocortex and subcortical regions from torpor (5°C) and euthermic (37°C) hamster brains. Western blot analysis is performed using modification-specific antibodies while fluorescence read-out allows simultaneous detection of specific posttranslational modifications and total tubulin. Immunostaining of brain sections will yield information about differentially affected cell types in various brain areas.
Results: In torpor state, I found that the total amount of tubulin decreases in all of the investigated brain regions. Some of the posttranslational modifications such as polyglutamylation and tyrosination are upregulated in some brain regions.
Conclusions: The presence of hyperphosphorylated tau and cold-induced instability may affect microtubule-integrity in brains of hibernating hamsters. The reversibility of cold-induced effects after torpor bouts calls for compensating effects on microtubles and microtubule-associated proteins. We show that posttranslational modification of tubulin may be associated with cold-induced stability.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0704 / #275

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

TAU OLIGOMER-MEDIATED STIMULATION OF THE NADK2-NADPH PATHWAY REWIRES MITOCHONDRIAL METABOLISM AND REGULATES ITS UPTAKE BY HUMAN NEURONS.

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Evelyn Pardo, Taylor Kim, Xuehan Sun, George Bloom, Andrés Norambuena
University of Virginia, Biology, Charlottesville, United States of America

Aims: Transcellular spread of pathological tau, mitochondrial dysfunction, and neuron loss are key signatures of Alzheimer's disease (AD). The evolutionarily conserved mitochondrial NADP+ kinase (NADK2) has been recently shown to regulate proline synthesis, cell proliferation, and cancer. However, whether dysregulation of mitochondrial NADK2 mediates tau-induced toxicity and propagation in AD remains unexplored.
Methods: Using recombinant (rTauOs) or brain-derived human tau (bdTauOs) oligomers, we evaluated mitochondrial metabolism by two-photon fluorescence lifetime microscopy in live NPC-derived human neurons. Lentiviral-mediated delivery of shRNA was used to downregulate LRP1 expression and CRISPR/CAS9 was used to generate both NADK2 and PYCR1-KO NPCs. A proteomic profile of NADK2-KO neurons was analyzed by mass spectrometry.
Results: Sublethal doses of rTauOs and bdTauOs increased the mitochondrial content of NADPH and the expression of NADK2, P5CS, PYCR1, and proline. These effects were absent in NADK2-KO and PYCR1-KO neurons. Mechanistically, these effects were mediated by LRP1, a major TauO receptor at the plasma membrane. Notably, NADK2 expression was upregulated in human AD brain. To understand the neuronal role of NADK2, we analyzed the proteomic profile of NADK2-KO human neurons using mass spectrometry. Among others, the expression of LRP1 was highly compromised in NADK2-KO neurons. Remarkably, the expression of LRP1 was increased in neurons treated with either rTauOs or bdTauOs and in neurons expressing P301S tau. Finally, the endocytosis of rTauOs was reduced by 50% in NADK2-KO human neurons, suggesting a decreased availability of LRP1 in the plasma membrane surface.
Conclusions: TauO-mediated dysregulation of NADK2 controls the expression of its own receptor, likely regulating a key aspect of TauO toxicity. Dysregulation of the NADK2 could be an early contributor to AD initiation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0705 / #2390

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

NEOCORTICAL TAU PROPAGATION IS A MEDIATOR OF CLINICAL HETEROGENEITY IN ALZHEIMER'S DISEASE

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Ana Pereira[1], Anjalika Chongtham[2]
[1]Icahn School of Medicine at Mount Sinai, Neurology, New York, NY, United States of America, [2]Icahn School of Medicine at Mount Sinai, Neurology, New York, United States of America

Aims: Heterogeneity in progression of clinical dementia obstructs the general therapeutic potential of current treatments for Alzheimer's disease (AD). Though the mechanisms of this heterogeneity remain unclear, the characterization of bioactive tau species and factors that regulate their seeding behavior might give valuable insight as tau is well correlated with cognitive impairment.
Methods: Here, we investigated the molecular basis involved in widespread, connectivity-based tau propagation that begins in the human post-mortem inferior temporal gyrus (ITG) and spreads to neocortical areas such as the prefrontal cortex (PFC) using tau seeding, several biochemical assays and RNA-sequencing.
Results: Biochemical analysis of postmortem human ITG and PFC tissues revealed considerable variability in tau seeding, which correlated with cognitive decline particularly in the ITG, a region known for promoting accelerated tau propagation. We propose that specific hyperphosphorylated high-molecular-weight and low-molecular-weight tau and its isoforms are likely mediators of seeding and cognitive decline. Further, we investigated the molecular heterogeneity in AD with RNA-seq analyses of ITG tissues with differential seeding potential. Patients with relatively higher levels of seed-competent tau showed more severely impaired synaptic and neural plasticity and increased neuroinflammation.
Conclusions: These findings provide further insights into multiple molecular mechanisms potentially involved in disease progression, highlight targets for early intervention, and improve patient subtyping, which is critical for developing precision medicines.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0706 / #1883

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

TRAUMATIC BRAIN INJURY DERIVED PATHOLOGICAL TAU POLYMORPHS INDUCE THE DISTINCT PROPAGATION PETTERN AND NEUROINFLAMMATORY RESPONSE

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Nicha Puangmalai[1], Nemil Bhatt[1], Alice Bittar[2], Cynthia Jerez[1], Nikita Shchankin[2], Rakez Kayed[1]
[1]University of Texas Medical Branch, Neurology, Galveston, United States of America, [2]University of Texas Medical Branch, Department Of Neurology, Galveston, United States of America

Aims: The misfolding and aggregation of the tau protein into neurofibrillary tangles constitute a central feature of tauopathies. Traumatic brain injury (TBI) has emerged as a potential risk factor, triggering the onset and progression of tauopathies. Our previous research revealed distinct polymorphisms in soluble tau oligomers originating from single versus repetitive mild TBIs. However, the mechanisms orchestrating the dissemination of TBI brain-derived tau polymorphs (TBI-BDTPs) remain elusive.
Methods: We explored whether TBI-BDTPs could initiate pathological tau formation, leading to distinct pathogenic trajectories. Wild-type mice were exposed to TBI-BDTPs from sham, single-blast (SB), or repeated-blast (RB) conditions, and their memory function was assessed through behavioral assays at 2- and 8-month post-injection.
Results: Our findings revealed that RB-BDTPs induced cognitive and motor deficits, concurrently fostering the emergence of toxic tau aggregates within the injected hippocampus. Strikingly, this tau pathology propagated to cortical layers, intensifying over time. Importantly, RB-BDTP-exposed animals displayed heightened glial cell activation, NLRP3 inflammasome formation, and increased TBI biomarkers.
Conclusions: Collectively, our results shed light on the intricate mechanisms underlying TBI-BDTP-induced tau pathology and its association with neuroinflammatory processes. This investigation enhances our understanding of tauopathies and their interplay with neurodegenerative and inflammatory pathways following traumatic brain injury.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0707 / #1905

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

ARC MEDIATES THE INTERCELLULAR SPREAD OF TAU

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Mitali Tyagi[1], Radhika Chadha[1], Bradley Hyman[2], Jason Shepherd[1]
[1]University of Utah, Department Of Neurobiology, Salt Lake City, United States of America, [2]Harvard Medical School, Massachusetts Alzheimer's Disease Research Center, Charlestown, United States of America

Aims: Aggregation of hyperphosphorylated tau is one of the hallmarks of Alzheimer's disease (AD) and correlates with cognitive decline in AD patients. During AD, tau pathology spreads across the brain in a stereotypical pattern. The spread of tau pathology occurs through intercellular transfer of pathological tau, but the underlying mechanisms remain unclear. Intercellular tau transfer may occur either through membrane-bound tau in extracellular vesicles (EVs) or as "naked" tau. Recent studies demonstrate that EV-tau may be more potent at seeding and spreading tau pathology. We recently discovered that the neuronal gene *Arc,* a critical regulator of synaptic plasticity and memory, mediates a novel form of intercellular communication. Arc protein self-assembles into viral-like capsids that are released from neurons in EVs that carry RNA/proteins to neighboring neurons. We hypothesized that Arc EVs may facilitate the release of pathological tau and intercellular spread.
Methods: To test if Arc facilitaes intercellular tau transfer, we virally expressed GFP-2A-human Tau (P301L) in wild-type and Arc knockout primary hippocampal neurons and in 6-month-old mouse entorhinal cortex. We also investigated if Arc and tau bind using GST pulldown assays and co-immunoprecipitation.
Results: We found intercellular tau transfer decreases significantly in the absence of Arc, both *in vitro* and *in vivo*. We also confirmed that Arc binds tau *in vitro* and *in vivo*.
Conclusions: Our findings suggest that Arc facilitates the intercellular spread of tau. We are now investigating the molecular mechanisms underlying Arc-dependent tau transfer.This study will uncover a novel mechanism for tau spread and seeding, potentially opening new therapeutic interventions for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0708 / #826

Poster Topic: *Theme B: Taupathies / B01.b. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

UNVEILING THE STRUCTURAL DIVERSITY OF TAUOPATHY STRAINS THROUGH SYSTEMATIC AMINO ACID PROFILING

POSTERS: B01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Jaime Vaquer Alicea[1], Victor Manon[1], Vaibhav Bommareddy[1], Peter Kunach[1], Ankit Gupta[1], Jim Monistrol[1], Valerie Perez[1], Vishruth Mullapudi[1], Du Siling[1], Sushobhna Batra[1], Charles White[2], Lukasz Joachimiak[1], Sarah Shahmoradian[2], Marc Diamond[2]
[1]University of Texas Southwestern Medical Center, Center For Alzheimer's And Neurodegenerative Diseases, Dallas, United States of America, [2]University of Texas Southwestern Medical Center, Department Of Pathology, Dallas, United States of America

Aims: The primary aim of this research is to unravel the structural diversity of tauopathy strains, including those observed in Alzheimer's disease (AD), Corticobasal Degeneration (CBD), and Progressive Supranuclear Palsy (PSP). This involves a systematic exploration of the role of individual amino acids in tau protein assembly, with a focus on understanding the amino acid dependencies within tau aggregates in cellular models. The study also seeks to develop a novel biosensor system for tauopathy classification, assess the fidelity of cellular models in replicating tau strain structures, and provide insights into potential diagnostic and therapeutic strategies.
Methods: To achieve our aims, we developed a cell-based assay that combines comprehensive tau mutagenesis with the detection of tau monomer incorporation into existing aggregates. This approach allowed us to systematically profile the amino acid contributions to tau strain stability and propagation. Synthetic tau strains were scrutinized in our models to assess their fidelity in replicating real-world tauopathy strain features. Furthermore, we extended our analysis to human tauopathy cases, investigating seeding activity profiles.
Results: Our study revealed the remarkable fidelity of simple cellular systems in replicating unique structural features of tau strains associated with specific tauopathies, such as AD, CBD, and PSP. Furthermore, the biosensor system successfully discriminated synthetic tau strains, providing a robust classification tool based on replication requirements. Analysis of human tauopathy cases demonstrated distinct seeding activity profiles for accurate disease differentiation.
Conclusions: We have successfully profiled amino acid contributions to tau strain stability and replication, leading to the development of a reliable classification system. The fidelity of cellular models in replicating tau strain features in patients underscores the potential of these models for future research. These findings have implications for diagnostics and therapeutic strategies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0709 / #2435

Poster Topic: *Theme B: Taupathies / B01.c. Disease Mechanisms, Pathophysiology: Inflammation*

DIFFERENTIAL EFFECT OF AMYLOID AND TAU PATHOLOGY ON PRO-INFLAMMATORY AND PRO-RESOLVING LIPID MEDIATORS IN TRANSGENIC RAT MODELS OF ALZHEIMER'S DISEASE

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Sonia Do Carmo[1], Surjyadipta Bhattacharjee[2], Marie-Audrey Kautzmann[2], Carolyn Steinberg[1], Nicolas Bazan[3], A Claudio Cuello[4]
[1]McGill University, Pharmacology And Therapeutics, Montreal, Canada, [2]School of Medicine, Louisiana State University Health New Orleans, Neuroscience Center Of Excellence, New Orleans, United States of America, [3]School of Medicine, Louisiana State University Health New Orleans andForeign Adjunct Professor of Neuroscience Karolinska Institutet, Stockholm, Sweden., Neuroscience Center Of Excellence, New Orleans, United States of America, [4]McGill University and Visiting Professor at Pharmacology, Oxford University, Pharmacology And Therapeutics, Montréal, Canada

Aims: Brain inflammation is characterized by glial cell activation and by the increased production of cytokines, chemokines, and lipid mediators (LMs) and contributes significantly to the development and progression of Alzheimer's disease (AD). However, little is known about the relative contribution of the amyloid and tau pathologies to the progression of neuroinflammation. Our objective was to investigate the differential impact of tau and amyloid pathology on the levels of cytokines, chemokines and bioactive pro-inflammatory and pro-resolving LMs.
Methods: We examined cohorts of homozygous McGill-R-Thy1-APP transgenic rats at 6 months of age when the amyloid beta (Aβ) pathology is restricted to the intraneuronal space and at 16 months of age when there is extensive Aβ plaque pathology. We also examined cohorts of heterozygous McGill-R962-hTau and McGill-R955-hTau transgenic at 10 and 20 months of age, representing progressive stages of tauopathy. Age-matched wild-type littermates were used as controls. Levels of cytokines, chemokines and LMs in cortical homogenates were probed applying well-established ECLIA, Western blotting and LC-MS/MS protocols.
Results: We found that in APP transgenic rats the cortical production of cytokines was already significantly elevated at pre-plaques stages while, in our rat models of tauopathy, an elevation in inflammatory mediators was only seen at late tau pathology stages. Our analyses also revealed that in our models, amyloid and tau pathologies had differential effects on levels of arachidonic (AA)-derived LMs prostaglandins, of docosahexaenoic acid (DHA)-derived pro-resolving mediators and of AA- and DHA-containing phospholipids.
Conclusions: Amyloid and tau pathology have differential effects on the abundance of bioactive LMs which vary with pathology progression. This suggests that tau and amyloid pathology have a different impact on the membrane properties and consequentially on signal transduction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0710 / #2804

Poster Topic: *Theme B: Taupathies / B01.c. Disease Mechanisms, Pathophysiology: Inflammation*

NEUROINFLAMMATION, ALPHA-SYNUCLEIN AND BETA-AMYLOID ANTIBODIES IN PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE.

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Dmitriy Labunskiy, Svetlana Kiryukhina, Vyacheslav Podsevatkin, Nikolay Kurgaev, Denis Baranov
Ogarev Mordovia State University, Neurology And Psychiatry, Saransk, Russian Federation

Aims: Neuroinflammation plays a very important role in the pathogenesis of a number of neurodegenerative diseases. Autoimmune reactions that come to the fore during neuroinflammation are accompanied by the release of specific antibodies to proteins that cause one or another neurodegenerative pathology. In Parkinson's disease (PD), this protein is alpha-synuclein (Alpha-S). In Alzheimer's disease (AD) it is amyloid beta (Beta-A). The purpose of our work was to identify specific antibodies (AB) to Alpha-S and Beta-A in these two neurodegenerative diseases, to determine the sensitivity and specificity of these antibodies, their affinity and cross-reactivity in patients suffering from BE and AD.
Methods: Under our supervision there were 13 PD and 16 AD patients, men and women aged from 47 to 84 years. The control group consisted of 23 healthy donors representing similar age and gender groups. ELISA and Western blot were used to detect AB to Alpha-S and Beta-A.
Results: AB to Alpha-S was detected in 67 percent of PD patients and 21 percent of AD patients. AB to Beta-A was detected in 74 percent of AD patients and 11 percent of PD patients. As a rule, in patients with each disease, ABs to both antigens (AGs) were detected; one antigen significantly exceeded that of the other antigen.
Conclusions: Analysis of the antibody response is important for assessing neuroinflammation in neurodegenerative diseases in order to develop new drugs for their treatment. Some anti-inflammatory drugs may be used.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0711 / #2261

Poster Topic: *Theme B: Taupathies / B01.c. Disease Mechanisms, Pathophysiology: Inflammation*

LPS INDUCED NEUROINFLAMMATION: MODIFIER OF PHOSPHORYLATION AND TAU TANGLE FORMATION

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Tomas Smolek, Neha Basheer, Muhammad Khalid Muhammadi, Norbert Žilka
Slovak Academy of Sciences, Institute Of Neuroimmunology, Bratislava, Slovak Republic

Aims: Tau spreading and neuroinflammation are two intimately connected processes. However, while epidemiological data suggests an early involvement of neuroinflammation in the etiopathogenesis of Alzheimer's Disease (AD), the lack of clinical efficacy observed for nonsteroidal anti-inflammatory drugs (NSAIDs), warrants further research. Consequently, with this study we aspired to apprehend the neuroinflammatory link to tau spreading and associated pathological changes by modulating microglial activation status.
Methods: We used R3m/4 transgenic mouse model expressing truncated 3 repeat tau (3 R tau, aa151-391). We induced chronic neuroinflammation for a period of two months with lipopolysaccharides (LPS). At final time point, animals were perfused, followed by immunohistochemical analysis to visualize hyper phosphorylated tau in hippocampus and tangle load in the brainstem, using tau specific antibody AT8. Glial cells, microglia and astrocytes were visualized using Iba 1 and GFAP antibodies respectively. Semi-automated histopathological quantification was performed on acquired images using open-source software QuPath.
Results: We found that LPS reduced tau phosphorylation in hippocampus and tau tangles load in the brain stem. We reported marginally significant cortical atrophy with no astrocytic reactivity in any of the groups. LPS entice a robust response in the form of microglial activation even a month after the last LPS insult and a directed migration towards the brainstem and hippocampal formation.
Conclusions: In summary, the present study suggests that relationship between inflammation and tau pathology is more complex. Our findings challenge the prevailing notion that chronic inflammation is solely responsible for the development of tau pathology. In fact, there is an active role of microglia in tau spreading and subsequent formation of pathological inclusion in vivo, which could manifest either way. **Acknowledgement:** This work was supported by JPND Multi-MeMo and VEGA 2/0127/22 research grants.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0712 / #2601

Poster Topic: *Theme B: Taupathies / B01.c. Disease Mechanisms, Pathophysiology: Inflammation*

EVALUATION OF HUMAN INDUCED PLURIPOTENT STEM CELL (HIPSC)-DERIVED TRI-CULTURE AS IN VITRO MODEL FOR NEUROINFLAMMATION

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Isabel Onofre, Chiara Formica, Leo Smit, Joyson Dcosta, Shushant Jain
Ncardia, Discovery Technologies, Leiden, Netherlands

Aims: Development of physiologically relevant models for neuroinflammation to address the unfilled gap in translatable human-based platforms.
Methods: Ncardia used neurons, astrocytes and microglia derived from iPSCs to set up tri-cultures and treated the cultures with recombinant mutant Tau (pre-formed fibrils) PFFs to establish a tauopathy model. Quantification of Tau aggregation and phagocytosis was performed using High content Imaging and measurement of cytokines and soluble Tau was performed by MSD and ELISA, respectively.
Results: We characterized the tri-culture model for cell type ratio and microglia activation for major biological processes that occur in the human brain: release of pro-inflammatory cytokines (IL-6, TNF-α, IL1-β and IL-18) and phagocytic activity. We observed tri-cultures exposed to lipopolysaccharide (LPS) released higher levels of cytokines and exhibited higher phagocytic activity assessed by uptake of pHrodo bioparticles. In a next step, we induced the phosphorylation (pTau) and aggregation of Tau, using Tau PFFs. This approach enabled a multi-parametric readout of neuronal and glial phenotypes including activation of microglia and astrocytes in the tri-culture. We observed increased levels of phagocyted pTau by microglia, mostly dependent on the phagocytosis of neurons expressing pTau and also increased levels of release of IL-6, TNF-α, IL1-β and IL-18. Together, these observations support a neurodegenerative phenotype, typical of tauopathies in which secreted or engulfed pTau activates microglia initiating the neuroinflammatory cascade.
Conclusions: Ncardia developed a tri-culture model that allow modulation of neuroinflammation and neurodegeneration *in vitro*. This model provides insight on cellular interactions such as microglia-neuron communication that play a role in recognizing apoptotic neurons and modulating neuronal activity which are crucial events in disease progression relevant for a biological disease processes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0713 / #1265

Poster Topic: *Theme B: Taupathies / B01.c. Disease Mechanisms, Pathophysiology: Inflammation*

NRF2 SIGNALING IMPAIRMENT FORERUN THE TAU AGGREGATION IN P301S TAUOPATHY MICE MODELS

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Sara Elfarrash[1,2], Ahmed Sabry Ibrahim[3], Karim Metwally[3], Mahmoud Elsayed[3], Mahmoud Ahmed[3], Eslam Serry[3], Hossam Eldin Gomaa[3], Ahmed Elshazly[3], Sara Eldusoky[1], Randa Elgamal[1,4]
[1]Mansoura University, Medical Experimental Research Center (merc), Mansoura, Egypt, [2]Mansoura University, Physiology, Mansoura, Egypt, [3]Mansoura University, Faculty Of Medicine, Mansoura, Egypt, [4]Mansoura University, Biochemistry And Molecular Biology, Mansoura, Egypt

Aims: Tauopathy is a group of neurodegenerative diseases characterized by tau deposits in neurons or glial cells. Clinical symptoms of tauopathies include cognitive impairments and motor disorders. From primary to secondary tauopathies, colossal work is underrunning to understand the pathophysiology of tau aggregation and disease progression. The role of inflammation and oxidative stress in the progression of tauopathies is demonstrated in different cellular and animal models. In the current study, we demonstrate that the Nrf2 expression is already impaired at the 8-week-old P301S transgenic mice model of tauopathy compared to the age-matching B6 wild-type mice. This data also takes us to further test Nrf2 activators as potential therapeutic agents for hindering the cognitive and pathological insults associated with disease progression in P301S mice.
Methods: P301S and B6 mice of 2, 4, and 6 months of age are used. Behavioral tests were done to evaluate cognitive and locomotor functions in each age group. Mice performances were recorded and analyzed by ANYMAZE. Following trans-cardiac perfusion, hippocampi were collected for quantitative PCR analysis of inflammation-related genes and interleukins, and other hemispheres were processed for immunohistopathology. For Nrf2 activation, two different Nrf2 activators were administrated IP for 6 weeks duration.
Results: The cognitive impairment of P301S is already evident in some tasks at the age of 2 months, and in all tasks by 6 months. mRNA expression of Nrf2 and its downstream hemoxygenase were already deficient in 2 months in P301S mice, suggesting a possible impaired cellular stress handling due to transgene expression. This proceeds tau aggregation that is only evident by 4 and 6 months.
Conclusions: Inflammation-related molecular changes proceed tau aggregation in P301S mice. Ongoing analysis is testing if increasing the cellular defense via enhancing Nrf2 signaling can be a potential therapeutic option for tauopathy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0714 / #2697

Poster Topic: *Theme B: Taupathies / B01.c. Disease Mechanisms, Pathophysiology: Inflammation*

DECIPHERING THE ROLE OF THE PERIPHERAL IMMUNE SYSTEM IN THE PATHOLOGY OF FRONTOTEMPORAL DEMENTIA

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Nazaret Gamez, Abdulmunaim Eid, Maria Pascual, Joseph Masdeu, Stanley Appel, Alireza Faridar
Houston Methodist Research Institute, Neurology, Houston, United States of America

Aims: Translational and clinical evidence support the contribution of chronic systemic inflammation in the etiopathology and progression of neurodegenerative diseases, including frontotemporal dementia (FTD). However, a comprehensive understanding of the intricate functional and mechanistic implications of how the peripheral immune system participates in neurodegeneration remains elusive. Here, we investigate the status of peripheral immune cells and the activation of inflammatory cascades in FTD individuals.
Methods: 24 FTD and 17 age-matched healthy control (HC) individuals were recruited by the Houston Methodist Nantz National Alzheimer´s Center. The immunophenotype and suppressive function of regulatory T cells (Tregs) were analyzed. The inflammatory transcriptomic changes of peripheral monocytes were assessed on the nCounter Human Panel for 770 immune markers. Plasma proteomics (Olink®) was performed for a total of 48 inflammatory cytokines and Peripheral Blood Mononuclear Cells (PBMCs) were submitted to single-cell mass cytometry by time-of-flight (CyTOF) analysis.
Results: The suppressive function of Tregs was compromised in FTD when compared to HC individuals. This was associated with the dysregulation of 136 inflammation-related transcripts in FTD monocytes. Plasma proteomics analysis identified increased levels of proinflammatory cytokines, including IFNG, CXCL9, CXCL10, and CXCL11 in FTD individuals. By integrating both transcriptomics and proteomics data, we identified the activation of the CXCL9-11/CXCR3 inflammatory cascade in FTD individuals. Moreover, the CyTOF proteomics analysis revealed that the CXCL9-11 ligands were mainly expressed by CD14-classical monocytes, whereas their receptor, CXCR3, was highly expressed by CD4 and CD8 T cells.
Conclusions: FTD individuals exhibit a compromised immunosuppressive function of Tregs along with the systemic activation of CXCL9-11/CXCR3 inflammatory cascade. Our findings demonstrate the activation of a novel inflammatory cascade in the clinical setting of FTD that merits further research as a potential therapeutic target.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0715 / #269

Poster Topic: *Theme B: Taupathies / B01.c. Disease Mechanisms, Pathophysiology: Inflammation*

NEURO PROTEINO-PATHY INDUCED BY POLYSTYRENE NANO PLASTIC VIA NLRP-3 ACTIVATION IN GLIAL CELLS

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Ariunzaya Jamsranjav[1,2], Hojin Park[3], Dongjun Lee[4], Hansang Cho[1,2,5]
[1]Sungkyunkwan University, Department Of Biophysics, Suwon, Korea, Republic of, [2]Sungkyunkwan University, Institute Of Quantum Biophysics, Suwon, Korea, Republic of, [3]Kookmin University, Department Of Nano Electric Physics, Seoul, Korea, Republic of, [4]Sungkyunkwan University, Department Of Biological Science, Suwon, Korea, Republic of, [5]Sungkyunkwan University, Department Of Intelligent Healthcare Medicine, Suwon, Korea, Republic of

Aims: Plastic nanoparticles have become a growing environmental concern due to their potential toxicity to nervous systems, including the brain, spinal cord, and peripheral nerves. The detrimental mechanism is, however, still unknown. This study aims to investigate the effect of nanoplastics on the mechanisms of neuroinflammation and neurodegeneration in the human brain environment.
Methods: Human brain cells were exposed to plain and amine-functionalized polystyrene nanoparticles. The internalization of nanoparticles was observed through live cell holotomography. The levels of chemokines and cytokines were measured using a human cytokine array.
Results: Human glial cells actively internalized PS-NP, resulting in Lc3b, LAMP-1 increase in lysosomes followed by Cathepsin-B. Consequently, the NLRP-3 inflammasome was activated, leading to increased activation of reactive astrocytes evidenced with GFAP and microglia evidenced with CD86 and TREM-2. This neuroinflammation leads to neurotoxic nitric oxides, as well as the release of proinflammatory mediators such as IL-1β, TNF-α, IL-6, IL-8, and chemotactic chemokines. Moreover, mild neuronal losses were observed with a 40% decrease in NeuN levels, accompanied by the occurrence of tau hyperphosphorylation and accumulation of phosphorylated alpha-synuclein.
Conclusions: Thus, this study confirms that polystyrene nano-plastics activate NLRP-3 inflammasomes in astrocytes and microglia, potentially causing neurodegenerative disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0716 / #2955

Poster Topic: *Theme B: Taupathies / B01.c. Disease Mechanisms, Pathophysiology: Inflammation*

MOUSE MODELS FOR NEUROINFLAMMATORY AND NEURODEGENERATIVE DISEASES

POSTERS: B01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Gunnar Flik, Mariette Heins, Ilona Vuist, Martha Olthuis
Charles River Laboratories, Discovery, Groningen, Netherlands

Aims: We aim to demonstrate the effects of different treatments, LPS, BzATP, LPS+BzATP or vehicle on neuroinflammation as well as the potential differences in peripheral effects of the tested set ups. Combined data should present us with guidelines for choosing optimal experimental designs for a variety of neuroinflammatory research questions. In addition, we will gain a better understanding of the timing effects of priming and activation of the inflammasome. Allowing better decisions to be made on test article administration for the various set ups.
Methods: A microdialysis probe (PP-PES200 2/3, CRL, the Netherlands) or a microperfusion cannula (Joanneum Research) was positioned in the right cortex of adult male C57Bl/6J mice and an ICV cannula in left ventricle. After several days of recovery, the experiment was initiated and microdialysate of microperfusate samples were collected at a flow rate of 0.5 µL/min in 60-minute intervals At the end of the experiment, terminal tissue samples were collected to serve as controls.
Results: Administration of LPS or LPS+BzATP showed pronounced IL-1β increases, while this is not observed in BzATP or vehicle administered animals. Effects were relatively more pronounced in the left and right cortices than in the striatum and hippocampus tissues. Blood levels of IL-1β were <LLOQ for the vehicle administered animals, while the LPS+BzATP dosed animals showed only a minor elevation in plasma (~60 pg/mL)
Conclusions: Our research has demonstrated that neuroinflammation of mouse brain tissue, without any major peripheral effects is feasible in a reproducible fashion both in an acute setting and in freely-moving cannulated animals. Microdialysis and microperfusion in mouse brain tissue will require further experimental optimization to establish a robust in vivo mouse model for the development of drugs that target neuroinflammatory processes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0717 / #1691

Poster Topic: *Theme B: Taupathies / B01.d. Disease Mechanisms, Pathophysiology: Synapse pathology*

MECHANISMS OF LOCUS COERULEUS DYSFUNCTION UNDERLYING EARLY PRECLINICAL SYMPTOMS IN NEURODEGENERATIVE DISEASES

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

Jochen Herms[1,2,3], Carolin Klaus[2,3], Theresa Niedermeier[1,2], Katharina Ochs[2,4], Stephan Müller[5,6], Stefan Lichtenthaler[5,7], Paul Feyen[8], Lars Paeger[2]
[1]Center for Neuropathology and Prion Research, Ludwig-maximilians University Munich, Munich, Germany, [2]German Center for Neurodegenerative Diseases, Translational Brain Research, Munich, Germany, [3]Munich Cluster for Systems Neurology, Synergy, Munich, Germany, [4]Ludwig-Maximilians-Universität München, Center For Neuropathology And Prion Research, Munich, Germany, [5]German Center for Neurodegenerative Diseases, Neuroproteomics, Munich, Germany, [6]Technical University of Munich, Neuroproteomics, School Of Medicine, Klinikum Rechts Der Isar, Munich, Germany, [7]German Center for Neurodegenerative Diseases, Dzne Munich, Munich, Germany, [8]German Center for Neurodegenerative Diseases (DZNE), Translational Brain Research, München, Germany

Aims: The locus coeruleus (LC) is one of the earliest brain regions affected in tauopathies and synucleinopathies. Non-cognitive clinical symptoms that relate to this early pathology in the LC are not well defined. Sleep disturbances, pathological anxiety as well as olfactory dysfunction can be potential early manifestations. Here, we seek to understand the mechanisms and consequences of LC dysfunction in the context of early symptoms in mouse models of neurodegenerative diseases using new in vivo imaging and molecular tools.
Methods: We employed in vitro and in vivo techniques including immunohistochemistry, behavioral experiments, slice electrophysiology, optogenetics and longitudinal in vivo 2P microscopy in AD and PD mouse models with early LC pathology. Either mouse models like the APPNL-G-F at early time points or induced LC-specific pathology via stereotactic injections of Cre-dependent AAVs carrying human Tau-P301S or α-synuclein preformed fibrils into the LC were analyzed. Mice expressing GFP in the mitochondrial membrane specifically in LC neurons enabled for genetic and proteomic analysis as well as in vivo imaging of mitochondria axonal transport.
Results: Our findings reveal an early loss of LC-noradrenergic axons exclusively in the olfactory bulb of APPNL-G-F mice which coincides with olfactory dysfunction. Moreover, stable, cell-type specific transduction of LC neurons with human P301S Tau recapitulate human LC Tau pathology. Proteomic analysis of isolated LC-mitochondria and in vivo imaging in human-Tau-expressing mice revealed multiple alterations in mitochondrial physiology and axonal transport.
Conclusions: Our study highlights the early-onset loss of LC-noradrenergic axons in the OB and its correlation with olfactory dysfunction in mouse models of neurodegenerative diseases. Moreover, we identified mitochondrial dysfunction and transport as a potential important mechanism in mediating axonal dysfunction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0718 / #2141

Poster Topic: *Theme B: Taupathies / B01.d. Disease Mechanisms, Pathophysiology: Synapse pathology*

SYNAPTIC DEGENERATION IN C. ELEGANS TAUOPATHY / AD MODELS

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

Jennifer Amrein[1], Brian Ackley[2]
[1]University of Kansas, Department Of Molecular Biosciences, Lawrence, United States of America, [2]The University of Kansas Department of Molecular Biosciences, Department Of Molecular Biosciences, Lawrence, United States of America

Aims: The mechanisms by which tau aggregation and/or mitochondrial function interact to manifest disease phenotypes is not entirely clear. To better understand whether mitochondrial stressors or tau aggregation could manifest disease-relevant phenotypes alone or in combination, we have developed novel *C. elegans* tauopathy models, in which we monitor synaptic integrity as a marker of early disease events.
Methods: Specifically, we developed new transgenic lines that express either wild-type human tau (hTau40), a disease-associated mutation (P301L), or a spontaneously aggregating variant (3PO) selectively in GABAergic neurons. Using a well-characterized synaptic marker (SNB-1::GFP) we have characterized the consequences of tau expression on synaptic integrity.
Results: We find that wild-type tau is well tolerated, causing no obvious changes to synapse numbers as animals age. In contrast, expression of either P301L or 3PO resulted in progressive synapse degeration during aging, with 3PO animals having a more severe phenotype. Separeately, we tested the consequences of treatment with juglone, which induces the formation of mitochondria-damaging reactive oxygen species (ROS). Larval treatment with juglone in otherwise wild-type animals caused synapse degeneration in young adults. Treatment of 3PO tau-expressing animals with juglone did not enhance the rate of degeneration observed, suggesting these may be affecting synaptic integrity via similar mechanisms.
Conclusions: These results suggest that early developmental stress, *i.e.,* tau aggregation and/or ROS production, could bias the development of synapse degeneration during adult aging. These results could indicate that events earlier in life may contribute to dememtias that manifest much later in life.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0719 / #2292

Poster Topic: *Theme B: Taupathies / B01.d. Disease Mechanisms, Pathophysiology: Synapse pathology*

ANALYSIS OF BRAIN SYNAPSE-ASSOCIATED PROTEINS IN TAUOPATHIES

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

Gunnar Brinkmalm[1], Johanna Nilsson[1], Elena Camporesi[1], Juan Lantero-Rodriguez[1], Tammaryn Lashley[2], Henrik Zetterberg[1], Kaj Blennow[1], Ann Brinkmalm[3]
[1]Department of Psychiatry and Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden, [2]Queen Square Brain Bank for Neurological Disorders, Department Of Clinical And Movement Neuroscience, London, United Kingdom, [3]University of Gothenburg Institute of Neuroscience and Physiology: Goteborgs universitet Institutionen for neurovetenskap och fysiologi, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden

Aims: Alzheimer's disease (AD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease (PiD) are neurodegenerative disorders characterized by aggregation and spreading of tau protein. While there are good diagnostic fluid biomarkers for AD, this is not the case for the other tauopathies. Our aim was to investigate synapse associated proteins in brain for possible translation to fluid biomarkers.
Methods: Seventeen synaptic proteins were quantified in soluble (tris-buffered saline, TBS) brain extracts using two different targeted mass spectrometry assays. Solid-phase extraction and parallel reaction monitoring mass spectrometry were used to quantify a protein panel including AP-2, beta-synuclein, gamma-synuclein, neurogranin, phosphatidylethanolamine-binding protein 1, 14-3-3 proteins, neuronal pentraxin-1 and -2, neuronal pentraxin receptor, and syntaxin-1B and 7. Immunoprecipitation combined with mass spectrometry was used to quantify four proteins, complexin-1 and -2, synptotagmin-1, and SNAP-25.
Results: In general controls had the highest levels followed by PSP, which generally was the least affected disease group. For SNAP25 CBD, followed by AD, had lower abundance. For gamma-synuclein and the neuronal pentraxins PiD, followed by CBD had lowest abundance; neuronal pentraxin-2 had lower abundance of AD and PSP as well. The 14-3-3 proteins also had lower abundance for all disease groups. A combination of selected peptides and previous data from p-tau217 made it possible to separate the five groups from each other.
Conclusions: By combining a few selected peptides PSP, CBD, and PiD could be separated from the other disease groups, which can be exploited to find fluid biomarkers for these tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0720 / #2812

Poster Topic: *Theme B: Taupathies / B01.d. Disease Mechanisms, Pathophysiology: Synapse pathology*

TARGETED PROTEOMICS OF SYNAPSE-ASSOCIATED PATHOLOGICAL PROCESSES IN TAUPATIES

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

Ann Brinkmalm[1], Johanna Nilsson[2], Juan Lantero-Rodriguez[2], Tammaryn Lashley[3], Henrik Zetterberg[4], Kaj Blennow[2], Gunnar Brinkmalm[2,5]
[1]University of Gothenburg, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden, [2]Department of Psychiatry and Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden, [3]Institute of Neurology, Ucl, London, United Kingdom, [4]The Sahlgrenska Academy at the University of Gothenburg, Institute Of Neuroscience And Physiology, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [5]Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden

Aims: We have recently developed CSF biomarker panels targeting synaptic dysfunction as well as pathological alterations in the endo-lysosomal and ubiquitin-proteasome systems. Several of the proteins that we have found to be significantly altered in CSF in early stages of AD or PD are synapse-associated membrane-proteins and in some cases, we have identified specific processed protein forms that seem to be disease related. Our aim in this study is to develop a selected reaction monitoring (SRM) mass spectrometry-based panel to characterize and quantify specific forms of synapse associated proteins in brain for possible translation to fluid biomarkers.
Methods: A central methodology in this project is targeted mass spectrometry for identification and quantification of proteins and protein forms. Low-flow liquid chromatography and high-resolution mass spectrometry is used to identify/characterize target peptides and fragments. High-flow liquid chromatography and high-selectivity mass spectrometric quantitation using SRM is used for quantitation. The quantitation is performed by adding heavy stable-isotope labelled peptides (internal standard [IS]) during the sample preparation.
Results: Solid-phase extraction and parallel reaction monitoring mass spectrometry were used to prepare TBS soluble brain homogenate fractions and almost 2000 proteins were identified with low-flow liquid chromatography and high-resolution mass spectrometry. High-flow liquid chromatography and SRM were used to develop a panel including SNAP-25, syntaxin-1A and B, VAMP2, complexin-1 and 2, SV2A, synaptophysin, and synapsin-1.
Conclusions: Differential patterns of CSF biomarkers associated with the synapse are probably due to differences in pathology mechanisms. The presented method could be used to compare the biomarkers' diagnostic and disease monitoring potential as well as to investigate specific pathological molecular patterns across and within neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0721 / #2890

Poster Topic: *Theme B: Taupathies / B01.d. Disease Mechanisms, Pathophysiology: Synapse pathology*

TAU AFFECTS POST-SYNAPTIC PROTEIN CONDENSATION

POSTERS: B01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY

Satabdee Mohapatra[1,2], Nils Rademacher[1], Caitlin Law[2], Alvaro Dominguez-Baquero[2], Sarah Shoichet[1], Susanne Wegmann[2]
[1]Charité – Universitätsmedizin Berlin, Neuroscience Research, Berlin, Germany, [2]DZNE, Neuroscience Research, Berlin, Germany

Aims: Tauopathies associate with deficits in synaptic function and plasticity, which rely on the formation and dynamics of the post-synaptic densities (PSD). Recent studies indicate that PSDs form via liquid-liquid phase separation (LLPS) of scaffold proteins, e.g. PSD95, along with multiple effector proteins, e.g., SynGAP. The microtubule associated protein Tau, an LLPS protein itself, was suggested to interfere with PSD function in Alzheimer's disease by interacting with PSD95 and SynGAP. We hypothesize that the disease-associated interaction of Tau with the PSD is based on interference with functional PSD condensation. We aim to 1) explore the interactions of Tau isoforms and frontotemporal dementia-related mutations with PSD95 condensation in vitro and in cells, and 2) how these interactions affect the functionality of synaptic PSDs in primary neurons.
Methods: The effect of Tau on PSD condensation is investigated in human cells (HEK293 cells) and in in vitro reconstitution using confocal microscopy, fluorescence recovery after photobleaching (FRAP) and other light microscopic techniques. The physiological significance of our findings is verified in primary hippocampal mouse neurons using similar techniques and LTP/LTD paradigms, as well as immunostaining and calcium imaging.
Results: We find that Tau promotes cellular and in vitro LLPS of PSD95 and decreases the mobility of PSD95 in PSD condensates in HEK cells and in synapses of primary neurons. We observe a complex interplay between Tau isoforms, post-translational modifications, and FTD-mutations and the molecular mobility of PSD95 in synaptic condensates.
Conclusions: Pathologically increased Tau concentrations in the post-synapse appear to decrease the molecular mobility of PSD95 within the PSD, which impacts PSD function and, hence, downstream signaling.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0722 / #1407

Poster Topic: *Theme B: Taupathies / B01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

STRUCTURAL INSIGHTS INTO THE ACTIVATION OF CDK5 BY SEROTONIN RECEPTOR 7

POSTERS: B01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Josephine Labus[1], Alina Brüge[1], Jana Ackmann[1], Lizaveta Gotina[2], Ae Nim Pae[2], Evgeni Ponimaskin[1]
[1]Hannover Medical School, Cellular Neurophysiology, Hannover, Germany, [2]Korea Institute of Science and Technology, Brain Science Institute, Seoul, Korea, Republic of

Aims: Aberrant phosphorylation and aggregation of the microtubule-associated protein tau are important neuropathological hallmarks of tauopathies. Several kinases are known to phosphorylate tau, with the Cyclin-dependent Kinase 5 (CDK5) being critically involved in pathological tau hyperphosphorylation. However, how cellular receptors contribute to CDK5 activation is only poorly understood. We have recently shown that the serotonin receptor 7 (5-HT7R) is involved in tau hyperphosphorylation by interacting directly with CDK5, independent of its activation by serotonin. Here, we studied the structural requirements for the interaction of 5-HT7R with CDK5.
Methods: Using an AI-based approach, we created a structural model of the 5-HT7R/CDK5 complex. Receptor mutants were generated by site-directed mutagenesis of potentially important amino acids. Biochemical and microscopic approaches were used to study the impact on CDK5 activation and tau phosphorylation in a cellular model of tauopathy.
Results: Our computational model identified 5-HT7R domains involved in the interaction with CDK5. In particular, two conserved phenylalanine residues, F278 and F281, within the third intracellular loop of the receptor were predicted to be crucial within the interaction interface. Substitution of these residues to alanine resulted in reduced 5-HT7R/CDK5 complex formation, CDK5 activation, and subsequent tau phosphorylation and aggregation. Importantly, G protein-mediated downstream signaling of the receptor was not affected by these mutations.
Conclusions: Our results provide the structural basis for the development of novel drugs targeting the 5-HT7R/CDK5 interaction interface for the selective treatment of tauopathies, including frontotemporal dementia and Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0723 / #414

Poster Topic: *Theme B: Taupathies / B01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

ALZHEIMER'S RISK GENE PTK2B LINKS TAUOPATHY, NEURONAL ELECTRICAL ACTIVITY AND AMYLOID-B IN HIPSC-DERIVED NEURONS

POSTERS: B01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Ana Raquel Melo De Farias[1], Alexandre Pelletier[2], Johanna Gadaut[1], Jean-Charles Lambert[3], Marcos Costa[4]
[1]Institut Pasteur de Lille, U1167, Lille, France, [2]Institut Pasteur de Lille, Umr1283-8199 - Cnrs, Lille, France, [3]Institut Pasteur de Lille | Université de Lille, Inserm U1167, Lille, France, [4]Institut Pasteur de Lille, Inserm U1167, Lille, France

Aims: In the human brain, the Alzheimer's disease (AD) risk gene PTK2B is mainly expressed in glutamatergic neurons and its expression declines with AD pathology progression. This reduced PTK2B expression in the brain of patients with AD coincides with the appearance of tauopathy and may contribute to neuronal dysfunctions observed in the disease, such as increased electrical excitability and synaptic loss. In this work, we investigated the impact of reduced PTK2B expression in human-induced neurons (hiNs).
Methods: We used two different isogenic human-induced pluripotent stem cell (hiPSC) lines to generate clones carrying PTK2B knockout (KO) and heterozygous (HET) mutations. These hiPSC lines were differentiated into hiNs expressing different levels of PTK2B in 2D and 3D (cerebral organoids) cultures. We then used functional and molecular assays to investigate the consequences of altered PTK2B expression in both physiological and AD-like contexts.
Results: We show that both PTK2B HET and KO hiNs display altered patterns of neuronal electrical activity when compared to WT. We also show that reduced expression of PTK2B leads to specific changes in gene expression in glutamatergic neurons, and that STAT3 could be a downstream target of PTK2B to regulate activity-dependent genes in hiNs. Reduced expression of PTK2B is also associated with increased phosphorylation of TAU at several epitopes associated with AD. Notably, exposure to $Aß_{1-42}$ increased the frequency of calcium transients in hiNs expressing PTK2B but not in KO hiNs, suggesting a possible role for PTK2B in mediating the effects of Aß on neuronal electrical activity.
Conclusions: Our study suggests that PTK2B may serve as a critical mediator linking amyloidopathy to changes in neuronal electrical activity and tauopathy. They also suggest STAT3 as a potential PTK2B downstream target regulating activity-dependent transcription in neurons.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0724 / #2627

Poster Topic: *Theme B: Taupathies / B01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress*

NHE6 LOSS-OF-FUNCTION DISRUPTS AUTOPHAGY AND TAU PHOSPHORYLATION IN CORTICOBASAL SYNDROME MODELS

POSTERS: B01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS

Katharina Stegen[1], Lena Loeffler[1], Theresia Zuleger[2], Angelos Skodras[3], Ana Velic[4], Lisa Schwarz[1], Brigitte Maurer[1], Lisa Wang[5], Dajana Grossmann[1], Christine Bus[1], Ulrich Müller[6], Günter Höglinger[7,8,9,10,11], Henry Houldon[12], Michael Deture[13], Bradley Boeve[14], Gerrit Machetanz[1], Boris Macek[4], Patrick May[15], Manu Sharma[5], Owen Ross[16], Zbigniew Wszolek[17], Olaf Reiss[18], Dennis Dickson[13], Angelika Riess[18], Tassula Proikas-Cezanne[2], Rejko Krüger[15], Julia Fitzgerald[1]
[1]Hertie Institute for Clinical Brain Research, Neurodegeneration, Tübingen, Germany, [2]Interfaculty Institute of Cell Biology, University of Tübingen, Molecular Biology, Tübingen, Germany, [3]Hertie Institute for Clinical Brain Research, Cellular Neurology, Tuebingen, Germany, [4]Interfaculty Institute of Cell Biology, University of Tübingen, Proteome Centre, Tübingen, Germany, [5]University of Tübingen, Centre For Genetic Epidemiology, Institute For Clinical Epidemiology And Applied Biometry, Tübingen, Germany, [6]Justus-Liebig University,, Institute For Human Genetics,, Giessen, Germany, [7]LMU hospital, Department Of Neurology, München, Germany, [8]Ludwig-Maximilian-University, Neurology, munich, Germany, [9]Ludwig Maximilian University, Department Of Neurology, Munich, Germany, [10]LMU University Hospital, Department Of Neurology, München, Germany, [11]German Center for Neurodegenerative Diseases (DZNE), Site Munich, Munich, Germany, [12]University College London, Inst. Neurology, London, United Kingdom, [13]Mayo Clinic Florida, Department Of Neuroscience, JACKSONVILLE, United States of America, [14]Mayo Clinic, Neurology, Rochester, United States of America, [15]University of Luxembourg, Lcsb, Esch, Luxembourg, [16]Mayo Clinic, Neuroscience And Clinical Genomics, Jacksonville, United States of America, [17]Mayo Clinic, Department Of Neurology, Jacksonville, United States of America, [18]University of Tuebingen, Institute Of Medical Genetics And Applied Genomics, Tübingen, Germany

Aims: NHE6 is an early endosomal cation exchanger where it helps maintain the pH of the lumen. *NHE6/SLC9A6* mutations cause a severe form of X-linked mental retardation. We investigated whether *SLC9A6* variants could contribute CBS/CBD in females and the biological relevance of NHE6 loss-of-function.
Methods: We performed a genetic screen for *SLC9A6* variants in an international cohort of 286 CBS/CBS cases and, 272 matched controls. We derived induced pluripotent stem cells from the fibroblasts of a female CSB patient carrying the p.T489Yfs *SLC9A6* mutation for differentiation into mature neurons. We also used inducible NHE6 knockdown in neuroblastoma cells. To investigate the relevance of NHE6 loss-of-function, we employed high throughput autophagy screening, mass spectroscopy and biochemical analyses of the endosomal-lysosomal system.
Results: There was no formal genetic association of *SLC9A6* variants with CBS, yet the cohort is relatively small since CBS/CBD is a rare neurodegenerative disease. We would therefore like to collect more samples through further collaborations. The T489Yfs NHE6 mutation confers loss-of-function due to truncation of the protein and failure of NHE6 to multimerize. Using p.T489Yfs patient-derived cells and loss-of-function models we report that NHE6 dysfunction causes blockage of the endosomal-lysosomal system and inhibition of autophagy initiation. Furthermore, there is a build-up of hyperphosphorylated Tau, (which was previously observed in *SLC9A6* knockout mice) and we identified specific, novel phosphorylation sites on Tau affected by NHE6 loss-of-function (Ser198 and Ser404) in patient derived neurons.
Conclusions: These data provide insight into possible underlying risk and biology of CBS/CBD, a

neurodegenerative disorder which is currently untreatable and incurable. The link between blockage of the endosomal-lysosomal system and build-up of phosphorylated tau may provide an entry point for the development of potential biomarkers and therapies for CBS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0725 / #1377

Poster Topic: *Theme B: Taupathies / B01.e. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

BETA-ADRENERGIC SIGNALLING PATHWAY REGULATES GENE EXPRESSION OF HS3ST2, A CRUCIAL ENZYME IN ALZHEIMER'S DISEASE RELATED TAU PATHOLOGY

POSTERS: B01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Heloise Merrick, Rafael Castillo Negrete, Wilton Gomez-Henao, Xavier Laffray, Minh Bao Huynh, Mohand Ou Idir Ouidja, Dulce Papy-Garcia
University Paris-Est Créteil (UPEC), Gly-crret Research Unit, Faculty Of Science And Technology, Creteil, France

Aims: Alzheimer's disease (AD) is the most common form of dementia, yet the mechanism triggering the disease remains unclear. AD is characterized by the two main classical hallmarks, senile plaques and neurofibrillary tangles. Among the less known hallmarks, the intracellular accumulation of 3-*O*-sulfated heparan sulfates (3S-HS) in neurons in AD vulnerable brain regions, such as the hippocampus. We have shown that the neuronal heparan sulfate 3-*O*-sulfotransferase 2 (HS3ST2) is associated with AD related tau pathology. However, the mechanisms underlying HS3ST2 gene expression regulation in neurons vulnerable to develop AD-related tau pathology remain unclear. Because the β-adrenergic pathway has been reported to be implicated in the regulation of HS3ST2 gene expression, we aim here to investigate whether regulation of this pathway can affect Hs3st2 gene expression in mouse hippocampus, which receives adrenergic afferences from the locus coeruleus (LC). Our aim is to decipher the involvement of the β-adrenergic pathway in the regulation of Hs3st2 gene expression in its relationship with the physiopathology of AD related tau pathology.
Methods: We analysed transcriptomic data from human and mouse brains and studied the β-adrenergic pathway by using agonists and antagonists of β-adrenergic receptors and related cell markers using *in vitro* and *in vivo* approaches in the rTg4510 model of tauopathy.
Results: We confirmed the presence of a specific set of β-adrenergic receptors in the hippocampus both in human and mouse and showed that modulating the β-adrenergic signalling pathway affects Hs3st2 gene expression *in vitro*. Then, we validated *in vivo* that the β-adrenergic pathway leads to a change in Hs3st2 expression, with effect in tau pathology.
Conclusions: Our results show that the β-adrenergic pathway can regulate Hs3st2 gene expression, allowing us to study the mechanisms leading to AD related tau pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0726 / #592

Poster Topic: *Theme B: Taupathies / B01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress*

NUTRIENT SENSING RECEPTOR GPRC6A SUPPRESSION ALTERS LYSOSOMAL FUNCTION AND REDUCES TAU PATHOLOGY IN PS19 MICE

POSTERS: B01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS

Kelsey Campbell[1,2], Chao Ma[2], Huimin Liang[2], Jerry Hunt[2], Madeline Killion[2], Daniel Lee[1,2]
[1]University of Kentucky, Neuroscience, Lexington, United States of America, [2]University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America

Aims: Arginine increases during course of Alzheimer's disease (AD) and in animal models of tauopathies. mTORC1 senses nutrients in eukaryotes and translocates to the lysosome during nutrient abundance to increase protein synthesis. During nutrient scarcity mTORC1 fails to translocate and autophagy is uninhibited. mTORC1 signaling can uncouple during neurodegenerative disease and precipitate proteinopathies. Arginine activates mTORC1 and signals through protein sensors such as GPRC6a, which also increases in AD brains and tauopathy models. We hypothesize that tau pathology promotes nutrient sensing dysfunction and hyper-mTORC1 activation. We posit that GPRC6a suppression activates autophagy, which rebalances proteostasis and hallmarks of tau pathology.
Methods: Tau transgenic mice (*PS19*) and non-transgenic littermates were bred to mice with GPRC6a hemizygous deletion to generate four genotypes: (*nTg, GPRC6a* $^{+/-}$*, PS19, PS19/GPRC6a* $^{+/-}$). Mice brains aged 7-9mo were harvested for western blot and bulk RNA-seq. Tau biochemistry, mTOR activation, lysosomal function, and autophagy were measured in detergent soluble or urea soluble fractions from anterior and posterior cortcies. Hippocampal tissue was used for bulk RNA seq Nanostring for transcriptome pathway analysis.
Results: Hemizygous deletion of GPRC6a (*PS19/GPRC6a* $^{+/-}$) decreased total tau and phospho-tau compared to *PS19* mice. GPRC6a suppression in PS19 mice significantly decreased mTORC1 activation compared to PS19 mice and increased autophagy and autophagosome formation. LC3-I and LC3-II increased in PS19/GPRC6a$^{+/-}$ mice compared to PS19 mice suggesting increased lysosomal biogenesis. PS19 mice showed increased transcripts associated with autophagy, neurogenesis, and proteotoxic stress compared to *nTg* littermates, and hemizygous deletion of GPRC6a (*PS19/GPRC6a*$^{+/-}$*)* normalized these signatures to control levels.
Conclusions: These data indicate that GPRC6a expression regulates proteostasis of tau and could serve as a therapeutic target in tauopathies. Additionally, our data suggests that GPRC6a impacts lysosomal function and mTORC1 activation state.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0727 / #875

Poster Topic: *Theme B: Taupathies / B01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress*

MAPT MUTATIONS DRIVE TAU ACCUMULATION VIA DEFECTS IN AUTOPHAGY AND ENDOLYSOSOMAL TRAFFICKING IN HUMAN NEURONS

POSTERS: B01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS

Farzaneh Mirfakhar[1], Jacob Marsh[1], David Perlmutter[2], Celeste Karch[1]
[1]Washington University in St. Louis, Psychiatry, st louis, United States of America, [2]Washington University in St. Louis, Pediatrics, st louis, United States of America

Aims: Lysosomal dysfunction and protein aggregation have been implicated in neurodegenerative disorders, including tauopathies. In a subset of tauopathies, rare mutations in the *MAPT* gene (which encodes the tau protein) are sufficient to cause disease; however, the exact mechanisms by which tau contributes to disease is unknown.
Methods: Here, we leveraged stem cell models to identify novel molecular mechanisms that influence the pathobiology of tauopathies and to identify therapeutics targeted to these mechanisms. Super resolution microscopy was used in human induced pluripotent stem cells (iPSC)-derived neurons expressing the FTD-associated *MAPT* p.R406W and isogenic controls (WT).
Results: In mutant neurons, the majority of lysosomes contained tau protein: pTau was enriched in the lysosomal membrane, while total Tau was enriched in the lysosomal lumen. Transcriptomic analyses revealed defects in genes enriched in pathways associated with lysosomal motility and maturation of autophagic vesicles. We observed several defects in retrograde transport that could impact lysosomal motility. Lysosomes were farther away from the perinuclear region, with slower motility and traveled shorter distances in mutant neurons. We found this may be due to dysregulation of JIP3, a dynein associated protein involved in retrograde transportation. Next, we evaluated maturation of autophagic vesicles. Mutant neurons exhibited an increase in autophagosomes (size and number), suggesting more autophagic flux. However, p62 and LC3-II were also increased, suggesting a defect autophagosome-lysosome fusion that may impact cargo degradation. Enhancing autophagy function was sufficient to rescue tau-specific defects in mutant neurons.
Conclusions: Together, our findings suggest that *MAPT* p.R406W may be sufficient to cause impaired autophagy and lysosomal function leading to disrupted tau degradation by lysosomes, which may contribute to the development of tau pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0728 / #1955

Poster Topic: *Theme B: Taupathies / B01.f. Disease Mechanisms, Pathophysiology: Lysosomes, ubiquitin, proteasome, ER stress*

PROTEOSTATIC RESPONSE TO TAU AGGREGATION REQUIRES CK1DELTA AND AUTOPHAGY TO FORM RESILIENT GVB-POSITIVE NEURONS

POSTERS: B01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS

Jasper Smits[1], Marta Jorge-Oliva[1], Skip Middelhoff[1], Thijmen Ligthart[1], Wiep Scheper[1,2]
[1]Centre for Neurogenomics and Cognitive Research, Functional Genomics, Amsterdam, Netherlands, [2]Amsterdam UMC, Human Genetics, Amsterdam, Netherlands

Aims: Neurons with tau pathology are not only faced with the direct proteostatic challenge imposed by pathological tau accumulation, but also with tau-induced impairment of the proteostatic machinery, resulting in a toxic vicious cycle of disturbed proteostasis. Here we aimed to gain more insight in the molecular pathways that mediate neuronal resilience to tau-induced proteostatic disturbance. To this end we investigated the mechanism and functional implications of the formation of granulovacuolar degeneration bodies (GVBs), a neuron-specific lysosomal response to tau aggregation, that contain endo- and autolysosomal cargo.
Methods: We employed a spontaneously aggregating tau model in primary mouse neurons to study the effect of tau aggregation and GVB accumulation on proteostasis. Quantitative high-content automated microscopy was used to measure the effect of our (genetic and pharmacological) interventions on protein synthesis, GVB accumulation and/or cargo accumulation to the GVB. Since CK1δ specifically targets to GVBs, we studied the effect of inhibition of CK1δ on GVB accumulation. We also tested the effect of inhibition and stimulation of autophagy on GVB accumulation.
Results: While tau aggregation reduces protein synthesis, the presence of GVBs rescues this phenotype. Moreover, GVB-positive neurons elicit a stronger proteostatic response than GVB-negative neurons. Furthermore, inhibition of CK1δ decreases GVB formation. Similar results were obtained when autophagy was inhibited, while stimulation of autophagy did not affect GVB accumulation.
Conclusions: Our data show that GVB-positive neurons are resilient to tau-induced proteostatic impairment. Furthermore, CK1δ activity as well as autophagy are required for the formation of GVBs. We conclude that CK1δ is an essential upstream regulator for the formation of GVBs as a protective neuron-specific, proteostatic stress response to tau pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0729 / #1024

Poster Topic: *Theme B: Taupathies / B01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

EFFECTS OF ESTETROL ON MITOCHONDRIAL FUNCTIONS IN CELLULAR MODELS OF ALZHEIMER'S DISEASE

POSTERS: B01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Aline Broeglin[1], Aurélien Riou[2], Valérie Dion[3], Céline Gérard[3], Anne Eckert[4], Amandine Grimm[2]
[1]University of basel, Department Of Biomedicine, Basel, Switzerland, [2]University of Basel, Department Of Biomedicine, Basel, Switzerland, [3]Mithra Pharmaceuticals, Estetra Srl, Liège, Belgium, [4]Neurobiology Lab for Brain Aging and Mental Health, Research Cluster, Molecular & Cognitive Neuroscience, Basel, Switzerland

Aims: Estrogens, such as estradiol (E2), are known to regulate cellular metabolism. They also have neuroprotective effects, and represent potential candidates for Alzheimer's disease (AD) prevention, especially as hormone replacement therapy (HRT) for post-menopausal women. However, these molecules are also associated with unwanted effects. Estetrol (E4), a natural estrogen exclusively produced by the human fetal liver during pregnancy, is currently under development as HRT and could be a safer therapeutic alternative. The aim of this study was to investigate the effect of E4 on cell viability and bioenergetic functions in control and AD cell models.
Methods: Cell viability and bioenergetic parameters were assessed in three cell lines: - Native SH-SY5Y neuroblastoma cells: control cells; - P301L mutant tau overexpressing SH-SY5Y cells: cellular model of AD-related tauopathy; - Amyloid precursor protein (APP) overexpressing SH-SY5Y cells: cellular model of amyloidopathy. Cells were treated with E4 or E2 (as control for comparison) for 48h. Cell viability tests and bioenergetic measurements, including adenosine triphosphate (ATP) level, mitochondrial membrane potential (MMP) and reactive oxygen species (ROS) level, were realized at the end of the treatment.
Results: Treatments with E4 and E2 improved cell survival and bioenergetic functions. ATP production and MMP were increased, while ROS production was decreased. The effects of E4 on cell metabolism slightly varied depending on the cell line.
Conclusions: The data indicate that E4 is able to modulate cellular bioenergetics with an overall similar or, for some parameters, better efficacy than E2. E4 and E2 treatment showed better efficacity in the cellular model of AD-related tauopathy than in the model of amyloidopathy. This statement must be verified with further experiments.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0730 / #2256

Poster Topic: *Theme B: Taupathies / B01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

PREVENTION OF PATHOLOGICAL TAU ABNORMALITIES BY NON-ANTIBIOTIC DERIVATIVES OF DEMECLOCYCLINE AND OXYTETRACYCLINE

POSTERS: B01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Patrick Pierre Michel[1], Thais Alves Fernandes[1,2], Rodrigo Tomas Grau[1,3], Aurore Tourville[1], Bianca Andretto De Mattos[1,2], Florencia González-Lizárraga[1,3], Ismaila Ciss[4], Rosana Chehin[3], Laurent Ferrié[4], Bruno Figadère[4], Elaine Del-Bel[2], Rita Raisman-Vozari[1]
[1]Hôpital de la Pitié Salpêtrière, Institut Du Cerveau - Icm, Inserm, Sorbonne Université, Cnrs, Paris, France, [2]University of São Paulo, Basic And Oral Biology, Ribeirão Preto, Brazil, [3]Universidad Nacional de Tucumán, Immca, Conicet-unt-siprosa, Tucumán, Argentina, [4]Université Paris-Saclay, Biocis, Cnrs,, Orsay, France

Aims: We established, here, experimental paradigms enabling the investigation of tau-related abnormalities (pathological phosphorylation, amyloid aggregation) in Alzheimer's disease (AD) and related tauopathies to evaluate the therapeutic potential of anti-tau molecules for these disorders. More specifically, we were interested in characterizing the effects of DDMC and DOT, two non-antibiotic tetracycline (TC) derivatives of demeclocycline and oxytetracycline, respectively.
Methods: To monitor pathological tau phosphorylation, we implemented cultures of mouse cortical neurons grown in astrocyte-conditioned medium (ACM) [Tourville et al, Antioxidants, 2023] and submitted them to sustained low-level insults generated by either catalytic iron or glutamate. Pathological tau was revealed with the AT8 antibody that identifies p-Ser202/p-Thr205 residues. We also adapted an ex vitro assay where amyloid aggregation of tau is achieved using heparin as a co-factor [Medina et al, Front Aging Neurosci, 2021].
Results: When exposed to iron (1.6 µM)-containing medium, p-tau accumulation culminated in neuronal somas 4 days after the change of culture medium, to decrease progressively thereafter when neurodegeneration had further advanced. When cultures maintained in ACM where challenged with glutamate, p-tau induction peaked earlier, i.e., 24h after initiating the excitotoxic insult. The use of two fluorogenic probes DHR-123 and TMRM revealed that p-tau accumulation correlated in both cases with an escalation of oxidative stress and a drop of mitochondrial membrane potential. Oxidative stress and p-tau build-up as well as ensuing neurodegenerative changes were efficiently prevented by either DDMC or DOT. Rescued neurons remained fully functional as they efficiently accumulated [^{3}H]-2-deoxyglucose. Interestingly, these two compounds also prevented heparin-activated tau aggregation, at low micromolar concentrations.
Conclusions: Based on present results, we suggest that the non-antibiotic TCs DDMC and DOT may have therapeutic value in preventing early tau-related abnormalities in AD and other tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0731 / #1882

Poster Topic: *Theme B: Taupathies / B01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

IMPACT OF ALZHEIMER'S TAU PATHOLOGY ON MITOCHONDRIA

POSTERS: B01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Muhammad Khalid Muhammadi[1,2], Tomas Smolek[2], Neha Basheer[2], Monika Žilková[2], Norbert Žilka[2]
[1]University of Veterinary Medicine and Pharmacy in Košice, Biology, Bratislava, Slovak Republic, [2]Slovak Academy of Sciences, Institute Of Neuroimmunology, Bratislava, Slovak Republic

Aims: Alzheimer's disease (AD) is a prevalent neurodegenerative disorder, marked by neurofibrillary tangles (NFTs) and beta amyloid plaques in human brain, linked to cognitive decline and memory loss. Mitochondrial dysfunction contributes to AD progression, as mitochondria provide neurons with ATP, regulate calcium balance, and modulate apoptosis. Clinical data indicate mitochondrial malfunctions, energy metabolism deficits, and oxidative damage in AD. However, the direct impact of tau pathology on mitochondria remains unclear, necessitating further investigation. This study examines influence of AD-tau pathology on mitochondria using in-vitro and in-vivo AD models.
Methods: In-vitro experiments employed RD P301S tau FRET Biosensor cell model, expressing P301L mutant tau protein. While, in-vivo experiments used SHR72 transgenic rats with truncated human tau protein, at an early terminal stage. Flow cytometry and Immunohistochemistry were employed to validate the AD-tau aggregation in-vitro and tau pathology in-vivo in free floating sections. While confocal microscopy and western blotting were utilized to analyse the effect on mitochondria. Furtermore, the reactive oxygen species (ROS) production was quantified using standard protocol for flow cytometry.
Results: We confirmed the induction of Tau pathology in both in-vitro and in-vivo settings. Mito-tracker fluorescence intensity was significantly reduced in AD tau-infected cells, and confocal imaging revealed disrupted mitochondrial network configuration. Likewise, elevated amount of mitophagy markers (PARKIN and PINK 1) were noted in transgenic animal models. The production of reactive oxygen species were increased in the cells infected with AD-tau.
Conclusions: Our findings suggest that AD-tau pathology might trigger mitochondrial dysfunction in Alzheimer,s disease, however, it requires further investigation. **Acknowledgement:** This work is supported by APVV-20-0331, APVV-19-0585, APVV-20-0585, and VEGA 2/0127/22grant.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0732 / #535

Poster Topic: *Theme B: Taupathies / B01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

MOLECULAR AND CELLULAR DETERMINANTS OF LOCUS COERULEUS-SPECIFIC TAU PATHOLOGY

POSTERS: B01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Katharina Ochs[1,2], Theresa Niedermeier[1], Stephan Müller[3,4], Stefan Lichtenthaler[3,4], Jochen Herms[2,5,6], Lars Paeger[1]
[1]German Center for Neurodegenerative Diseases, Translational Brain Research, Munich, Germany, [2]Ludwig-Maximilians-Universität München, Center For Neuropathology And Prion Research, Munich, Germany, [3]German Center for Neurodegenerative Diseases, Neuroproteomics, Munich, Germany, [4]Technical University of Munich, Neuroproteomics, School Of Medicine, Klinikum Rechts Der Isar, Munich, Germany, [5]Center for Neuropathology and Prion Research, Ludwig-maximilians University Munich, Munich, Germany, [6]Munich Cluster for Systems Neurology, Synergy, Munich, Germany

Aims: The locus coeruleus (LC) is a small nucleus in the brainstem and the sole source of the neurotransmitter noradrenalin in the forebrain (1). In Alzheimer's disease, it is among the first regions affected by Tau pathology and early neurodegeneration (2). However, the spatiotemporal development of Tau pathology as well as the underlying reasons for the selective vulnerability of LC neurons is still unclear. Given the high-energy demand of their unmyelinated long-ranging axons, tau-mediated mitochondrial impairment has been proposed as one important driver for the development of this neuropathological phenotype. 1. Poe, G.R., Foote, S., Eschenko, O. et al. Locus coeruleus: a new look at the blue spot. Nat Rev Neurosci 21, 644–659 (2020). https://doi.org/10.1038/s41583-020-0360-9 2. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 2011 Nov;70(11):960-9. doi: 10.1097/NEN.0b013e318232a379. PMID: 22002422.
Methods: We performed stereotactic injections of Cre-dependent AAVs carrying either human Tau-P301S-mKate2 or mKate2 into the LC of mice expressing GFP in the outer mitochondrial membrane (OMM) specifically in LC neurons. We applied immunofluorescent analysis, 3D reconstructions as well as magnetic-activated cell sorting (MACS) of mitochondria for subsequent Mass Spectrometry analysis.
Results: Our findings reveal a stable transduction of LC neurons and hyperphosphorylated Tau, recapitulating human Tau pathology. Importantly, we observed the localization of Tau with mitochondria. Proteomic analysis of isolated LC-mitochondria in human Tau-expressing mice revealed multiple alterations.
Conclusions: Here, we provide insights into a new Tau model to better understand the earliest pathological defects. Our findings point towards a mitochondrial dysfunction and their crucial involvement in the intriguing vulnerability of LC neurons.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0733 / #1023

Poster Topic: *Theme B: Taupathies / B01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

SPERMIDINE RESCUES ABNORMAL TAU-INDUCED IMPAIRMENTS IN MITOCHONDRIAL RESPIRATION AND MITOPHAGY

POSTERS: B01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Aurélien Riou[1], Amandine Grimm[1], Fairley Lauren[2], Imane Lejri[2], Anne Eckert[3]
[1]University of Basel, Department Of Biomedicine, Basel, Switzerland, [2]Universitäre Psychiatrische Kliniken, Neurobiology Lab For Brain Aging And Mental Health Research Cluster, Molecular & Cognitive Neuroscience, Basel, Switzerland, [3]Neurobiology Lab for Brain Aging and Mental Health, Research Cluster, Molecular & Cognitive Neuroscience, Basel, Switzerland

Aims: Mitochondria are essential organelles that play a predominant role in cellular bioenergetics, notably by providing the main source of cellular energy via adenosine triphosphate (ATP) generation. However, in tauopathies, abnormal tau proteins impair almost all mitochondrial functions, from respiration to mitophagy.
Spermidine (SPD) is a polyamine known to exert cardioprotective, neuroprotective and lifespan-promoting effects by triggering autophagy as its main mode of action. However, the effects of SPD on mitochondrial dysfunction induced by abnormal tau protein have not yet been investigated. Therefore, the present study aimed at evaluating the effects of SPD on mitochondrial function in a cellular model of tauopathy.
Methods: SH SY5Y cells expressing the mutant tau P301L (P301L cells) or the empty vector (vector cells) were treated with SPD at a concentration of 0,1µM for 48h. Then, bioenergetic parameters such as ATP production, mitochondrial membrane potential (MMP), cell respiration and cell metabolic activity were assessed. Effects of SPD on autophagy and mitophagy in vector and P301L cells were also investigated in this study.
Results: SPD improved mitochondrial bioenergetics, characterized by an increase of the mitochondrial membrane potential, mitochondrial respiration, and adenosine triphosphate (ATP) production, in both control and P301Ltau-expressing cells. In addition, SPD decreased the level of free radicals, increased autophagy, and restored P301Ltau-induced impairments in mitophagy.
Conclusions: This study suggests that SPD supplementation might represent an attractive therapeutic approach to prevent/counter-act tau-related mitochondrial impairments. This research was funded by a Natvantage grant from the Wilhelm Doerenkamp-Foundation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0734 / #1025

Poster Topic: *Theme B: Taupathies / B01.g. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

IMPACT OF GINKGO BILOBA EXTRACT ON MITOPHAGY AND AUTOPHAGY IN TAU MUTANT CELLS

POSTERS: B01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Ina Vukalovic[1], Fairley Lauren[1], Amandine Grimm[2], Anne Eckert[1]
[1]University Psychiatry Clinics UPK Basel, Neurobiology Lab For Brain Aging And Mental Health, Basel, Switzerland, [2]University of Basel, Department Of Biomedicine, Basel, Switzerland

Aims: Mitochondrial impairment, including impaired mitophagy, has been identified as an early feature of tauopathies, leading to the accumulation of damaged or dysfunctional mitochondria. This study aimed to explore standardized Ginkgo biloba extract (GBE) potential as a therapeutic agent of tauopathies by investigating its effects on mitophagy, autophagy and associated protein expression in cells expressing the P301L mutant tau.
Methods: Human neuroblastoma cells SH-SY5Y, overexpressing the P301L mutant tau, were used. Cells were transiently transfected with DsRed-LC3 and then treated with either GBE (LI1370; 100µg/ml) or DMSO vehicle for a 24-hour period. Autophagic flux was assessed using bafilomycin A1 or DMSO, while mitophagy was assessed with FCCP. Mitochondria were visualized with a mitotracker. Autophagy and mitophagy were quantified by measuring fluorescence intensity and assessing colocalization. To analyze gene expression, total RNA was extracted from cells using the RNeasy Mini kit. RT-qPCR was employed for amplifying and quantifying mRNA expression levels.
Results: Under baseline condition, no impact of a GBE treatment on P301L mutant tau cells was observed. Following stimulation with FCCP, P301L mutant tau cells displayed reduced mitophagy compared to control cells. Baseline levels of LC3 were increased in P301L cells due to impaired autophagosome degradation. Treatment with GBE reduced LC3 levels in P301L cells, indicating improved autophagosome degradation, while it increased in control cells, suggesting enhanced autophagosome formation. Further, treatment with GBE led to changes in the gene expression of PARK2, PINK1 and P62.
Conclusions: Treatment with GBE was able to alleviate mitophagy deficits in P301L mutant tau expressing cells, improve autophagic flux and increase the expression of genes related to mitophagy and autophagy pathways.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0735 / #1096

Poster Topic: *Theme B: Taupathies / B01.h.Disease Mechanisms, Pathophysiology: Microglia*

VPS35 DOWNREGULATION IN MICROGLIA LEADS TO ENHANCED PATHOLOGICAL TAU ACCUMULATION AND ALTERED INFLAMMATORY STATE IN A MOUSE MODEL OF NEURODEGENERATION

POSTERS: B01.H.DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Yamini Mutreja[1], Domenico Pratico[2]
[1]Lewis Katz School of Medicine, Alzheimer's Center At Temple, Philadelphia, United States of America, [2]Temple University, Alzheimer's Center At Temple, Philadelphia, United States of America

Aims: Endosomal protein sorting is orchestrated by the multimeric protein complex called retromer complex. Dysfunction of this complex is associated with several neurodegenerative disorders including Alzheimer's disease. Vps35 is the core component of the retromer complex. Its relation to Aβ/APP functioning and pathophysiology has been demonstrated in recent years, however its relation to tau biology is less well established. Growing amount of evidence also incriminates microglial dysfunction as a contributing factor towards neurodegenerative pathology. Microglial dysfunction can lead to an aberrant neuroinflammatory response. Microglia are also involved in clearance of pathological tau as well as transcellular transport of tau. The current study aims to delineate the relation between microglial protein trafficking machinery particularly the retromer core protein Vps35, and pathophysiologic changes in a mouse model of neurodegeneration.
Methods: We utilized PS19 mice overexpressing P301S tau to generate a conditional knockout of Vps35 in microglial cells. We performed behavioral analysis to assess memory function, biochemical and histochemical analysis to assess accumulation of pathological tau, and whole brain cytokine analysis to understand neuroinflammatory alterations.
Results: We found that the loss of microglial Vps35 results in enhanced accumulation of tau and phospho epitopes of tau with aging although no major effect was observed on the memory function of these mice. Our data also indicates an altered inflammatory state possibly via dysregulated chemokine signaling.
Conclusions: Dysregulation of endosomal protein trafficking pathways within microglia are a contributing factor for tau accumulation in the brain. Retromer pathways within microglia could also be important for chemokine receptor recycling and a disruption of such signaling could lead to a miscommunication between various brain cell types leading to a dysregulated neuroinflammatory response.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0736 / #172

Poster Topic: *Theme B: Taupathies / B01.h.Disease Mechanisms, Pathophysiology: Microglia*

STREM2 IS ASSOCIATED WITH ATTENUATED TAU AGGREGATES ACCUMULATION

POSTERS: B01.H.DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Fardin Nabizadeh
Iran University of Medical Science, Tehran, Iran, School Of Medicine, Tehran, Iran

Aims: Triggering Receptor Expressed on Myeloid Cell 2 (TREM2) plays a crucial role in the transition of microglia from a state of homeostasis to a state associated with the disease. Mutations in TREM2 are strongly linked with a higher risk of developing neurodegenerative diseases, including Alzheimer's disease (AD). There have been contradictory findings regarding the potential detrimental or protective effects of microglial activation and TREM2-related microglial responses in AD. Although previous studies reported increased CSF soluble TREM2 (sTREM2) in different clinical stages of AD, the exact association between AD hallmarks such as Aβ and tau pathology remains unclear. In the present study, I aimed to investigate the association between TREM2-related microglial responses and tau accumulation in the presence and absence of Aβ pathology in order to give a better view of the role of microglial activation in AD development.
Methods: Imaging data of 178 non-demented participants including 107 Aβ-negative participants, 71 Aβ-positive were recruited from ADNI. The CSF sTREM2 was used as an in vivo indicator of microglial responses associated with TREM2. Furthermore, I used longitudinal tau-PET and resting-state fMRI connectomes in order to investigate the association of TREM2-related microglial activation and tau spreading through functional connections.
Results: A higher level of sTREM2 was associated with slower tau aggregates accumulation in non-demented Aβ-positive. Furthermore, measuring the tau spreading through inter-connected regions using fMRI connectomes confirms that the TREM2-related microglial activity might be a protective factor against tau pathology in brain tissue.
Conclusions: These findings demonstrate that in individuals with initial Aβ abnormalities, TREM2-related microglial activation is linked to reduced regional accumulation of tau aggregates and also, spreading across interconnected brain regions, as evaluated through fMRI connectomes during the early stages of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0737 / #2533

Poster Topic: *Theme B: Taupathies / B01.k. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

TAU PATHOLOGY ACCOMPANIED WITH IMPAIRED HIPPOCAMPAL-DEPENDENT SPATIAL NAVIGATION AND ANXIETY-LIKE BEHAVIORS IN DB/DB MICE

POSTERS: B01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Mohammed Al-Onaizi[1,2], Kawthar Braysh[2], Dalal Alasousi[2], Selma Alkafeef[2], Dana Altarrah[2], Heba Al-Hussaini[2], Fahd Al-Mulla[3], Fawaz Alzaid[1]
[1]Dasman Diabetes Institute, Neurometabolism, Kuwait, Kuwait, [2]Kuwait University, Anatomy, Kuwait, Kuwait, [3]Dasman Diabetes Institute, Chief Scientific Officer, Kuwait, Kuwait

Aims: Type 2 diabetes mellitus (T2DM) has been associated with impaired cognitive behaviors. However, the impact of T2DM on specific hippocampal-associated cognitive domains and tau pathology has not been fully characterized. Here, we investigated the effects of T2DM on several cognitive and psychiatric domains and tau pathology using the leptin receptor-deficient db/db mouse model of T2DM.
Methods: To assess cognitive function, we tested db/db male mice and age-matched lean controls on the novel object task, the Morris Water Maze task, and the pariwise visual discrimination touchscreen task. We then assesed anxiety-like behaviors using the open field task. Tau pathology was assesed by protein expression in the cortex and hippocampus using antibodies targeting the phosphorylation sites: Ser202/Thr205, and Thr231. RNA-sequencing was then performed to determine the effects of insulin resistance on the forebrain of insulin resistant mice on tau-mediated gene expression. This was associated with the impact of insulin resistance on synaptic health.
Results: We found that db/db mice had significant impairments in both acquisition and reversal learning test in the touchscreen task. We also showed that db/db mice had impaired spatial navigation in the Morris Water Maze task, and the novel object recognition task. Severe anxiety-like patterns were observed in db/db mice in the open field test. Moreover, db/db mice showed significant age-related changes in tau pathology and synaptic health in both the cortex and the hippocampus. RNA-sequencing data showed differential gene expression in genes associated with neuronal health in db/db mice.
Conclusions: Our data provides direct evidence on the consequences of insulin resistance on specific cognitive and pyschiatric domains. Our findings also indicate a role for metabolic health in modulating central tau pathology and synaptic function.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0738 / #2128

Poster Topic: *Theme B: Taupathies / B01.j. Disease Mechanisms, Pathophysiology: Blood-brain barrier*

SENOLYTIC THERAPY MAINTAINS BBB INTEGRITY, ALLEVIATES CEREBRAL HYPOMETABOLISM AND STABILIZES MICROGLIA HOMEOSTATIC SUBTYPE IN THE PS19 MOUSE MODEL

POSTERS: B01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: BLOOD-BRAIN BARRIER

Wenzhen Duan[1,2], Minmin Yao[3], Zhiliang Wei[4], Qian Wu[3], Ruoxuan Li[3], Aaron Kakazu[3], Yuxiao Ouyang[3], Jiadi Xu[3,4], Manisha Aggarwal[3,4], Hanzhang Lu[4]
[1]Johns Hopkins University, Psychiatry, Neuroscience,, Lutherville, United States of America, [2]School of Medicine, Johns Hopkins University, Psychiatry, Neuroscience,, Baltimore, United States of America, [3]Johns Hopkins University, Psychiatry, Baltimore, United States of America, [4]Johns Hopkins University, Radiology And Radiological Science, Baltimore, United States of America

Aims: Cellular senescence has been observed in both Alzheimer's disease (AD) patients and animal models. In this study, we investigated the effects of senolytic therapy in the PS19 mouse model by exploring human translatable MRI measures and mechanisms involved in senolytic therapy in the Tau model.
Methods: PS19 mice were treated with dasatinib plus quercetin (DQ) from 3 months of age for 6 months. T2 relaxation under spin tagging (TRUST) and phase contrast (PC) MRI was used to assess cerebral metabolic rate of oxygen (CMRO2), water extraction with phase-contrast arterial spin tagging (WEPCAST) MRI was employed to detect the blood-brain barrier (BBB) permeability longitudinally. Brain volumes were analyzed by diffusion tensor imaging (DTI) at the end of study. Cognitive function was evaluated by the tracing fear conditioning test along MRI measures.
Results: PS19 mice displayed significantly reduced cerebral CMRO2 and increased BBB permeability to water at 9 months of age. Meanwhile hippocampal atrophy and impaired cognitive function were evident in PS19 mice at the same age. DQ senolytic treatment dramatically mitigated cerebral hypometabolism, maintained BBB integrity, attenuated hippocampal atrophy, reduced tauopathy and improved cognitive function. Furthermore, the DQ treatment led to a shift of microglia from a disease-associated subtype to a homeostatic subtype.
Conclusions: These findings provide evidence for the potential therapeutic benefits of senolytic therapy and highlight the involvement of microglia in the underlying mechanisms. The use of human translatable biomarkers in the PS19 mouse model contributes to our understanding of the brain functional changes associated with tauopathy and the effects of senolytic therapy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0739 / #235

Poster Topic: *Theme B: Taupathies / B01.k. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

TAU LOSS OF FUNCTION, BY DELETION OR AGGREGATION, CONTRIBUTES TO PERIPHERAL INSULIN RESISTANCE

POSTERS: B01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Rabab Al-Lahham, Nicolas Mendez
The University of Texas Health Science Center at Houston, Neurology, Houston, United States of America

Aims: Several epidemiological data revealed an association between Alzheimer's disease (AD) and type 2 diabetes, and impaired glucose metabolism and insulin signaling has been shown in AD patients and animal models of AD. Researchers concentrated on brain insulin resistance with little emphasis on the link between systemic insulin resistance and AD,even though the incidence of type 2 diabetes is higher in AD patients and that impairment in insulin signaling is a risk factor for AD. The goal of this study is to determine the role of systemic insulin resistance in the pathogenesis of Alzheimer's disease by evaluating the consequences of tau loss-of-function on peripheral insulin sensitivity.
Methods: Primary hepatocytes isolated from transgenic mouse models (Tau KO, P301 L) and wild type mice (C57BL/6) were evaluated for their insulin sensitivity using glucose uptake assays and biochemical analysis of insulin signaling markers. Wild type hepatocytes were treated with subtoxic concentrations of TauO to explore the effect of TauO on insulin signaling.
Results: Our data show that tau deletion or loss of function promotes peripheral insulin resistance as seen in primary hepatocytes isolated from Tau KO and P301 L mice, respectively. Furthermore, exposure of wild-type primary hepatocytes to sub-toxic concentrations of tau oligomers (TauO) results in a dose-dependent inhibition of glucose uptake, associated with downregulation of insulin signaling. TauO-induced inactivation of insulin signaling proteins was rescued by inhibition of p38 MAPK, suggesting the involvement of p38 MAPK.
Conclusions: This is the first study testing tau role in peripheral insulin resistance at the cellular level using multiple transgenic mouse models. Moreover, this study suggests that tau should be functional for insulin sensitivity, therefore, any loss of function by deletion or aggregation would result in insulin resistance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0740 / #881

Poster Topic: *Theme B: Taupathies / B01.k. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

NEURONAL AMPK REGULATES MICROGLIAL LIPID DROPLET ACCUMULATION IN TAUOPATHY BRAIN

POSTERS: B01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Xu Chen[1], Yajuan Li[1], Yuhang Nie[1], Daniel Munoz-Mayorga[1], Ningxin Kang[1], Lingyan Shi[2]
[1]University of California, San Diego, Department Of Neurosciences, La Jolla, United States of America, [2]University of California, San Diego, Department Of Engineering, La Jolla, United States of America

Aims: Neurodegenerative diseases are commonly linked to impaired metabolism in the brain. In aging and Alzheimer's disease (AD), lipid droplets (LDs) accumulate in the brain. Yet, the cellular and molecular mechanism underlying this phenomenon is largely unknown. We aim to elucidate the LD phenotype in tauopathy brains and the mechanistic underpinings.
Methods: We used label-free stimulated Raman scattering (SRS) imaging technique to visualize *in situ* LD accumulation in mouse and fly models of tauopathy, and *in vitro* neuronal and glial cultures. Using heavy water (D_2O)-probed stimulated Raman scattering (DO-SRS) imaging, we assessed lipid turnover within LDs accumulated in tauopathy fly brains and in Tau^{V337M} neurons. In addition, we dissected the role of AMPK in regulating LD accumulation and inflammation.
Results: We found striking *in situ* LD accumulation in tauopathy mouse and fly brains primarily in microglia that correlated with neuronal loss and neuroinflammation. DO-SRS imaging revealed impaired lipid turnover within LDs accumulated in tauopathy fly brains. LDs also accumulated in induced pluripotent stem cell (iPSC)-derived human neurons bearing the Tau^{V337M} mutation, which transferred lipids to microglia through conditioned media, resulting in microglial LD accumulation, oxidative stress, impaired phagocytosis and a proinflammatory response. Activation of neuronal AMPK, a key regulator of lipid metabolism, alleviated lipid burden in neurons via inhibiting lipogenesis and promoting lipophagy, thereby decreasing lipid flux to microglia. Neuronal AMPK overexpression in tauopathy fly brain alleviated LD accumulation, while neuronal AMPK depletion in prodromal tauopathy mouse brain increased LD accumulation and exacerbated proinflammatory microgliosis.
Conclusions: Our results provide direct evidence of LD accumulation in tauopathy brains, new mechanistic insight into the anti-aging and neuroprotective effects of AMPK pathway, and highlight the metabolic crosstalk between neurons and glia in the setting of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0741 / #2079

Poster Topic: *Theme B: Taupathies / B01.k. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

OBESITY, APOE4 AND METABOLIC MANIFESTATIONS OF PATHOLOGICAL TAU

POSTERS: B01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Johanna Gentz[1,2], Gerda Mitteregger[2], Jochen Herms[1,2], Lars Paeger[1,2]
[1]German Center for Neurodegenerative Diseases, Translational Brain Research, Munich, Germany, [2]Center for Neuropathology and Prion Research, Ludwig-maximilians University Munich, Munich, Germany

Aims: Recent research has unveiled a complex interplay between neurodegenerative diseases and metabolic dysfunction. In turn, metabolic changes due dietary choices and genetic dispositions may critically influence disease severity. Here, we aim to investigate the pivotal role of metabolism in neurodegeneration, being both target and player in disease progression.
Methods: We use longitudinal high resolution metabolic and behavioural phenotyping in a mouse model of tauopathy (PS19) along with rectal and intraabdominal temperature measurements and immunohistochemical analysis from animals aged 3-9 month. Further, animals are subjected to either a high fat diet (HFD) or normal control diet (NCD) for specified durations with or without combination of a human ApoE4 knock-in (PS19 x APOE4-KI) to display bidirectional metabolic interactions with tauopathy.
Results: Reduced bodyweight correlated with decreased core temperature in PS19 mice compared to WT littermates and increased locomotor activity. In line, our histological findings reveal early elevated levels of phosphorylated tau and activated astrocytes in the hypothalamus, including the temperature- and sleep- regulating preoptic area. In turn, HFD-feeding induced obesity increased the amount of phosphorylated tau and activated astrocytes in the cortex, hippocampus, amygdala and hypothalamic regions of both PS19 and compared to NCD. Importantly, the presence of the ApoE4 knock-in appeared to intensify diet-induced obesity and pathological changes in PS19 animals.
Conclusions: Our results highlight the hypothalamus as an early affected region in tauopathy impacting metabolic processes assigning metabolic changes in early disease diagnosis. In turn, bad dietary choices may exacerbate existing pathology and inflammatory response. Thus, especially in the ApoE4 background, nutrition may be an important factor impacting neurodegenerative disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0742 / #550

Poster Topic: *Theme B: Taupathies / B01.l. Disease Mechanisms, Pathophysiology: Neural networks & plasticity*

HUMAN MICROPHYSIOLOGICAL SYSTEM TO AUTOMATE THE SCREENING OF COMPOUNDS TARGETING ALZHEIMER'S DISEASE

POSTERS: B01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

Carolin Madwar, Margaret Magdesian, Victoria Kwok
Ananda Devices Inc., Biochemistry, Laval, Canada

Aims: There is no cure and no efficient therapy for most neurological disorders, including Alzheimer's Disease (AD), a progressive type of dementia largely associated with the loss of synapses in the brain. It is estimated that 99.6% of the drugs targeting neurological diseases, such as AD, that pass animal tests fail on human trials. Animal experiments are currently the gold standard to test toxicity and efficacy of compounds. However, it is not feasible to test all compounds in the market with current guidelines due to high costs; long testing times, high number of animals required and low reproducibility. New, human based, more predictive models are required to accelerate the development of effective therapies. At Ananda Devices, we developed technology for rapid growth and precise organization of human neuronal networks, adapted to multi-well microplates (NeuroHTS™) and automated analysis of multiple parameters on neuronal morphology, neurite growth, synapse formation and network dynamics in 3000 individual neurons per plate.
Methods: In this study, we used the Ananda Devices microphysiological system to compare neuronal morphology, network dynamics, synapses and electrical function of neurons derived from iPSC cells from Healthy and Alzheimer's Disease donors.
Results: Using this high-definition analysis, we were able to identify key differences in axonal growth, axonal thickness, neuronal connections, synapse formation, synaptic maturity, tau distribution in cells derived from Alzheimer's Disease donors and Healthy donors. The results were validated using RNAseq analysis highlighting key signaling pathways involved in neurodegeneration.
Conclusions: The high sensitivity of the NeuroHTS™ platform enables rapid and automated compound screening directly on patient's derived cells. The main advantages of the technology are faster acquisition of neuronal data and generation of more predictive data of compounds' safety and efficacy prior to exposure to humans.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0743 / #1761

Poster Topic: *Theme B: Taupathies / B01.k. Disease Mechanisms, Pathophysiology: Metabolism, insulin*

EXPLORING THE RELATIONSHIP BETWEEN INSULIN RESISTANCE AND ALZHEIMER'S DISEASE USING A NOVEL IN-VITRO MODEL

POSTERS: B01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METABOLISM, INSULIN

Rashi Kumar[1], Ritu Varshney[2], Sharad Gupta[2]
[1]Indian Institute of Technology, Gandhinagar, Department Of Cognitive Science, Gandhinagar, India, [2]Indian Institute of Technology Gandhinagar, Department Of Biological Science And Engineering, Gandhinagar, India

Aims: To investigate the relationship between Alzheimer's disease and insulin resistance with a particular emphasis on examining the role of glucose transporter 4 (GLUT4) by creating an in-vitro model using the SH-SY5Y neuroblastoma cell line. GLUT4 is an insulin-dependent transporter and is found in the hippocampus, amygdala, and cortex region of the brain. Our objective was to discern whether insulin resistance serves as a driver for the onset of Alzheimer's disease or if AD pathology, conversely, contributes to the development of insulin resistance.
Methods: To achieve our aim, we employed the following methods: 1. Transfection of SH-SY5Y cells with either a wild-type tau plasmid or a mutant tau plasmid to create the AD pathology. 2. Induction of insulin resistance in these cells using high glucose or dexamethasone. 3. Conducting a glucose uptake assay to measure glucose concentration. 4. Utilizing immunocytochemistry to assess the expression of insulin-dependent glucose transporter 4 (GLUT4), which is pivotal in the development of insulin resistance.
Results: 1. A significant increase in glucose concentration was observed in the AD condition. 2. There was a marked decrease in the expression of GLUT4 in the neuronal cells in the AD condition.
Conclusions: Our study provides evidence supporting the notion that insulin resistance is a contributing risk factor for the development of Alzheimer's pathology later in life. The presence of tau aggregates can increase the likelihood of developing insulin resistance by impairing the insulin signalling pathway, ultimately leading to Type 2 diabetes. The findings suggest that impaired insulin signalling in the brain may contribute to the pathogenesis of Alzheimer's, by decreased GLUT4 expression, hyperglycemia, cellular hypertrophy. The development of this model offers a tool for further understanding the GLUT4 expression, concentration and translocation in AD

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0744 / #478

Poster Topic: *Theme B: Taupathies / B01.l. Disease Mechanisms, Pathophysiology: Neural networks & plasticity*

MORPHOLOGICAL DIFFERENCES BETWEEN HUMAN IPSC-DERIVED NEURONS FROM ALZHEIMER'S S VERSUS PARKINSON'S DISEASE PATIENT

POSTERS: B01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

Margaret Magdesian, Carolin Madwar, Victoria Kwok
Ananda Devices Inc., Biochemistry, Laval, Canada

Aims: There is no cure and no efficient therapy for most neurological disorders, including Alzheimer's Disease (AD), and Parkinson's Disease (PD). Today, 99.6% of the drugs targeting neurological diseases that pass animal tests fail on human trials and currently available animal models fail to reproduce the pathological complexities of AD or PD. For the successful development of new therapies, robust alternative approaches methods (NAMs) that specifically recapitulates the human neuronal signaling pathways are required to elucidate the mechanism of neurodegeneration in AD, PD and other neurological diseases. Ananda Devices developed a microphysiological system (MPS) for rapid growth and precise organization of human neuronal networks-on-a-chip, in scalable multi-well microplates, enabling automation of the analysis of multiple neuronal parameters in 3000 individual neurons per plate (NeuroHTS™ platform). In this study, the aims were to identify key morphological parameters in neurons derived from iPSC cells from patients to understand and measure AD and PD Disease progression.
Methods: In this study, we used the NeuroHTS™ platform to compare neuronal morphology, network dynamics, synapses, and electrical function of excitatory neurons derived from human induced pluripotent cells from healthy and AD donors as well as dopaminergic neurons derived from human induced pluripotent cells from healthy and PD donors.
Results: showed key differences in axonal growth, axonal thickness, neuronal connections, synapse formation, synaptic maturity, and tau distribution.
Conclusions: The data highlight how Ananda Devices' human based, in vitro, NeuroHTS™ platform enables rapid and automated compound screening directly on patient's derived cells.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0745 / #980

Poster Topic: *Theme B: Taupathies / B01.l. Disease Mechanisms, Pathophysiology: Neural networks & plasticity*

IN VIVO CALCIUM AND VOLTAGE IMAGING TO STUDY CELL-TYPE SPECIFIC CONSEQUENCES OF PV NEURON TAUOPATHY

POSTERS: B01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

Paul Feyen[1], Carsten Vos[1], Lars Paeger[1], Teodoro De Vecchi[2], Jochen Herms[1,2,3]
[1]German Center for Neurodegenerative Diseases, Translational Brain Research, Munich, Germany, [2]Ludwig-Maximilians-Universität München, Center For Neuropathology And Prion Research, Munich, Germany, [3]Munich Cluster for Systems Neurology, Synergy, Munich, Germany

Aims: Tauopathies feature pTau accumulation in cortical neurons and glia. Although neurons are heterogeneous, varying in molecular and morphological characteristics, the subtypes susceptible to tauopathy and their role in disease progression remain unidentified. Our study aimed to (1) assess pTau distribution in cortical neurons of Tauopathy patients, (2) create a cell-type-specific in vivo model for tauopathy of affected population, and (3) characterize morphological and neural activity changes of novel models utilizing chronic in vivo imaging.
Methods: Multiplexed IF staining of human Tauopathy cortical tissue and a deep learning pipeline was used to assess pTau accumulation in excitatory and inhibitory neuron subtypes. Guided by finding of abundant pTau+ Parvalbumin (PV) neurons, we generated a PV-specific tauopathy model using custom AAVs and cre-driver line. Awake in vivo Ca2+ and voltage imaging via AO-2P microscopy was used to study the response properties of PV neurons to multisensory stimulation, and to assess their integration in the cortical network. The model was further characterized via 6-month chronic in vivo 2-photon imaging.
Results: Ca2+ imaging uncovered poor fidelity of sensory representations in PV neurons of secondary motor cortex. First ever optical voltage recordings of neurons in neurodegenerative models, enable longitudinal imaging of the same neurons at a single action potential resolution in awake mice, offering unparalleled spatio-temporal resolution of the consequences of Tauopathy on neural activity. Chronic 6 month imaging revealed progressive axonal swellings and cell-loss.
Conclusions: We find Parvalbumin neurons present pTau accumulation in Tauopathy. Our observation of early deficits in sensory processing in PV-tauopathy model, indicates a role for PV in symptomatic landscape of CBD and PSP, potentially by loss of feedforward inhibition. Cell-type specific tauopathy models serve as effective platforms to isolate cell-autonomous disease processes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0746 / #1629

Poster Topic: *Theme B: Taupathies / B01.l. Disease Mechanisms, Pathophysiology: Neural networks & plasticity*

EFFECT OF HEAVY ALCOHOL CONSUMPTION ON THE ONSET AND DEVELOPMENT OF ALZHEIMER'S DISEASE

POSTERS: B01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: NEURAL NETWORKS & PLASTICITY

Marcos Uceta[1], Fernando Maestú[2], Alberto Muñóz[1]
[1]Universidad Complutense of Madrid, Faculty of Biology, Department Of Cellular Biology, Madrid, Spain, [2]Universidad Complutense de Madrid, Psicología Experimental, Procesos Cognitivos Y Logopedia, Pozuelo de Alarcón, Spain

Aims: In this study, we seek to ascertain the relationship between alcohol consumption during the early stages of neurodevelopment (characterized as Binge Drinking) and the onset and progression of Alzheimer's disease. Therefore, our fundamental objectives are to characterize the primary transformations identified both in the inhibitory neurons of the key areas associated with the disease and in the glial cells (astrocytes and microglia) linked to the characteristic neuroinflammatory state induced by such agents.
Methods: Using a murine model of P301S tauopathy, we will aim to administer alcohol (5 g/kg/d - 25% EtOH) or water at an equivalent volume to different experimental groups during a period of their life analogous to human adolescence (P20-P25), following a pattern associated with adolescent Binge Drinking (2-2, on-off). Subsequently, we will allow normal development of the animals until P200, at which point they will be euthanised for sample collection and immunohistological analysis of the primary neurons and target structures.
Results: We anticipate a significant increase in neurofibrillary tangles in those animals that have consumed alcohol. Additionally, we expect an increase in glial cell reactivity in these animals, along with an augmentation of distinct extracellular structures (PNNs) characteristic of the inhibitory neurons.
Conclusions: In this study, we expect to conclude that alcohol consumption during adolescence seemingly exerts effects not only in the short term but also in the long term, manifesting in an earlier and more aggressive onset of the tauopathy characteristic of Alzheimer's disease. Furthermore, the inhibitory connections and networks, typically distorted in the early stages of the disease, possess a barrier that is not only physiological but also physical in the form of proteoglycans and sugars, enhancing the rigidity of the network and reducing its flexibility and plasticity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0747 / #2041

Poster Topic: *Theme B: Taupathies / B01.m. Disease Mechanisms, Pathophysiology: transcriptional & translational regulation, micro RNAs*

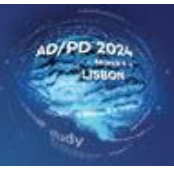
XBP-1S TRANSCRIPTIONAL TARGETS IN THE ENDOPLASMIC RETICULUM UNFOLDED PROTEIN RESPONSE AMELIORATE TAUOPATHY

POSTERS: B01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Brian Kraemer[1], Sarah Waldherr[2], Marina Han[2]
[1]SIBCR, Grecc, SEATTLE, United States of America, [2]VAPSHCS, Grecc, Seattle, United States of America

Aims: Protein homeostasis (proteostasis) mechanisms fail with aging and disease, promoting toxic protein accumulation. Neurons are particularly vulnerable to proteostatic disruption leading to aging related neurodegeneration. Abnormal activation of the endoplasmic reticulum unfolded protein response (UPR^{ER}) is implicated in tauopathies, a group of neurodegenerative diseases characterized by pathological accumulation of the microtubule-associated protein tau. Previous work showed neuronal overexpression of IRE1a branch UPR^{ER} transcription factor XBP-1s suppresses tauopathy in *C. elegans*.
Methods: We conducted RNA sequencing of mRNAs to analyze the transcriptome of xbp-1s and tau transgenic animals.
Results: Transcriptomic analysis of XBP-1s animals showed upregulation of the following genes with human homologs: *csp-1, F42G8.7, F41E7.6, Y19D10A.16, C01B4.6, dnj-28, hsp-4, ckb-2, mct-2, lipl-3,* and *eol-1*. Surprisingly, each one of these genes is required for *xbp-1s*-mediated suppression of tauopathy, suggesting that XBP-1s activates a broad and non-redundant network of cellular mechanisms to reduce tau pathology. Of these, we examined the critical UPR^{ER} regulator BiP/hsp-4, the ER resident HSP70 homolog. *Hsp-4* loss of function, but not loss of the cognate ER resident DNAJ protein *dnj-28*, eliminates *xbp-1s*-mediated suppression of tauopathy. While *hsp-4* loss of function exacerbates tau-induced behavioral deficits, tau protein level and phosphorylation are unaffected. High level overexpression of *hsp-4* exacerbates tau-induced behavioral deficits and protein accumulation, while moderated *hsp-4* overexpression ameliorates this phenotype. Furthermore, caspases also appear to play an important role downstream of XBP-1s: both the XBP-1s target *csp-1* and its non-XBP-1s target gene family member *ced-3* are required for *xbp-1s*-mediated suppression of tauopathy.
Conclusions: We present a dataset illuminating the mechanism of *xbp-1s*-mediated suppression of tauopathy involving a suite of diverse transcriptional targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P0748 / #3004

Poster Topic: *Theme B: Taupathies / B01.o. Disease Mechanisms, Pathophysiology: Aging*

A COMPARISON BETWEEN EARLY PRESENTATION OF ALZHEIMER'S DISEASE, PARKINSON'S DISEASE AND DEMENTIA WITH LEWY BODIES IN ROUTINE PRIMARY CARE AND UK BIOBANK DATA.

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Thomas Nedelec
Paris Brain Institute, Aramis, Paris, France

Aims: Understanding the shared and specific clinical manifestations of neurodegenerative diseases in the prodromal phase is key to understanding their complexity and specific pathophysiologies.
Methods: Using the longitudinal THIN database in the UK, we contrasted clinical characteristics from individuals with a final diagnosis of Parkinson's disease (PD), Alzheimer's disease (AD), dementia with Lewy Bodies (DLB), and controls without neurodegenerative disorders. We tested the association (OR) of each neurodegenerative disorder for a selected list of symptoms including motor, autonomic, and neuropsychiatric features, as well as broad families of treatments (laxatives, antihypertensives, statins, benzodiazepines and neuroleptics). We subsequently tested whether the association were different between disorders, in recognition that the difference may indicate possible disease-specific effects. We replicated the main findings in the UK Biobank (UKB).
Results: We used 28,222 patients with PD, 20,214 with AD, 4,682 with DLB and 20,214 controls, from the THIN UK Database. Neurodegenerative disorders were significantely associated with the presence of multiple clinical characteristics before their diagnosis including memory problems, tremor, confusion, hallucinations, constipation, sleep disorders, anxiety, depression, falls, hypotension, urinary tract disorders and abnormal weight loss, and less frequent use of agents acting on the renin–angiotensin–aldosterone system and selective beta-2-adrenoreceptor agonists. Benzodiazepines and serotonin reuptake inhibitors consumption was more frequent in individuals who later developed all three diseases while antidiabetic medication consumption was lower in both future AD and PD patients.
Conclusions: In addition to a range of non-motor features, benzodiazepines and serotonin reuptake inhibitor use was increased in individuals at a pre-diagnosis stage of neurodegenerative diseases, while agents acting on the renin–angiotensin–aldosterone system and selective beta-2-adrenoreceptor agonists were less prescribed.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0749 / #1319

Poster Topic: *Theme B: Taupathies / B01.o. Disease Mechanisms, Pathophysiology: Aging*

A UNIQUE SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE OF HUMAN ASTROCYTES FOLLOWING CHRONIC INFLAMMATORY STIMULATION

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Jong-Heon Kim[1], Jong Hyuk Yoon[2], Ho-Won Lee[3], Jun-Yeong Lee[4], Kyoungho Suk[5]
[1]Brain Science & Engineering Institute, Kyungpook National University, Daegu, Korea, Republic of, [2]Korea Brain Research Institute, Neurodegenerative Diseases Research Group, Daegu, Korea, Republic of, [3]Kyungpook National University Chilgok Hospital, Department Of Neurology, Daegu, Korea, Republic of, [4]Kyungpook National University, School Of Life Sciences, Bk21 Four Knu Creative Bioresearch Group, Daegu, Korea, Republic of, [5]School of Medicine, Kyungpook National University, Department Of Pharmacology, Daegu, Korea, Republic of

Aims: Senescent astrocytes are prominent in brain tissues from patients with neurodegenerative diseases, such as Alzheimer's disease. The accumulation of senescent astrocytes in the aging brain can contribute to Aβ accumulation, tau hyperphosphorylation, and the deposition of neurofibrillary tangles. These astrocytes exhibit impaired homeostatic function and secretion of senescence-associated secretory phenotype (SASP) factors exerting detrimental effects, such as persistence of neuroinflammation, impairment of synaptic plasticity, and blood–brain barrier dysfunction. Cultured astrocytes can enter a senescent-like state when exposed to various stimuli, including oxidative stress, oligomerized amyloid beta peptide, and SASP factors such as IL-1β. Importantly, SASP factors produced by senescent astrocytes can induce neighboring cells to undergo senescence, thereby amplifying both the population of senescent cells and these detrimental phenotypes. However, implications of SASP in neurodegenerative diseases remain to be fully understood. In this study, we conducted a combined analysis of human astrocyte secretome and profiling of transcription factor (TF) binding motifs.
Methods: We examined the secretome of human fetal astrocytes in culture following chronic stimulation with pro-inflammatory cytokine mixtures containing TNF-α, IL-1β, and IFN-γ. We also analyzed the occurrence of TF binding motifs at the promoter surrounding region of the genes encoding the astrocyte secretome.
Results: The combined analysis identified a unique profile of senescence-associated secretory phenotype proteins and their regulatory TFs in the long-term cytokine-treated astrocytes, which were distinct from acutely activated astrocytes.
Conclusions: Our study provides the resource for potential biomarkers and therapeutic targets, shedding light on the intricate relationship among chronic neuroinflammation, astrocyte senescence, and neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0750 / #316

Poster Topic: *Theme B: Taupathies / B01.n. Disease Mechanisms, Pathophysiology: Autophagy, apoptosis, cell death*

RECONSTITUTING THE FIRST STEPS OF AUTOPHAGY IN ALZHEIMER'S DISEASE

POSTERS: B01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, APOPTOSIS, CELL DEATH

Kryštof Knapp, Oliver Daumke
Max Delbrück Center, Ag Daumke, Berlin, Germany

Aims: To deal with protein aggregation and misfolding, living organisms have developed several mechanisms to recognize and recycle these targets: the protein quality control system. Autophagy is one of the modules of PQC that is capable of tackling larger targets, such as organelles or protein aggregates (aggrephagy).
Selective autophagy receptors are essential components of the autophagy machinery that recognize cellular material, and cargo, labeled for degradation. p62, also known as sequestome 1, is a member of this family responsible for the detection of ubiquitinated cargo and the recruitment of other components of the autophagy machinery. Although p62 is highly enriched in tau protein aggregates, which should trigger autophagy and tau recycling, this is not the case in the brains of patients with tauopathies.
Therefore, we aim to understand the initial steps of autophagy from a structural point of view.
Methods: To establish a working aggrephagy model, which can reconstitute the first steps of autophagy of tau aggregates one has to introduce ubiquitination into the system. To achieve that we use several non-canonical approaches including DNA origami, *in vitro* aggregation of ubiquitin-tau fusion constructs, and cellular models of tau aggregation.
The resulting biological assemblies of cargo with selective autophagy receptors are then studied using single-particle electron cryo-microscopy and electron cryo-tomography.
Results: To this end, we established a new approach for studying the initial stages of aggrephagy using DNA origami as the carrier of the ubiquitination signal which can trigger the initial steps of aggrephagy. This will allow us to better understand the architecture inside pathological condensates, highly enriched for selective autophagy receptors.
Conclusions: Reconstitution experiments in combination with cellular models can help us to better understand autophagy impairment in neurodegenerative diseases on a molecular level.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0751 / #2224

Poster Topic: *Theme B: Taupathies / B01.o. Disease Mechanisms, Pathophysiology: Aging*

REPLICATIVE MICROGLIA SENESCENCE: A POTENTIAL MECHANISM UNDERLYING PATHOLOGICAL BRAIN AGEING.

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Bangyan Liu
Weill Cornell Medical College, Neuroscience Program, New York, United States of America

Aims: Microglia, the resident immune cells of the central nervous system, play critical roles in the neuroinflammatory alterations indicated in the pathogenesis of age-dependent neurodegenerative diseases including Parkinson's and Alzheimer's disease. However, the connection between microglia dysfunctions and chronological aging remains unclear. In the current study, we investigated the effect of telomere shortening, a critical hallmark of aging, in the both an *in vitro* and an *in vivo* model.
Methods: By inhibiting the telomerase activity, we successfully shortened the telomeres of the microglia in the mouse brain and generated iPSC-derived human microglia with shorter telomeres. We analyzed the transcriptomic changes of the microglia and tested the functional impacts of telomere shortening via behavioral studies.
Results: We identified strong senescence signals in the microglia with shorter telomeres in both our *in vitro* and *in vivo* models. Meanwhile, we identied an unique senescence-associated-secretory-phenotype (SASP) signautre that has potential effects on both neurons and oligodendrocytes. Our behavioral studies also demonstrated a detrimental effect of telomere shortening on the congnitive abilibities of mice.
Conclusions: Overall, our current data lead to the conclusion that replicative microglia senescence caused by telomere attrition disrupts homeostatic microglia-neuron and microglia-oligodendrocyte interactions and can potentially contributes to the pathogenesis of age-related neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0752 / #1029

Poster Topic: *Theme B: Taupathies / B01.o. Disease Mechanisms, Pathophysiology: Aging*

THE AGE-ASSOCIATED MITOCHONDRIAL DONOR SIGNATURE IS PERCEIVED IN THE IPSCS DERIVED NEURONS (IPSCSN) AND DIRECTLY CONVERTED NEURONS (INS)

POSTERS: B01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AGING

Nimmy Varghese[1,2], Leonora Szabo[1,2], Amandine Grimm[1,2], Zameel Cader[3], Imane Lejri[1,2], Anne Eckert[1,2]
[1]University Psychiatric Clinics Basel, Neurobiology Lab For Brain Aging And Mental Health, Basel, Switzerland, [2]University of Basel, Research Cluster Molecular And Cognitive Neurosciences, Basel, Switzerland, [3]University of Oxford, Nuffield Department Of Clinical Neuroscience, Oxford, United Kingdom

Aims: For neurodegenerative disorders, including tau pathology, it is crucial to comprehend the human brain aging on the mitochondrial level, which serves as the neuronal powerhouse. However, finding suitable models to study human brain aging is challenging due to limitations and ethical constraints. Advanced human neuronal in vitro models like iPSCs-derived neurons and directly induced neurons are of interest. There remains uncertainty in these model systems surrounding the potential to undergo rejuvenation or maintain an aging-associated donor signature, especially for the iPSCsN. The study aimed to investigate the degree to which iPSCsN and iNs retain the aging donor signature focusing on bioenergetics.
Methods: The total ATP level, mitochondrial membrane potential (MMP), reactive oxygen species (ROS), mitochondrial respiration (OCR), mitochondrial mass, mitochondrial morphology, and glycolysis were compared between iPSCsN and iNs from the same young (n = 4, Agemean = 31 years) and aged (n = 4, Agemean = 69 years) donors.
Results: Our preliminary findings demonstrated that both the iNs and the iPSCsN could preserve an aging- associated phenotype compared to the equivalent young neurons. The aged neurons showed a decrease in ATP, MMP, and OCR and an increase in ROS, glycolysis, and mitochondrial mass. The mitochondrial dynamics were characterized by a more fragmented mitochondrial shape.
Conclusions: Our preliminary findings indicate that iNs and iPSCsN display an aging-associated at the mitochondrial level phenotype contrary to the belief that aged iPSCsN would fully rejuvenate. Further investigation is needed to determine the extent of this preservation. Overall, this work will help us better understand how accurately "aged" iNs and iPSCsN simulate human brain aging and contribute to the development of cutting-edge methods for discovering pharmacological targets to enhance human health during aging and in tau pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0753 / #2888

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

PATIENT-DERIVED IGLON5 AUTOANTIBODIES TRIGGER PATHOLOGICAL TAU CHANGES AND NEUROINFLAMMATION IN VIVO

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Bilge Askin[1,2], Sophie Duong[3,4], César Gómez[3], Cagla Kilic[3], Valentine Thomas[5], Andrew Newman[6], Alexander Goihl[7], Péter Körtvélyessy[8], Jessica Wagner[9,10], Dirk Reinhold[7], Paul Turko[11], Jonas J. Neher[12], Dietmar Schmitz[1], Benjamin Rost[3], Lisa Diez[3], Harald Pruess[3], Susanne Wegmann[1]
[1]Einstein Center for Neurosciences Berlin, Charité Universitätsmedizin, Berlin, Germany, [2]German Center for Neurodegenerative Diseases, Dzne, Berlin, Germany, [3]German Center for Neurodegenerative Diseases, (dzne), Berlin, Germany, [4]Charité Universitätsmedizin Berlin, Department Of Neurology And Experimental Neurology, Berlin, Germany, [5]Institut Pasteur, Paris, Île-de-france, France, France, [6]Institute of Cell Biology and Neurobiology, Charité-universitätsmedizin Berlin, Berlin, Germany, [7]Institute of Immunology, Otto-von-guericke-university Magdeburg, Magdeburg, Germany, [8]Charité - Universitätsmedizin Berlin, Department Of Neurology, Berlin, Germany, [9]German Center for Neurodegenerative Diseases, Dzne, Tübingen, Germany, [10]Hertie Institute for Clinical Brain Research, University of Tübingen, Department Of Cellular Neurology,, Tübingen, Germany, [11]Institut für Integrative Neuroanatomie, Charité-universitätsmedizin Berlin, Berlin, Germany, [12]Hertie Institute for Clinical Brain Research, University of Tübingen, Cellular Neurology, Tübingen, Germany

Aims: In anti-IgLON5 disease, autoantibodies against the surface protein IgLON5 trigger Tau pathology and neurotoxicity. Understanding how these autoantibodies targeting surface proteins can trigger Tau changes and exert neurotoxicity would help to conceptually understand why Tau reacts in different diseases and to design therapeutic approaches for anti-IgLON5 and similar neurological diseases. We attempt to understand: 1) Whether patient-derived IgLON5 autoantibodies directly trigger pathological Tau changes, and 2) how they induce neurotoxicity?
Methods: We use IgLON5 autoantibodies (AABs) purified from the serum of a clinically verified IgLON5 patient and study their effect on Tau pathology (immunocytochemistry, biochemistry) and neuronal activity (Calcium imaging, electrophysiology in autaptic cultures) in wildtype primary hippocampal mouse neurons, as well as on neuroinflammation in mice (immunohistochemistry, bulk RNAseq). AAB application into mice is achieved through ventricular infusion of AABs for 2 weeks.
Results: Our findings show that intraventricular infusion of patient-derived IgLON5 AABs into wildtype mice leads to phospho-Tau (PHF-1) accumulation in mossy fiber projections, corpus collosum, and cells of the dentate gyrus granule layer. In addition, we observe a neuroinflammatory response in the brain of these animals. In cultured primary mouse neurons, Tau phosphorylation and somatodendritic re-sorting induced by IgLON5 AABs was time- and dose-dependent, and followed a period of acute neuronal hyperactivity.
Conclusions: Collectively, our results indicate that IgLON5 AABs trigger prolonged (days) Tau phosphorylation and resorting by acutely (minutes to hours) stimulating high neuronal activity, which in the brain is associated with glia cell activation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0754 / #1153

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

SINGLE-CELL EXCITABILITY OF INHIBITORY AND EXCITATORY NEURONS UNDER EARLY TAU PATHOLOGY

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Emmie Banks, Annie Goettemoeller, Kelly South Pham, Matthew Rowan
Emory University, Department Of Cell Biology, Atlanta, United States of America

Aims: Circuit hyperexcitability is a phenotype in preclinical Alzheimer's disease (AD), yet the interaction between neuronal dysfunction and the emergence of classic AD pathology remains unclear. Here we investigate how the emergence of pathological tau impacts the biophysical properties and intrinsic excitability of both inhibitory and excitatory neurons in a murine model of AD.
Methods: We used an adult-onset, region-specific AAV approach to model pre-tangle tau pathology in preclinical sporadic AD. Thus, we stereotaxically injected the wild-type human *MAPT* gene (hMAPT) into the lateral entorhinal cortex (LEC) of adult wild-type mice. This short-term viral approach eliminates the effects of transgene expression during development and restricts transgene delivery to the first forebrain region to show pathological tau in human AD. We then performed immunohistochemistry to characterize the pathological tau species produced by viral hMAPT expression, as well as patch-clamp electrophysiology to measure intrinsic changes in excitability.
Results: We demonstrate that 2-3 weeks of hMAPT-AAV expression produces hyperphosphorylated tau and oligomeric tau in the somatic compartment of LEC neurons, which is exacerbated with co-expression of the human *APP* gene. We further show how this pathological tau in the LEC affects the intrinsic excitability and passive membrane properties of each excitatory neurons and parvalbumin-expressing interneurons. We also demonstrate the presence of axonal swelling in the perforant pathway, reminiscent of dystrophic neurites, potentially suggesting the beginnings of transynaptic pathological spread to the dentate gyrus.
Conclusions: These results give us insight into the potential effects of early tau pathology on network dysfunction in a highly vulnerable region in AD, at a timepoint when intervention may still be preventative.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0755 / #596

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

ULTRASTRUCTURAL CHARACTERIZATION OF HUMAN BRAIN TISSUE VITRIFIED AT TIME OF AUTOPSY USING CRYO-ELECTRON TOMOGRAPHY WITH CRYO-PLASMA FOCUSED ION BEAM MILLING

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Benjamin Creekmore[1], Kathryn Kixmoeller[2], Ben Black[2], Yi-Wei Chang[2], Edward Lee[1]
[1]University of Pennsylvania, Translational Neuropathology Research Laboratory, Philadelphia, United States of America, [2]University of Pennsylvania, Biochemistry And Biophysics, Philadelphia, United States of America

Aims: We sought to develop a method to image unfixed never previously frozen human brain at high resolution by cryo-electron tomography (cryo-ET) to identify and describe phenomena not easily recapitulated by cellular or animal models.
Methods: We obtained human brain tissue at time of autopsy from several individuals diagnosed with neurodegenerative disease. This tissue was sectioned and plunge-frozen directly onto cryo-electron microscopy (cryo-EM) grids. We used xenon plasma focused ion beam (PFIB) milling at cryogenic temperatures to generate lamellae directly on cryo-EM grids, thereby avoiding cryo-sectioning and cryo-liftout. We imaged these lamellae by transmission EM, ultimately using cryo-ET to generate three-dimensional tomograms of targets of interest.
Results: We developed a method to freeze human brain tissue up to at least 180μm thick directly onto cryo-EM grids via plunge-freezing as opposed to high-pressure freezing that has been used before for thick samples. Using PFIB, we developed a method to efficiently generate lamellae suitable for cryogenic transmission EM. By using PFIB as opposed to gallium FIB, we were able to use ion beam currents never previously used on biological samples to ultimately make on-grid milling of large samples, like human brain tissue, feasible. From these lamellae we identified intact subcellular structures such as components of autophagy and potential Alzheimer's disease tau fibrils. Additionally, we identified intact compact myelin and other myelin components such as cytoplasmic channels, ultimately using our data to further describe how myelin basic protein (MBP) functions.
Conclusions: We developed a method whereby we can now generate lamellae suitable for high resolution, relatively artifact free cryo-ET imaging in unfixed, never previously frozen human brain samples to better study and understand phenomena, like neurodegenerative disease, that are not easily recapitulated in cell or animal models.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0756 / #687

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

PROTECTIVE EFFECT OF SYNTAXIN-6 KNOCKOUT ON BEHAVIOURAL AND NEUROPATHOLOGICAL READOUTS IN A HUMANISED P301S TAUOPATHY MOUSE MODEL

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Elizabeth Hill, Michael Farmer, Jacqueline Linehan, Nicholas Kaye, Craig Fitzhugh, Sebastian Brandner, Silvia Purro, John Collinge, Thomas Cunningham, Simon Mead
UCL, Mrc Prion Unit, London, United Kingdom

Aims: Variants in and near to the syntaxin-6 (*STX6*) gene are genetic risk factors for progressive supranuclear palsy (PSP) and sporadic Creutzfeldt-Jakob disease (sCJD), with an increase in *STX6* expression being the likely genetic mechanism driving disease risk. Increased syntaxin-6 protein levels are causally associated with Alzheimer's disease (AD) further suggesting syntaxin-6 has pleiotropic risk effects in neurodegenerative diseases. This work aims to functionally validate a role of syntaxin-6 in tau pathogenesis *in vivo* by assessing the effect of syntaxin-6 knockout on behavioural, neuropathological and biochemical readouts in h*Tau*$^{P301S/P301S}$ mice.
Methods: We crossed *Stx6*$^{-/-}$ mice with h*Tau*$^{P301S/P301S}$ mice to generate cohorts of *Stx6*$^{-/-}$;h*Tau*$^{P301S/P301S}$, *Stx6*$^{+/+}$;h*Tau*$^{P301S/P301S}$, *Stx6*$^{-/-}$;m*Tau*$^{+/+}$ and *Stx6*$^{+/+}$;m*Tau*$^{+/+}$ mice (n=20/genotype). Rotarod was assessed monthly and gait assessed at 5.5 months. h*Tau*$^{P301S/P301S}$ mice were humanely culled at endpoint. A 3 and 5 month timed cull (n=10/genotype) was also conducted for biomarker, biochemical and pathological measurements.
Results: We found an early protective effect of syntaxin-6 knockout on rotarod performance in h*Tau*$^{P301S/P301S}$ mice. This partial phenotypic rescue coincided with reduced neuronal loss in the superficial cortex seen early in the disease course. h*Tau*$^{P301S/P301S}$ mice with syntaxin-6 knockout also had partial rescue of some gait parameters. These observations could not be explained by gross differences in levels of total tau. Later in the disease, no differences were seen between *Stx6*$^{-/-}$;h*Tau*$^{P301S/P301S}$ and *Stx6*$^{+/+}$;h*Tau*$^{P301S/P301S}$ mice. We present a range of additional pathological and biomarker endpoints in correlation with a modified early behavioural phenotype.
Conclusions: Syntaxin-6 knockout in h*Tau*$^{P301S/P301S}$ mice appears to have an early beneficial effect on disease progression providing complementary evidence for a role of syntaxin-6 in tau pathogenesis and experimental support that syntaxin-6 lowering could be employed as a potential therapeutic approach in tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0757 / #677

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

TAUOPATHY RESEARCH USING A NOVEL TRAUMATIC BRAIN INJURY MODEL

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Taeko Kimura[1], Masami Masuda-Suzukake[2], Masashi Hashimoto[2], Shin-Ichi Hisanaga[3], Taisuke Tomita[4], Masato Hasegawa[2]
[1]The University of Tokyo, Department of neuropathology and neuroscience Graduate school of pharmaceutical sciences, Tokyo, Japan, [2]Tokyo Metropolitan Institute of Medical Science, Department Of Brain And Neurosciences, Tokyo, Japan, [3]Tokyo Metropolitan University, Laboratory Of Molecular Neuroscience, Department Of Biological Sciences, Hachioji City,, Japan, [4]The University of Tokyo, Department Of Neuropathology And Neuroscience Graduate School Of Pharmaceutical Sciences, tokyo, Japan

Aims: Chronic traumatic encephalopathy (CTE) is a tauopathy caused by traumatic brain injury (TBI). Since the onset and cause of CTE are clear, it is possible to track the progression of the disease. In this study, we developed a CTE animal model using a new system called CHIMERA, which is quantitative and can reproduce human sports and traffic accident injuries.
Methods: Mild repetitive TBI was administered to wild-type and P301S tau transgenic (Tg) mice, and changes were observed 1and 2 months post-TBI. We also investigated the impact of TBI on tau propagation.
Results: After TBI was administered to wild-type and Tg mice, axonal damage in the optic tract and superior colliculus was observed up to two months later, and inflammation positive for Iba1 and GFAP was seen. However, pathological tau phosphorylation (AT8) was not observed. Subsequent analysis in the cerebral cortex, where pathology is seen in CTE patients, revealed no tau pathology in wild-type mice. In Tg mice, two months post-TBI, there was an increase in AT8-positive neurons in layers IV and V of the motor and sensory cortex. Phosphorylation of tau at these sites was analyzed by mass spectrometry, revealing elevated phosphorylation at S262, S235, and S416. Moreover, in mice inoculated with tau fibrils, there was a trend for increased propagation of tau pathology in the cerebral cortex due to TBI.
Conclusions: These results suggest the successful construction of a CTE mouse model. In the future, we will investigate the mechanism of pathology in layers IV and V neurons caused by TBI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0758 / #1802

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

TAU DRIVES EARLY TRANSCRIPTOMIC CHANGES IN A C. ELEGANS MODEL OF TAU AND TDP-43 CO-PATHOLOGY

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Vaishnavi Jadhav[1], Randall Eck[1], Samuel Smukowski[1], Paul Valdmanis[1], Brian Kraemer[1,2], Nicole Liachko[1,2]
[1]University of Washington, Medicine, Seattle, United States of America, [2]VA Puget Sound Health Care System, Grecc, Seattle, United States of America

Aims: TDP-43-positive inclusions are present as a co-pathology in over half of patients with Alzheimer's disease (AD). AD patients with TDP-43 pathology have a faster disease course, more rapid cognitive decline, and increased neurodegeneration, but the molecular mechanisms underlying this are unknown. It is possible that synergies between pathological proteins drives worsened outcomes in these patients.
Methods: Using *C. elegans* models of mixed pathology in AD, we have previously shown that TDP-43 specifically synergizes with tau but not Aβ, resulting in enhanced neuronal dysfunction, selective neurodegeneration, and increased accumulation of pathological tau. However, cellular responses to co-morbid tau and TDP-43 preceding neurodegeneration have not been characterized. In this study, we evaluate transcriptomic changes at time-points preceding frank neuronal loss using a *C. elegans* model of tau and TDP-43 co-expression.
Results: We find significant differential expression and exon usage in genes enriched in multiple pathways including lipid metabolism and lysosomal degradation. We test loss-of-function mutations in a subset of tau and TDP-43 responsive genes, identifying new modifiers of neurotoxicity.
Conclusions: Characterizing early cellular responses to tau and TDP-43 co-pathology is critical for understanding protective and pathogenic responses to mixed proteinopathies, and an important step in developing therapeutic targets protecting against pathological tau and TDP-43 in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0759 / #1322

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

SOMATIC MUTATIONS IN CHRONIC TRAUMATIC ENCEPHALOPATHY IDENTIFIED BY SINGLE-NEURON GENOME SEQUENCING

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Michael Miller[1], Chanthia Ma[1], Guanlan Dong[2], Samuel Naik[1], Gannon Mcdonough[1], Shulin Mao[2], Ann Mckee[3], August Huang[2], Alice Lee[2], Christopher Walsh[2]
[1]Brigham and Women's Hospital, Pathology, Boston, United States of America, [2]Boston Children's Hospital, Genetics And Genomics, Boston, United States of America, [3]Boston University / VA, Pathology, Boston, United States of America

Aims: Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative tauopathy associated with repetitive head trauma. The pathogenesis of neuronal dysfunction and loss in CTE is poorly understood, highlighting a need to probe disease mechanisms from a broad lens. Neurons each harbor somatic single-nucleotide variants (sSNV) in their genomes, which we have found accumulate with age and increase in Alzheimer's disease (AD). Somatic mutational patterns provide fingerprints of cellular disease mechanisms, identified through signature analysis.
Methods: We performed single-cell whole-genome sequencing on neurons from CTE and age-matched controls, and analyzed the burden of somatic mutations and associated nucleotide change signatures for mutational patterns.
Results: We found that neurons in CTE harbor significantly increased sSNV, compared to non-diseased control neurons. Signature analysis showed specific disease-related patterns in the somatic mutations that accumulate in CTE. Somatic mutations in CTE neurons share certain signature features with AD, but also show distinct mutational signatures that suggest CTE-specific pathogenic mechanisms impacting the neuronal genome.
Conclusions: CTE, a neurodegenerative disease associated with repetitive head trauma, shows neuronal somatic mutation accumulation, a finding also seen in sporadic neurodegeneration in AD. The somatic mutational signatures of CTE illuminate divergent mechanisms from AD, but also point to common mutational features that may constitute broader hallmarks of neurodegeneration. The identification of somatic mutation in distinct neurodegenerative diseases will enable further dissection of pathogenesis cascades, to illuminate diagnostic and therapeutic targets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0760 / #173

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

BILE ACID PROFILE ASSOCIATED WITH CSF AND PET BIOMARKERS IN ALZHEIMER'S DISEASE

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Fardin Nabizadeh[1], Parya Valizadeh[2], Mohammad Sadegh Fallahi[2]
[1]Iran University of Medical Science, Tehran, Iran, School Of Medicine, Tehran, Iran, [2]Tehran University of Medical Science, Tehran, Iran, School Of Medicine, Tehran, Iran

Aims: Recent studies have shown that gut microbiota can affect the development of Alzheimer's disease (AD) through various mechanisms. Bile acids (BAs), which are the final byproducts of cholesterol metabolism created through both the human body and gut microbiome, appear to be influenced by gut microbiota and may impact AD pathological characteristics such as the accumulation of tau and amyloid-β. We aimed to investigate the associations between various serum BAs and CSF biomarkers (including Aβ, total tau, and p-tau). Additionally, we sought to examine the longitudinal changes in brain Aβ and tau through PET imaging in relation to BAs profile.
Methods: The data of 828 subjects including 491 diagnosed with mild cognitive impairment (MCI), 119 patients diagnosed with AD, and 267 cognitively normal (CN) participants were obtained from ADNI. The baseline and longitudinal [^{18}F] florbetapir and [^{18}F] flortaucipir PET standard uptake value ratios (SUVR) measures were obtained to assess the accumulation of tau and Aβ. Moreover, baseline levels of serum BAs and CSF Aβ1-42, tau, and p-tau were used.
Results: After FDR correction we observed that five BAs level and relevant calculated ratios were associated with CSF p-tau and tau, three with CSF Aβ1-42. Furthermore, three BAs level and relevant calculated ratios were associated with the tau-PET rate of change, and two with the Aβ rate of change.
Conclusions: The findings from our study suggest a correlation between altered profiles of BAs and CSF and imaging biomarkers associated with AD. These results provide supporting evidence for the link between the gut microbiome and the pathological features of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0761 / #2400

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

CELL TYPE-SPECIFIC HIPPOCAMPAL ALTERATIONS UNDERLIE MEMORY DEFICITS IN NOVEL APP/TAU MICE

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Arnaldo Parra-Damas[1,2], Angel Deprada[1,2], Maria Capilla-López[1,2], Carlos A. Saura[1,2]
[1]Universitat Autònoma de Barcelona, Institut De Neurociències, Department De Bioquímica I Biologia Molecular, Bellaterra, Spain, [2]Centro de Investigación Biomédica en Red (CIBER), Ciber Enfermedades Neurodegenerativas (ciberned), Madrid, Spain

Aims: Excitatory/inhibitory neurotransmission imbalance in memory neural circuits affected by amyloid-β and tau pathologies are thought to underlie memory deficits in Alzheimer's disease (AD). However, the specific cellular mechanisms by which these neuropathological hallmarks induce dysfunction of excitatory and inhibitory hippocampal neurons remain poorly understood. Here, we report differential deleterious effects of amyloid-β and tau on hippocampal-dependent memory and synaptic plasticity as well as cell type-specific pathology in novel APP/Tau transgenic mice expressing human familial AD-linked mutant amyloid precursor protein (APP) and microtubule-associated protein tau (MAPT) genes.
Methods: We combined behavioral, molecular, biochemical, as well as conventional and advanced histological and microscopy analyses, including tissue clearing and expansion microscopy, to assess the effect of Aβ and Tau accumulation on the hippocampus of APP/Tau mice, focusing on Pvalb-expressing interneurons. Furthermore, we applied cell type-specific RNA-seq analyses in hippocampal excitatory neurons (CaMKIIα+) and inhibitory interneurons (Pvalb+) of APP/Tau;RigoTag mice.
Results: Histopathological analyses reveal that Aβ and pTau are expressed in hippocampal CaMKIIα+ neurons but not Pvalb+ interneurons in 6 month-old APP/Tau mice. Accordingly, cell type-specific gene expression profiling using APP/Tau;CamK2α-Cre;RigoTag and APP/Tau;Pvalb-Cre;RiboTag mice show that APP and Tau gene expression is restricted to excitatory neurons. Importantly, 6 month-old Tau and APP/Tau mice show spatial learning and memory deficits, which are associated with reduced levels of synaptic proteins and synaptic Tau accumulation, as revealed by biochemical and expansion microscopy analyses. Moreover, APP/Tau mice show a selective reduction and altered morphology of hippocampal inhibitory Pvalb-expressing neurons, accompanied by age-dependent alterations in perineuronal nets (PNNs).
Conclusions: Altogether, APP/Tau mice reproduce AD pathological changes, showing cell type-specific alterations in excitatory and inhibitory neurons, making this model a useful tool for studying the molecular mechanisms underlying selective cellular vulnerability in AD.

P0762 / #1325

Poster Topic: *Theme B: Taupathies / B02.a. Therapeutic Targets, Mechanisms for Treatment: Tau, phosphorylation, truncation*

IDENTIFICATION AND EVALUATION OF EBSELEN AS AN INHIBITOR OF P-TAU AND AB FOR TREATING EARLY ONSET OF ALZHEIMER'S DISEASE

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

Shaohua Qi, Li Yang, Michael Chan, Bill Chan, Zheng Yin, Stephen Wong
Houston Methodist Academic Institute, T. T. & W. F. Chao Center For Brain, Houston, United States of America

Aims: Alzheimer's disease (AD) remains a challenging condition with no cure to halt its progression. Drug repositioning, an expedited drug development strategy, offers promise in the pursuit of effective AD therapeutics. This study presents a comprehensive investigation into the potential of ebselen, a knowledge drug, in targeting AD.
Methods: Utilizing a systematic Alzheimer's disease drug repositioning (SMART) framework, we conducted high throughput AD 3D cell culture systems, computational cellular analysis, and iterative procedures for effective drug repositioning. Our screening involving 4,600 known drugs and bioactive compounds and employed AD murine models for in *vivo* validation of promising hits, assessing the efficacy of ebselen in alleviating pathological features of AD.
Results: The study identified eight drug candidates capable of alleviating p-Tau accumulation and/or Aβ burden in a multi-well formatted 3D culture assay. Ebselen, an organoselenium compound, emerged as a top candidate, demonstrating significant potential both *in vitro* and *in vivo*. Acute and chronic treatments with ebselen exhibited substantial improvements in neurite abundance, intensity, and p-tau inhibition in the high-throughput 3D cell assay. Behavior assessments further demonstrated the cognition enhancement achieved with ebselen administration. Notably, biosafety evaluations indicated minimal adverse effects even with high dosage and long-term ebselen treatment, underscoring its potential as a safe therapeutic option for early onset of AD.
Conclusions: Ebselen shows a promising drug candidate for the treatment of early onset AD. This study not only demonstrated its efficacy in alleviating pathological markers of AD but also highlighted its favorable biosafety profile. The findings offer important implications for AD treatment and further clinical investigations are warranted to validate the potential of ebselen in human subjects, bringing us closer to a viable therapeutic solution to Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0763 / #1049

Poster Topic: *Theme B: Taupathies / B01.p. Disease Mechanisms, Pathophysiology: Other*

ALZHEIMER'S DISEASE WITH ALPHA-SYNUCLEIN CO-PATHOLOGY: CO-LOCALIZATION OF PHOSPHODIESTERASE 1 AND MGLUR1 WITH ALPHA-SYNUCLEIN AND PHOSPHO-TAU IN THE FRONTAL CORTEX

POSTERS: B01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Doris Weissenbrunner[1,2], Mochen Cui[1,2], Paul Feyen[2], Antonia Neubauer[1], Felix Struebing[1,2], Jochen Herms[1,2,3]
[1]University of Munich, Center For Neuropathology And Prion Research, Munich, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Translational Brain Research, München, Germany, [3]Munich Cluster for Systems Neurology, Synergy, Munich, Germany

Aims: OBJECTIVES:
Alzheimer's disease (AD) is characterised pathologically by the aggregation of β-Amyloid plaques (Aβ) and hyperphosphorylated tau deposits. Additionally, up to 50% of AD cases exhibit the accumulation of α-synuclein (ASYN). Single nucleus RNA-sequencing (sn-RNA-seq) on frontal cortex tissue has identified differentially expressed genes in neuronal clusters of cases with AD and AD+ASYN. Interestingly, most of these genes were upregulated in AD+ASYN. Some of them encode proteins, such as Phosphodiesterase 1A (PDE1A) and mGluR1 (GRM1), which have previously been linked to neurodegenerative diseases in the literature. The primary aim of this study is to elucidate whether these proteins are colocalized with α-synuclein and phospho-Tau in human brain tissue in the frontal cortex.
Methods: METHODS:
We intend to conduct immunofluorescence co-staining using primary antibodies against PDE1A, GRM1, α-Synuclein and phospho-Tau on post-mortem human brain tissue obtained from four cases with AD, four cases with AD+ASYN and four control cases. Furthermore, the tissue will be stained with DAPI and Methoxy, to determine cellular localization of the antigens and their association with Aβ. Images will be acquired and statistically analysed exploring potential variations between AD, AD+ASYN and control cases.
Results: RESULTS:
The sn-RNA-seq analysis revealed a set of genes which were significantly upregulated in AD patients with α-synuclein co-pathology. Immunohistochemistry may demonstrate the co-localisation of some of the proteins coded by these upregulated genes with α-synuclein aggregates and phospho-Tau in the frontal cortex.
Conclusions: DISCUSSION:
The potential co-occurrence of PDE1A and GRM1 with the pathological hallmarks of AD+ASYN may indicate pathophysiological convergence, necessitating further research. These findings will contribute to our understanding of the mechanisms underlying this co-pathology and may have implications for the development of targeted therapies for AD patients with α-synuclein involvement.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0764 / #899

Poster Topic: *Theme B: Taupathies / B02.a. Therapeutic Targets, Mechanisms for Treatment: Tau, phosphorylation, truncation*

EVALUATION OF A MICROTUBULE-DYNAMIN BINDING INHIBITOR PEPTIDE (PHDP5) AS A POTENTIAL TOOL FOR RESCUING COGNITIVE IMPAIRMENT IN TRANSGENIC TAUOPATHY MICE

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

Anna Chiajung Chang, Zacharie Taoufiq, Tetsuya Hori, Tomoyuki Takahashi
Okinawa Institute of Science and Technology, Cellular And Molecular Synaptic Function Unit, Okinawa, Japan

Aims: Accumulation of soluble tau causes *synaptic* dysfunction leading to cognitive impairment in tauopathies including Alzheimer's disease (AD). Dynamin plays a key role in synaptic vesicle endocytosis and recycling in the presynaptic terminal, thereby supporting synaptic strength. Our previous studies at the calyx of Held in mouse brainstem slices suggest that soluble tau over-assembles microtubules (MTs). Since dynamin is a MT-binding protein, sequestration of free dynamin by MTs impairs vesicle endocytosis and synaptic transmission. A synthetic dodecapeptide, PHDP5, corresponding to amino acids 560–571 of the dynamin 1 pleckstrin-homology (PH) domain, can inhibit the MT-dynamin interaction and significantly rescue endocytic impairments, suggesting its potential value for AD treatment. In this study, we investigated whether PHDP5 can rescue memory deficits in the tauopathy model mice Tau609.
Methods: We conjugated PHDP5 to FITC and a cell-penetrating TAT peptide (CPP) as FITC-PHDP5-CPP. We also prepared PHDP5 scrambled control conjugated to FITC and CPP. In six-month old male Tau609 mice, we administered FITC-PHDP5-CPP intranasally for one month, and then tested their spatial learning and memory abilities in the Morris water maze.
Results: *In vitro,* FITC-PHDP5-CPP significantly inhibited MT-dynamin1 binding like unconjugated PHDP5. After intranasal administration of FITC-PHDP5-CPP in mice, FITC signal was found in the hippocampal CA1 region, indicating that the peptide crossed the blood brain barrier (BBB). In comparison to non-treated or scramble peptide controls, FITC-PHDP5-CPP-treated mice exhibited significant cognitive improvements including shorter latencies to the escape platform and increased time spent in the target quadrant of the water maze.
Conclusions: Intranasal administration of FITC-PHDP5-CPP can be an effective therapy for cognitive decline associated with AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0765 / #1311

Poster Topic: *Theme B: Taupathies / B02.a. Therapeutic Targets, Mechanisms for Treatment: Tau, phosphorylation, truncation*

THERAPEUTIC POTENTIAL OF NICOTINIC ACID IN PS19 TAUOPATHY MICE.

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

Israel Coronel[1], Paul Fallen[1], Henika Patel[1], Shweta Puntambekar[1], Pablo Martinez[1], Disha Soni[2], Rian Delvecchio[1], Abigail Wallace[1], Adrian Oblak[2], Cristian Lasagna-Reeves[1], Gary Landreth[1], Miguel Moutinho[1]
[1]Stark Neurosciences Research Institute, Indiana University, School of Medicine, Anatomy, Cell Biology And Physiology, Indianapolis, United States of America, [2]Stark Neurosciences Research Institute, Indiana University, School of Medicine, Department Of Radiology & Imaging Sciences, Indianapolis, United States of America

Aims: Alzheimer's disease (AD) is the most common type of dementia, for which there is no effective treatment. AD is characterized by a robust immune response, the presence of extracellular amyloid-β (Aβ) plaques, and intraneuronal neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau. We have recently shown that nicotinic acid activates the microglial receptor HCAR2 to induce a protective phenotype in an amyloid mouse model of AD, attenuating disease severity. However, the therapeutic potential of HCAR2 in tauopathy has not been assessed. We **aimed** to investigate whether the activation of HCAR2 with the FDA-approved agonist Niaspan® is a potential therapeutic approach to reduce tau pathology.
Methods: *Hcar2* expression was analyzed by qPCR and IHC in brain tissue of the tauopathy mouse model PS19. At 9 months of age, PS19 mice exhibited a severe pathological phenotype and were treated with Niaspan® daily by oral gavage (100 mg/kg) for 30 days. Treated mice were assessed for motor tasks and their brain tissue used for biochemical and imaging analysis.
Results: HCAR2 expression was significantly induced by microglia in 9-month-old PS19, particularly in the hippocampus. Niaspan® treatment rescued the motor coordination deficits, reduced tau hyperphosphorylation, and microgliosis.
Conclusions: Our results indicate that in 9-month-old PS19 mice, there was an increase in hippocampal HCAR2 expression. Moreover, treatment with Niaspan® improved motor coordination but did not affect the clasping reflex nor inflammatory markers. These results indicate that niacin may be acting via microglial HCAR2, attenuating disease severity. However, additional studies are necessary to determine the exact mechanisms of this process. Overall, this work could support the repurposing of marketed niacin-formulations a potential therapy for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0766 / #913

Poster Topic: *Theme B: Taupathies / B02.a. Therapeutic Targets, Mechanisms for Treatment: Tau, phosphorylation, truncation*

TORPOR INDUCES ROBUST AND REVERSIBLE TAU HYPERPHOSPHORYLATION IN HUMAN TAU EXPRESSING MICE

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

Christina De Veij Mestdagh[1], Guus Smit[2], Ronald Van Kesteren[2], Rob Henning[3]
[1]Alzheimer Center Amsterdam, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Neurology, Amsterdam, Netherlands, [2]Vrije Universiteit, Molecular And Cellular Neurobiology, Amsterdam, Netherlands, [3]University Medical Center Groningen, Clinical Pharmacy And Pharmacology, Groningen, Netherlands

Aims: Tau protein hyperphosphorylation is a key pathological event in neurodegenerative tauopathies such as Alzheimer's disease. Interestingly, seasonal hibernators show extensive, yet completely reversible tau hyperphosphorylation during periods of hypothermia and hypometabolism followed by rapid rewarming and metabolic reactivation, so called torpor and arousal cycles. Using seasonal hibernators to unravel torpor-associated mechanisms that reverse and protect against pathological effects of tau hyperphosphorylation is challenging and focusses on native tau which might not model human tau properly. We therefore aimed to assess the effects of daily torpor on tau phosphorylation dynamics in human tau expressing mice.
Methods: We induced daily torpor in wildtype mice that express mouse tau (mtau), and uniquely in mice that lack mouse tau and instead express human tau (htau). AT8 immunoblotting and immunohistochemistry were used to assess tau (hyper)phosphorylation at two phosphorylation sites, Ser202 and Thr205, commonly used for Alzheimer's disease staging.
Results: Torpor robustly and reversibly increased the levels of phosphorylated tau in the hippocampus of both mtau and htau mice. Immunohistochemistry revealed four brain areas with prominent tau phosphorylation: the hippocampus, posterior parietal cortex, piriform cortex and cortical amygdala. Whereas wildtype mice primarily showed increased levels of phosphorylation of diffusely organized tau, htau mice had somato-dendritic accumulation of AT-8 reactivity resembling tau pre-tangles as observed in Alzheimer patient brain. Interestingly, this AT8 positive accumulation also disappeared upon arousal, and overall tau phosphorylation at 24h after arousal was even lower than observed at baseline in euthermia.
Conclusions: Daily torpor in htau mice offers a quick, controllable and standardized method to study tau (hyper)phosphorylation, accumulation and clearance in a model relevant for neurodegeneration. It therefore offers opportunities to discover new mechanisms underlying the clearance of hyperphosphorylated tau.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0767 / #917

Poster Topic: *Theme B: Taupathies / B02.a. Therapeutic Targets, Mechanisms for Treatment: Tau, phosphorylation, truncation*

POTENTIAL NEUROPROTECTIVE PROPERTIES OF CART (COCAINE- AND AMPHETAMINE-REGULATED TRANSCRIPT) PEPTIDE ANALOGS IN IN-VIVO MODEL OF OBESITY AND TAU HYPERPHOSPHORYATION

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

Andrea Pacesova[1], Lenka Maletínská[1], Blanka Železná[1], Jaroslav Kuneš[2]
[1]IOCB CAS Prague, Biochemistry And Molecular Biology, Prague, Czech Republic, [2]Institute of Physiology, Experimental Hypertension, Prague, Czech Republic

Aims: Hypothermia, a phenomenon observed in elderly patients with obesity and type 2 diabetes mellitus as well as in mouse models of obesity (e.g. leptin deficient ob/ob obese mice), was linked to development of Alzheimer's disease (AD), especially hyperphosphorylation of Tau protein. Currently, anorexigenic and antidiabetic substances, such as cocaine- and amphetamine-regulated transcript peptide (CARTp), are examined as possible neuroprotective agents.
Methods: We employed a mouse model of obesity with hypothermia, insulin resistance, and increased hippocampal Tau hyperphosphorylation, namely mice with monosodium glutamate (MSG)-induced obesity, to explore potential neuroprotective properties of natural CARTp, CART(61-102), administered intracerebroventricularly to the 3rd ventricle (ICV, 1 µg/day/mouse for 2 weeks) and its novel palmitoylated analog, palm-CART, administered subcutaneously (SC, once daily 10 mg/kg for 3 weeks); control lean or obese MSG mice were treated with saline. We examined peripheral and central insulin resistance and neuropathological changes in the hippocampus using the method of western blot.
Results: Compared to saline-treated MSG mice, MSG mice treated with CART(61-102) or palm-CART significantly decreased food intake and body weight, as well as increased the body temperature. MSG mice developed peripheral insulin resistance expressed by QUICKI (quantitative insulin sensitivity check index); the treatment with palm-CART tended to reverse it. In the hippocampi, we observed only insignificant reduction in activation of insulin signaling cascade, and no significant changes in its activation after the treatment with both peptides. However, we detected significantly increased Tau hyperphosphorylation at Thr212 or Ser404 in hippocampi of MSG mice, which was attenuated by the treatment with CARTp analogs.
Conclusions: Analogs of CARTp were able to reduce food intake and body weight, increased body temperature of obese MSG mice, and attenuated Tau hyperphosphorylation in hippocampi.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0768 / #2547

Poster Topic: *Theme B: Taupathies / B02.a. Therapeutic Targets, Mechanisms for Treatment: Tau, phosphorylation, truncation*

CHRONIC TREATMENT WITH DOXYCYCLINE PREVENTS TAU PATHOLOGY AND COGNITIVE IMPAIRMENTS IN A MOUSE MODEL OF TAUOPTAHY

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

M. Elena Avale[1], Javier Muñiz[1], Indiana Páez-Paz[1], Carolina Facal[1], Rita Raisman-Vozari[2], Patrick Pierre Michel[3]
[1]Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Instituto De Investigaciones En Ingeniería Genética Y Biología Molecular (ingebi), CABA, Argentina, [2]Hôpital de la Pitié Salpêtrière, Institut Du Cerveau - Icm, Inserm, Sorbonne Université, Cnrs, Paris, France, [3]Paris Brain Institute-ICM, Inserm Cnrs Hôpital De La Pitié Salpêtrière, Sorbonne Université, Paris, France

Aims: The tetracycline doxycycline (Dox) has been reported to have neuroprotective effects unrelated to its antibiotic activity. Our present aim was to determine whether Dox could prevent behavioral and biochemical phenotypes related to abnormal tau accumulation in a htau mouse model of tauopathy.
Methods: htau mice were analyzed in the open field, rotatord and novel object recognition test to determine time course of behavioral deficits. From 3 months-old mice were treated chronically with doxycycline in the diet during 6 months. Phenotypic rescue was analyzed by behavioral and biochemical studies. Phospho tau and insoluble tau contents were determined as well as autophagy markers.
Results: Htau mice display deficits in motor coordination and novel object recognition test which correlates with the presence of insoluble and hyperphosphorylation tau in the prefrontal cortex. Dox treatment precluded the onset of cognitive deficits at 6 and 12 months old. Moreover olfactory dysfunction and motor coordination impairments were also prevented.
Conclusions: Dox prevents tau pathology and cognitive deficits when administered at aearly stages of disease. These results highlight the potential of doxycycline treatment for therapeutic application in human tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0769 / #2839

Poster Topic: *Theme B: Taupathies / B02.a. Therapeutic Targets, Mechanisms for Treatment: Tau, phosphorylation, truncation*

EVALUATION OF TARGETED PROTEIN DEGRADATION MODALITY FOR TAU AGGREGATES

POSTERS: B02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: TAU, PHOSPHORYLATION, TRUNCATION

Marija Usenovic[1], Alicja Krasowska-Zoladek[1], Sokreine Suon[1], Jeffrey Lusen[2], Laura Price[2], Brian Magliaro[2], Paul Tawa[2], Beata Zamlynny[2], Smaranda Bodea[3], An Chi[3], Serene Keilani[3], Brent Whitehead[3], Remond Moningka[4], Thomas Bara[4], Dmitri Pissarnitski[4], Yuhua Huang[4], Yuriy Slutskyy[4], Raphaelle Berger[4], Sean Smith[1], Jason Uslaner[1], Jacob Marcus[1]
[1]Merck Sharp & Dohme, Neuroscience, Rahway, United States of America, [2]Merck Sharp & Dohme, Quantitative Biosciences, Rahway, United States of America, [3]Merck Sharp & Dohme, Chemical Biology, Rahway, United States of America, [4]Merck Sharp & Dohme, Discovery Chemistry, Rahway, United States of America

Aims: In Alzheimer's disease (AD) levels of aggregated tau protein correlate with neuronal dysfunction and cognitive decline. Therefore, clearing tau aggregates may modify disease progression in AD and primary tauopathies. The growing field of proximity induced modalities that enable targeted degradation of proteins of interest prompted us to explore these approaches for clearance of pathological, aggregated tau. Selective removal of pathological intracellular protein aggregates using a small molecule represents a novel approach towards the development of a future therapeutic.
Methods: We tested a set of published heterobifunctional tau degraders that utilize Cereblon E3 ligase in a human iPSC neurons overexpressing aggregation-prone tau, and in B35 rat neuroblastoma and CHO-K1 Tau P301L cell-lines with tau pathology induced by tauopathy mouse brain seeds. We performed global proteome profiling to explore putative off-targets of tau degraders.
Results: Using imaging and AlphaLISA assay we confirmed a decrease of tau aggregates with treatment of degraders in human iPSC tau model. However, global proteome profiling indicated degradation of GSPT1 protein, a translation termination factor and a reported thalidomide/CRBN off-target, with the treatment of putative tau degraders. Additionally, tested published tau degraders that did not reduce GSPT1 did not decrease tau levels without accompanying cytotoxicity. Hypothesizing that this lack of an effect and observed cytotoxicity could be specific to iPSC neurons, we tested putative tau degraders in additional tau pathology assays in rodent cells, B35 and CHO-K1. Again, we did not observe a decrease in tau levels without cytotoxicity.
Conclusions: Our efforts highlight the challenge in conclusively demonstrating reduction of tau pathology using proximity induced degradation and emphasize a need for in depth understanding and confirmation of the mechanisms of action that lead to observed tau decreases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0770 / #1617

Poster Topic: *Theme B: Taupathies / B02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

EFFICACY OF A NEW VACCINE TARGETING TAU IN MOUSE MODELS

POSTERS: B02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Christopher Brown[1], Louise Kelly[1], Jeanne Brooks[2], Matthew Longo[2], Justin Boyd[2], Roxana Carare[1], Jean-Cosme Dodart[2]
[1]University of Southampton, Faculty Of Medicine, Southampton, United Kingdom, [2]Vaxxinity, Neurology, Merritt Island, United States of America

Aims: A novel class of vaccines, based on a technology where a synthetic, promiscuous Th-cell epitope linked to functional antigenic peptides, are being developed by Vaxxinity to target tau in Alzheimer's disease (AD). These vaccines generate antibodies that have demonstrated binding to pathological tau *in vitro*, and efficacy in cell-based tau aggregation assays comparable to monoclonal antibodies. Here we report the ability of one such tau-targeting vaccine to prevent the progression of tau pathology *in vivo* using two distinct mouse models.
Methods: The onset of phenotypes associated with the progression of tau pathology in P301L mice, such as ataxia and premature death, were measured over 210 days. Saline-inoculated control mice were compared to mice inoculated with the tau-targeting vaccine, p5555kb. The efficacy of vaccines against tau seeding *in vivo* was assessed by injecting C57BL6 mice with tau fibrils purified from post-mortem human AD brain tissue via differential centrifugation of the sarkosyl-insoluble brain fraction. Mice were inoculated with p5555kb, and the extent of tau pathology compared to saline-inoculated controls was measured by immunohistochemistry after 9 months.
Results: P301L mice vaccinated with p5555kb showed greater survival rates at 210 days than saline-inoculated control mice. The onset of ataxia was also delayed in vaccinated mice compared to controls. Mice injected with purified human AD tau developed inclusions of phosphorylated tau in the contralateral hippocampus 9 months post-injection. Vaccination with p5555kb significantly reduced the amount of tau inclusions detected by immunohistochemistry, as compared to saline inoculation.
Conclusions: These studies demonstrate that the vaccine p5555kb tested is effective at preventing onset of adverse phenotypes associated with tau pathology *in vivo* and can prevent the transfer of tau pathology between neuroanatomically connected brain regions via tau seeding.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0771 / #1582

Poster Topic: *Theme B: Taupathies / B02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

HIGH-AFFINITY ANTI-TAU IMMUNOTHERAPY TARGETING THE CORE EXHIBITS INHIBITION OF TAU PATHOLOGY IN A MOUSE MODEL OF TAUOPATHY

POSTERS: B02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Lewis Penny[1], Mohammad Arastoo[1], Richard Lofthouse[1], Aya Abdallah[1], Peter Imoesi[1], Karima Schwab[1], Valeria Melis[1], Gernot Riedel[1], Andy Porter[1], Soumya Palliyil[1], Charlie Harrington[1,2], Claude Wischik[1,3]
[1]University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom, [2]2. TauRx Pharmaceuticals Ltd., King Street, Aberdeen, United Kingdom, [3]2. TauRx Pharmaceuticals Ltd., King Street, Aberdeen, United Kingdom

Aims: Immunotherapy is an attractive proposition to prevent the spread of pathologic tau in Alzheimer's disease and other tauopathies. S1D12, a chimeric IgG2a isolated via phage display, targets the disease-causing core of tau. S1D12 recognises tau341-353 with high affinity (200 pM) and prevents tau aggregation and propagation in biochemical and cellular assays, respectively. The objective was to assess the potential of anti-tau immunotherapy targeting the core to prevent tau pathology in tau transgenic mice.
Methods: Four-weekly doses followed by four-fortnightly doses of S1D12 (30 mg/kg) or negative control (n=10 per group) were administered via intraperitoneal injection to tau transgenic mice (Line 66; Melis et al., 2015) that were sacrificed one week after their final dose. Dosing was performed on two cohorts of mice starting from 2 months and 4.5 months of age, respectively, with baseline animals sacrificed for reference. Endpoints included quantification of oligomeric tau and phosphorylated tau in brain homogenate and neurofilament light and core tau in plasma.
Results: In both cohorts of mice, S1D12 inhibited generation of oligomeric tau and phosphorylation at p202/p205 and p396. This was associated with a reduction in neurodegeneration and an increase in core tau in plasma. In the 4.5-month cohort, S1D12 did not remove already established tau pathology below baseline.
Conclusions: High-affinity anti-tau immunotherapy targeting the core offers great potential for inhibiting progression of tau pathology. Mechanism of action of core immunotherapy appears exclusive to inhibition rather than removal of established pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0772 / #462

Poster Topic: *Theme B: Taupathies / B02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

COMPARATIVE ANALYSIS OF TAU N-TERMINAL ANTIBODIES IN VITRO AND IN A MOUSE MODEL OF TAUOPATHY

POSTERS: B02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Esteban Cruz[1], Rebecca Nisbet[2], Pranesh Padmanabhan[1], Ashley Van Waardenberg[3], Mark Graham[4], Godfrey Nkajja[1], Phil Robinson[4], Jürgen Götz[1]
[1]University of Queensland, Queensland Brain Institute, Brisbane (St Lucia Campus), Australia, [2]The University of Melbourne, The Florey, Melbourne, Australia, [3]iSynapse, Isynapse, Cairns, Australia, [4]The University of Sydney, Children's Medical Research Institute, Westmead, Australia

Aims: The microtubule-associated protein Tau has gained significance as a therapeutic target in Alzheimer's disease and various other tauopathies. To date, clinical development of antibodies targeting Tau's N-terminus has yielded disappointing outcomes. However, the observation that antibodies targeting the N-terminus can show drastically different binding profiles to aggregated pathological forms of Tau has been overlooked. Here, we aimed to assess how the reactivity against aggregated forms of Tau impacts the therapeutic efficacy of Tau N-terminal antibodies.
Methods: We generated a novel pan-Tau antibody, RNJ1, which binds to a region in Tau's N-terminus adjacent to the epitope of the clinically tested HJ8.5 (murine version of tilavonemab), which we used here as a benchmark for comparison of therapeutic efficacy. Given the proximity of their epitopes, we compared both antibodies' capacity to bind and neutralize aggregated Tau seeds in two independent Tau FRET biosensor cell lines. We then compared the therapeutic efficacy of both antibodies, alone or in combination, in a longitudinal passive immunization study in the K3 mouse model of tauopathy.
Results: Our findings show that despite the proximity to the HJ8.5 epitope, RNJ1 displays higher reactivity against aggregated Tau and neutralizes Tau seeds from various tissue sources with higher efficiency in our biosensor seeding assays. In our passive immunization study, RNJ1 treatment improved behavioral outcomes across the treatment duration, with no efficacy achieved in the HJ8.5 or combination arms. Furthermore, biochemical and histological examination of antibody-treated mice showed reductions in Tau pathology with RNJ1.
Conclusions: Our study presents RNJ1 as a promising Tau antibody with enhanced therapeutic potential and underscores the importance of exploring Tau's N-terminus in pathology and as a therapeutic target.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0773 / #2608

Poster Topic: *Theme B: Taupathies / B02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

CLEARANCE OF INTRACELLULAR TAU PATHOLOGY AND ENHANCED COGNITIVE FUNCTIONS IN AGED TAUOPATHY MICE BY NASAL IMMUNOTHERAPY

POSTERS: B02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Sagar Gaikward[1], Nicha Puangmalai[1], Minal Sonawane[2], Anamika Ray[1], Rakez Kayed[1]
[1]University of Texas Medical Branch, Department Of Neurology, Galveston, United States of America, [2]utmb galveston, Department Of Neurology, GALVESTON, United States of America

Aims: This study aimed to develop toxic tau conformation-specific monoclonal antibody-loaded micelles (TTCM2-ms) for the selective recognition and clearance of intracellular tau aggregates, targeting disease-relevant tau species. Additionally, the study aimed to investigate the mechanisms underlying the therapeutic effects of intranasally delivered TTCM2-ms on cognitive function in tauopathy mice.
Methods: We developed TTCM2-ms and characterized their selectivity for disease-relevant tau aggregates in brain tissues from patients with Alzheimer's disease, progressive supranuclear palsy, and dementia with Lewy bodies. We assessed the inhibitory effects of TTCM2-ms on tau-seeding activity, a crucial process in tauopathy progression. Intranasal delivery of TTCM2-ms was employed to investigate their ability to reach various regions and intracellular compartments in the brain of tauopathy mice. The therapeutic efficacy of a single intranasal dose of TTCM2-ms was evaluated by measuring the clearance of pathological tau, the increase in synaptic protein levels, and the improvement in cognitive functions in aged tauopathy mice. Mechanistic studies were conducted to elucidate the role of tripartite motif-containing 21 (TRIM21) in TTCM2-ms-mediated clearance of tau pathology.
Results: Our findings revealed that TTCM2-ms selectively recognized disease-relevant tau aggregates, effectively inhibited tau-seeding activity, and efficiently reached the brain when administered intranasally. A single intranasal dose of TTCM2-ms led to the clearance of pathological tau, increased synaptic protein levels, and improved cognitive function in tauopathy mice. Mechanistic studies demonstrated that TTCM2-ms cleared intracellular, synaptic, and seed-competent tau aggregates through the involvement of TRIM21, an intracellular antibody receptor, and E3-ubiquitin ligase.
Conclusions: These findings offer valuable mechanistic insights into the role of TRIM21 in reducing intracellular and synaptic tau pathology upon intranasal immunotherapy. This study provides a foundation for the development of fast and effective tau immunotherapy strategy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0774 / #749

Poster Topic: *Theme B: Taupathies / B02.c. Therapeutic Targets, Mechanisms for Treatment: Kinases, phosphatases, other enzymes*

COMPARATIVE EFFICACY AND SELECTIVITY OF PHARMACOLOGICAL INHIBITORS OF DYRK AND CLK PROTEIN KINASES

POSTERS: B02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, PHOSPHATASES, OTHER ENZYMES

Mattias Lindberg, Emmanuel Deau, Laurent Meijer
Perha Pharmaceuticals, Neurosciences, Roscoff, France

Aims: Dual specificity, tyrosine phosphorylation regulated kinases (**DYRKs**) and cdc2-like kinases (CLKs) play a large variety of cellular functions, regulating alternative splicing, DNA damage repair, chromatin transcription, cell cycle, apoptosis, neuronal cytoskeleton and axonal transport, synaptic plasticity, etc. There is thus growing interest in pharmacological inhibitors of as research reagents to evaluate the cellular functions of these Ser/Thr kinases. There is also growing interest in the development of drug candidates specifically targeting some of these kinases, especially in the context of Down syndrome, Alzheimer's disease and Parkinson's disease (DYRK1A), diabetes (DYRK1A, DYRK1B), viral infections (DYRKs, CLKs), etc.
Methods: In this study, we made an unbiased **comparative evaluation** of the kinase inhibitory activity of a **library of 56 reported DYRK/CLK inhibitors**.
Results: All inhibitors were compared, side-by-side, in a dose-dependent manner, for catalytic activity on a panel of 12 recombinant human kinases (CDK5/p25, CK1ε, CLK1-4, DYRK1A, 1B, 2-4, GSK3β), enzyme kinetics allowing the determination of residence time and Kd (DYRK1A, CLK1, GSK3β), in-cell inhibition of Thr-212-Tau phosphorylation (a DYRK1A specific site particularly relevant to Alzheimer's disease) and cytotoxicity. The 26 most active inhibitors were modelled in the crystal structure of DYRK1A. Results show a rather large diversity of potency and selectivity among the reported inhibitors, and emphasize the difficulties to avoid "off-targets" in this area of the kinome.
Conclusions: Strengths and weaknesses of each inhibitor are discussed. The use of a **panel of selected DYRKs/CLKs inhibitors** is suggested to analyze the functions of these kinases in cellular processes, especially in the CNS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0775 / #2309

Poster Topic: *Theme B: Taupathies / B02.d. Therapeutic Targets, Mechanisms for Treatment: Neurotransmitters & receptor-based*

THE NEUROLEPTIC DRUG AMISULPRIDE AS A NOVEL THERAPEUTIC APPROACH FOR TAUOPATHIES

POSTERS: B02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

Alina Brüge[1], Sungsu Lim[2], Enza Lacivita[3], Kim Yun[2], Leopoldo Marcello[3], Evgeni Ponimaskin[1], Josephine Labus[1]
[1]Hannover Medical School, Cellular Neurophysiology, Hannover, Germany, [2]Korea Institute of Science and Technology, Brain Research Institute, Seoul, Korea, Republic of, [3]University of Bari Aldo Moro, Department Of Pharmacy-drug Sciences, Bari, Italy

Aims: Tauopathies manifest as progressive neuronal cell loss and cognitive decline caused by the accumulation of hyperphosphorylated tau. Recently, we identified the serotonin receptor 7 (5-HT7R) as a novel target in the treatment of tauopathies. We demonstrated that the neuroleptic drug amisulpride efficiently blocks the 5-HT7R constitutive activity and demonstrated its therapeutic effects on various aspects of tau pathology, e.g., phosphorylation, aggregation and cognition (Jahreis et al., Alzheimer's & dementia, 2023). However, amisulpride treatment is associated with dopamine receptor-related extrapyramidal side effects. Here, we aim to improve the therapeutic potential of amisulpride while minimizing its adverse side effects. Since the (R)-enantiomer of amisulpride has a higher affinity for 5-HT7R than for dopamine receptors, we investigated its therapeutic potency compared to the (S)-enantiomer.
Methods: Therapeutic effects on tau pathology were investigated in different cellular models of tauopathy including neuroblastoma cells overexpressing the disease-associated mutant tau[R406W] and the tau aggregation cell line HEK tau-BiFC using biochemical and microscopic approaches. Furthermore, transgenic tau[P301L]-BiFC mice were intraperitoneally treated with the racemic amisulpride and its enantiomers. Effects on cognition and motor side effects were assessed with behavioral experiments followed by tissue analysis to examine tau pathology after treatment.
Results: The (R)-enantiomer of amisulpride ameliorates tau pathology *in vitro* to the same extent as amisulpride, whereas (S)-amisulpride shows no beneficial effects. In the transgenic mouse model, both, (R)- and (S)-amisulpride have a pro-cognitive effect. However, we observe different effects of the enantiomers on locomotor activity. While mice treated with amisulpride and (S)-amisulpride show reduced activity, (R)-amisulpride-treated animals exhibit fewer dopaminergic side effects.
Conclusions: (R)-amisulpride shows an improved safety profile, highlighting the potential for further chemical refinement to increase 5-HT7R affinity and thereby enhance drug efficacy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0776 / #1368

Poster Topic: *Theme B: Taupathies / B02.d. Therapeutic Targets, Mechanisms for Treatment: Neurotransmitters & receptor-based*

LEAD PHENOXYTACRINE DERIVATIVE AS NOVEL NEUROPROTECTIVE COMPOUND IN VIVO

POSTERS: B02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: NEUROTRANSMITTERS & RECEPTOR-BASED

Ondrej Soukup[1], Anna Misiachna[2], Marketa Chvojkova[3], Jan Korabecny[1], Karel Vales[3], Martin Horak[2]
[1]University Hospital Hradec Králové, Biomedical Research Center, Hradec Králové, Czech Republic, [2]Czech Academy of Sciences, Institute Of Experimental Medicine, Prague, Czech Republic, [3]National Institute of Mental Health, Experimental Neurobiology, Klecany, Czech Republic

Aims: The aim of our study was to prepare a series of compounds derived from the hit compound 7-FEOTA and investigate its biological properties rising from their dual action. After assessing in vitro affinities for all 30 compounds within the series, we applied a selection *in vitro/in vivo* process, where the most promising compounds was highlighted, in particular by favorable behavioral and neuroprotective effect *in vivo* using various models.
Methods: In vitro evaluation done by Ellman´s method and patch-clamp for block of acetylcholinesterase and NMDA receptors respectively. Rat wistar model was used to evaluate pharmacokinetics and acute toxicity. Behavioral effects was investigated using MK-801 in the open field test, Morris water maze and prepulse inhibition. Neuroprotection was evaluated using NMDA-induced model of hippocampal lession
Results: A series of 30 compounds derived from 7-phenoxytacrine was evaluated the inhibitory potency towards acetylcholinesterase and hGluN1/hGluN2B receptor. We have selected.**I-52, III-52 and III-56** as the most effective NMDA-blockers and **II-52** as the compound with dual effect. After evaluating BBB penetration and acute toxicity in vivo we further selected **I-52** and **II--52** and performed behavioral tasks. Applying open field assessment and PPI the results indicate that unlike MK-801, the compounds **I-52** and **II-52** at selected doses (2 and 5 mg/kg, respectively) possess low risk of serious behavioral side effects of NMDA receptor antagonists. Furthermore, **I-52** (2 mg/kg) but not **II-52** (5 mg/kg) mitigated the scopolamine-induced cognitive deficit. Finally, NMDA-induced session experiment showed the neuroprotective effect of **I-52** against the neurodegeneration.
Conclusions: We have developed a lead compounds **I-52** 7-(2-methoxyphenoxy)-1*H*,2*H*,3*H*-cyclopenta[*b*]quinoline-9-amine hydrochloride) showing neuroprotective effect and no side effect in vivo typical for the class of NMDA antagonists. The mechanism of action involves the interaction with NMDA receptors with uncertain contribution of AChE.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0777 / #2613

Poster Topic: *Theme B: Taupathies / B02.f. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, NFT, misfolding, chaperones*

DEVELOPMENT OF ROBUST IPSC-BASED A-SYNUCLEIN, TAU AND TDP-43 AGGREGATION PATHOLOGY IN VITRO MODELS FOR DRUG DISCOVERY

POSTERS: B02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES

Chiara Formica, Jessica Koepke, Isabel Onofre, Carola Van Berkel, Tatjana Wüst, Leo Smit, Joyson Dcosta, Kimberley Riegman, Benoit Samson-Couterie, Shushant Jain
Ncardia, Discovery Technologies, Leiden, Netherlands

Aims: Proteinopathies are a group of diseases characterized by the accumulation of specific proteins within the brain. Among the most notable examples of proteinopathies are Alzheimer's disease, Parkinson's Disease (PD) and Amyotrophic lateral sclerosis (ALS). Ncardia has developed *in vitro* disease pathology models for synucleinopathies (e.g PD), Tauopathies (TAU aggregation) and ALS (TDP-43 aggregation) using iPSC-derived neuronal cell models. These robust *in vitro* assays, developed in physiologically relevant human models, are amenable to various therapeutic to support all stages of the drug discovery process (i.e. hit ID, hit-2-lead and lead optimization).
Methods: Ncardia used iPSC-derived cortical neurons (iPSC-CN) treated with SNCA and Tau recombinant pre-formed fibrils (PFFs) to model disease relevant phenotypes of synucleinopathies and Tauopathies. Using high content imaging, aggregate localization, size, counts and intensity as well as co-localization with phosphorylated forms (pS129 α-syn and pTau (AT8)) were calculated. To model ALS, Ncardia used TDP-43 mutant iPSC-derived motor neurons (iPSC-MN) to quantify mis-localization and aggregation of TDP-43, as well as the human specific mis-splicing of STMN2. Additionally, Ncardia determined the electrophysiological deficits of the iPSC-MN in healthy and disease conditions.
Results: Modulators of protein degradation, both inhibitors and activators, were able to significantly increase or decrease (respectively) the counts and size of SNCA and counts of pS129 α-syn in a concentration-dependent manner. Stressor-treated TDP-43 mutant and wild type iPSC-MN showed disease-specific mis-localization of TDP-43 to the cytoplasm, aggregation of TDP-43, reduction of STMN2 and appearance of the truncated variant.
Conclusions: Ncardia developed three custom assays for the aggregation of α-synuclein, Tau and TDP-43 using human iPSC-derived neuronal cell models, providing clinically relevant readouts to support drug developers at various stages of drug development while reducing the use of laboratory animals.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0778 / #2010

Poster Topic: *Theme B: Taupathies / B02.f. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, NFT, misfolding, chaperones*

TAU CONFORMATION MONOCLONAL ANTIBODIES MODULATE TOXIC TAU OLIGOMERS IN VITRO AND EX VIVO

POSTERS: B02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES

Md. Anzarul Haque, Nemil Bhatt, Rakez Kayed
University of Texas Medical Branch Galveston, Department Of Neurology, Galveston, United States of America

Aims: Aims: The pathological aggregation and accumulation of toxic tau is a common feature various neurodegenerative diseases that are collectively known as tauopathies. Tau oligomers are thought to be the major neurotoxic species in AD, but there is currently a gap in knowledge concerning standardized methods for isolating and biochemical characterization of tau oligomers.
Methods: Methods: Biochemical and biophysical techniques were used to characterize recombinant tau oligomers and brain-derived tau oligomers from Alzheimer's disease in the presence and absence of antibodies tau oligomer specific antibody (TOMA1) and toxic tau conformational monoclonal antibody (TTCM1), Montalbano, M. at. Al. 2023 and Carranza, D. L at. al. 2015. I used Isothermal calorimetry for affinity characterization between tau oligomers and antibodies. Propagation and toxicity of tau oligomers were performed using cell-based antibody neutralization assays in cell models.
Results: Results: TOMA 1 and TTCM1 have strong affinity with tau oligomers and modulate its aggregation state resulting in the formation of tau structures with decreased toxicity and seeding behavior in human neuroblastoma SH-SY5Y cell line and primary cortical neuron cultures.
Conclusions: Conclusion: These results provide novel insights into tau confirmational and toxicity, which can be modulated using high affinity conformational antibodies. Using conformational antibodies could be a powerful therapeutic strategy that advances the diagnostic field for the detection of toxic tau oligomers and early diagnosis for tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0779 / #122

Poster Topic: *Theme B: Taupathies / B02.f. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, NFT, misfolding, chaperones*

TAU LIQUID-LIQUID PHASE SEPARATION IS REGULATED BY THE CALCIUM-BINDING S100B CHAPERONE

POSTERS: B02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES

Guilherme Moreira, Cláudio Gomes
Faculdade de Ciências da Universidade de Lisboa, Bioisi - Biosystems & Integrative Sciences Institute, Lisboa, Portugal

Aims: The phenomenon of liquid-liquid phase separation (LLPS) involving tau is increasingly acknowledged as a contributory process in the onset of tau aggregation and the generation of pathogenic conformers within Alzheimer's disease (AD). Neuroinflammation accompanies tau pathology, with late-stage astrocyte-released alarmin exacerbating the condition, while early inflammatory responses encompass protective functions. This applies to the Ca^{2+}-binding protein S100B, which we recently implicated as a proteostasis-regulator that inhibits amyloid-β (Cristóvão et al. 2018 Sci Adv) and tau aggregation/seeding (Moreira et al. 2021 Nat Commun). These findings suggest a broad holdase-type chaperone function for S100B in counteracting the malformation of protein structures. Our study aims to elucidate S100B's role in tau LLPS.
Methods: PEG-induced tau LLPS was followed by spectroscopy measurements of light absorbance (400nm) and tau fluorescently labelled. Co-localization of S100B within tau droplets was achieved using fluorescence-labelled proteins and FLIM-FRET. Evaluation of droplet fluidic characteristics encompassed fluorescence recovery after photobleaching (FRAP) and observation of fusion events.
Results: Phase diagrams indicate significant suppression of tau droplet formation by Ca^{2+}-S100B, preserving droplet liquid properties. The introduction of Ca^{2+} to PEG-induced LLPS with apo-S100B promptly reduces tau droplet levels, highlighting the dynamic, calcium-triggered nature of Ca^{2+}-S100B's action. Likewise, S100B effectively halts PEG-free Zn^{2+}-induced tau LLPS due to its combined Zn^{2+}-buffering and tau-interaction capabilities.
Conclusions: Our results establish S100B as a calcium-dependent suppressor of tau LLPS. Collectively, these findings suggest that S100B, functioning as a chaperone, regulates the formation of various pathological conformers and phase-separated systems, strengthening its pivotal role as a proteostasis regulator in early neurodegeneration. Acknowledgments: EU for funding Twinning Grant EU-TWIN2PIPSA/GA101079147, FCT/MCTES (Portugal) for funding UIDB/04046/2020 and UID/MULTI/04046/2020 (BioISI) and PhD grant 2020.06443.BD (GGM) and Agilebio for funding LabCollector Scientific Award 2021 (CMG).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0780 / #1290

Poster Topic: *Theme B: Taupathies / B02.g. Therapeutic Targets, Mechanisms for Treatment: Gene and RNAi therapy*

RNAI KNOCKDOWN OF MICROTUBULE-ASSOCIATED PROTEIN TAU AS A THERAPEUTIC STRATEGY FOR TAUOPATHIES

POSTERS: B02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE AND RNAI THERAPY

Jeffery Haines[1], Jon Farley[2], Sean Gannon[1], Kara Crowley[1], Mark Schlegel[2], Adam Castoreno[2], Anna Bisbe[2], Ivan Zlatev[2], Jeff Rollins[2], Diana Cha[2], Bret Bostwick[2], Andreja Avbersek[1], Kirk Brown[2], Lynn Macdonald[1], Min Gao[1], Matthew Anderson[1]
[1]Regeneron Pharmaceuticals Inc, Neuroscience, Tarrytown, United States of America, [2]Alnylam Pharmaceuticals, Biology, Cambridge, United States of America

Aims: The hyperphosphorylation and subsequent aggregation of the microtubule-associated protein Tau (encoded by the *MAPT* gene) is one of the major histopathological hallmarks of numerous tauopathies, including Alzheimer's disease and progressive supranuclear palsy. The intracellular accumulation of aggregated Tau is associated with neuronal loss and disease progression in tauopathies. There is a high-unmet need to identify strategies to target the intracellular accumulation of Tau aggregates with the aim of slowing tauopathy progression.
Methods: Using Alnylam's lipophilic C16-conjugated siRNA for CNS delivery, we identified potent molecules targeting the *MAPT* gene both in vitro and in mice carrying multiple copies of a transgene with a prion promoter driving human *MAPT* with human tauopathy-inducing mutation P301S.
Results: P301S mice treated with a single intracerebroventricular injection of Tau siRNA at eight months of age, had a sustainable decrease in *MAPT* mRNA and soluble Tau protein for three months following siRNA treatment (reduced ~83% and ~59%, respectively). siRNA treatment also prevented the progressive decrease in body weight and abrogated axonal damage, evidenced by decreased neurofilament light (NFL) chain in plasma and cerebrospinal fluid of eleven-month-old mice. Importantly, immunohistochemical analysis of misfolded Tau *in vivo* and HEK293-4RD-CFP/YFP Tau aggregate biosensor assay testing *in vitro* revealed a ~97% decrease of Tau aggregates in the eleven-month-old mice, suggesting there exists a yet-to-be identified mechanism of Tau fibril clearance. Furthermore, in a 16-week non-human primate study, we observed robust target engagement resulting in sustained reduction of *MAPT* transcript and Tau protein in brain tissue and cerebrospinal fluid.
Conclusions: Together, these results suggest an RNAi therapeutics approach targeting of *MAPT* mRNA may be sufficient to improve multiple parameters of tauopathy disease progression and a provide a compelling rationale for further development of Tau-lowering strategies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0781 / #1074

Poster Topic: *Theme B: Taupathies / B02.f. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, NFT, misfolding, chaperones*

HETEROTYPIC INTERACTIONS DRIVE ANTI-AGGREGATION ACTIVITY OF NANOBODIES AGAINST S100B ON TAU AGGREGATION

POSTERS: B02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES

Margarida Simões[1], Joana Cristóvão[1], Els Pardon[2], Jan Steyaert[2], Cláudio Gomes[1]
[1]Faculdade de Ciencias da Universidade de Lisboa, Bioisi - Biosystems & Integrative Sciences Institute, Lisboa, Portugal, [2]Vrije Universiteit Brussel, Vib-vub Center For Structural Biology, Brussels, Belgium

Aims: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the World Health Organization as a public health priority. The pathology is characterized by the aggregation of amyloid-β (Aβ) and Tau protein into amyloid-β plaques and neurofibrillary tangles, respectively. Neuroinflammation is also implicated in AD and is responsible for the secretion of alarmins, which include the S100B protein. S100B is highly studied in the context of AD, and it's known for its dual function as a detrimental pro-inflammatory mediator and a beneficial anti-aggregation chaperone over Aβ and tau, making it an amenable drug target. Since there is still no cure for AD and is highly attractive to target chaperones with an already reported anti-aggregation activity, a library of single-domain antibodies (or nanobodies) targeting S100B was developed to potentiate S100B chaperone activity and modulate tau aggregation.
Methods: Here, we employed ThT-monitored kinetics of heparin-induced K18 aggregation to study the effect of nanobodies alone and in combination with S100B on K18 aggregation. Moreover, we performed mechanistic analysis to determine which step of the aggregation reaction are targeted by the nanobodies.
Results: Several nanobodies potentiated S100B inhibitory effect over K18 (Tau244-372), possibly by harnessing S100B in a more competent conformation to bind K18. Surprisingly, control experiments revealed that some nanobodies alone significantly inhibit K18 aggregation even at sub-stoichiometric ratios. This striking observation is discussed in the context of possible heterotypic interactions between the nanobody CDR3 region and Tau/K18. Further, mechanistic analysis demonstrates that different nanobodies target multiple steps of K18 fibrillation.
Conclusions: These findings uncover the therapeutic potential of anti-S100B nanobodies, which can be used as modulators of K18 aggregation or as activators of S100B chaperone activity. Funded by EU-TWIN2PIPSA/GA101079147 and FCT-Portugal BD/11023/2022 (MCS)/UID/MULTI/04046/2020 (BioISI).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0782 / #2747

Poster Topic: *Theme B: Taupathies / B02.g. Therapeutic Targets, Mechanisms for Treatment: Gene and RNAi therapy*

SCREENING OF NOVEL ASOS AGAINST TAU PROTEIN

POSTERS: B02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE AND RNAI THERAPY

Carlos Campos-Marques[1], Bruno Mdc Godinho[2], Jonathan K Watts[2], Nuno Sousa[3], Ioannis Sotiropoulos[4], Joana Silva[3]
[1]Life and Health Sciences Research Institute, School Of Medicina, University Of Minho, Braga, Portugal, [2]University of Massachusetts Medical School, Rna Therapeutics Institute, Worcester, United States of America, [3]Life and Health Sciences Research Institute, School Of Medicine, University Of Minho, Braga, Portugal, [4]NCSR Demokritos, Institute Of Biosciences And Applications, Athens, Greece

Aims: Considering recent evidence from Alzheimer's disease (AD) field about the essential role of Tau in AD brain pathology, we aimed to screen novel antisense oligonucleotides (ASOs) designed for lowering total Tau or 4R-Tau levels, addressing these objectives: i.Design, generate and test *in vitro* novel ASOs against mouse or human Tau, using cell lines; ii. Select and test the most efficient ASOs in primary neurons; and iii.Test the efficiency of the selected ASOs in mouse brain.
Methods: This project tested several ASOs with different chemical modifications against Tau protein in cell lines and primary neurons, identifying novel ASOs with high efficiency reducing Tau levels or 4R-Tau, measured by qRT-PCR, Western blot and immunofluorescence. After selecting the most potent ASOs from *in vitro* studies, we performed a pilot study to assess the efficiency of ASOs *in vivo*.
Results: Firstly, mouse-Tau ASOs and human-Tau ASOs were tested on mouse and human neuroblastoma cells, respectively. After qRT-PCR analysis, 13 of each were re-tested for protein level assessment, through Western blot. Next, the 4 most efficient mouse-Tau and human-Tau ASOs were tested in primary neurons. Their efficiency on reducing Tau levels was confirmed, and we evaluated their impact on neuronal morphology, revealing significant alterations in complexity. Finally, mouse-Tau ASOs were tested in a pilot in vivo study using wild-type mice, whereas human Tau-ASOs were tested in THY-Tau22 mice, revealing significant reductions in both mRNA and protein levels of Tau.
Conclusions: Altogether, these data provide the first *in vitro* and *in vivo* confirmation of the efficiency of novel ASOs against Tau, that can further support future studies focusing on ASOs as an innovative RNA-based therapeutic approach against AD, Down Syndrome, and other Tau-related brain pathologies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0783 / #2852

Poster Topic: *Theme B: Taupathies / B02.g. Therapeutic Targets, Mechanisms for Treatment: Gene and RNAi therapy*

INTRAVENOUS ADMINISTRATION OF BBB-PENETRANT AAV CONTAINING PRIMARY ARTIFICIAL MICRORNA TARGETING TAU REDUCES TAU BROADLY AND ROBUSTLY IN HTAU MOUSE BRAIN

POSTERS: B02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE AND RNAI THERAPY

Wencheng Liu[1], Hechen Bao[1], Shiron Lee[1], Cansu Colpan[2], Elisabeth Knoll[2], Ching Lien Fang[1], Barbara Bueno[1], Gretchen Rivera[2], Maneesha Paranjpe[1], Brian Ezell[2], Kyle Grant[3], Dinah Sah[1], Todd Carter[1]
[1]Voyager Therapeutics, Neuroscience, Cambridge, United States of America, [2]Voyager Therapeutics, Vector Engineering, Cambridge, United States of America, [3]Voyager Therapeutics, Vector Production, Cambridge, United States of America

Aims: Progression and spread of tau pathology in the brain correlates very well with cognitive decline in Alzheimer's disease (AD). Reduction of tau is being pursued as a promising therapeutic approach. Lowering tau with anti-sense oligonucleotides (ASOs) has been shown to reduce tau and tau pathology in preclinical and clinical studies; however, this approach requires repeated administration of the ASO either intra-ventricularly or intrathecally. To evaluate the potential of intravenous (IV) administration of AAV to provide therapeutically relevant levels of tau knockdown broadly through the brain with one-time administration, we have evaluated the use of a blood-brain barrier (BBB)-penetrant capsid containing a primary artificial microRNA (pri-amiRNA) specifically targeting tau mRNA.
Methods: 1. Candidate siRNA sequences were screened in silico and in vitro in multiple cell lines to identify siRNAs that lower tau mRNA for subsequent AAV vectorization into proprietary pri-amiRNA backbones. 2. A pri-amiRNA targeting tau mRNA, vectorized with a BBB-penetrant capsid (9P39) was tested using IV administration in hTau transgenic mice, with subsequent quantitation of vector genome and tau mRNA levels.
Results: At 4 weeks post-dosing with this AAV9P39.tau pri-amiRNA in hTau mice, we observed a dose-dependent increase in vector genome levels, concomitant with a dose-dependent decrease in tau mRNA levels, in multiple brain regions. Tau mRNA reductions ranged from 70% to 90% relative to the vehicle control group.
Conclusions: These studies demonstrate that robust lowering of tau in hTau mice was achieved by treatment of mice with an AAV.pri-amiRNA specifically targeting tau mRNA. These encouraging results suggest that the combination of a potent pri-amiRNA targeting tau mRNA together with IV dosing of a BBB-penetrant capsid could be a useful one-time treatment for AD and other tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0784 / #844

Poster Topic: *Theme B: Taupathies / B02.h. Therapeutic Targets, Mechanisms for Treatment: Microglia*

CSF1R INHIBITION INDUCES A SEX-SPECIFIC RESILIENT MICROGLIAL PHENOTYPE AND EXTENDS THE LIFESPAN OF TAUOPATHY MICE

POSTERS: B02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Noah Johnson[1,2], Peng Yuan[1,3], Erika Castillo[1], T. Peter Lopez[1], Weizhou Yue[1], Annalise Bond[1], Brianna M. Rivera[1], Miranda C. Sullivan[1], Masakazu Hirouchi[1,4], Kurt Giles[1], Atsushi Aoyagi[1,4], Carlo Condello[1]
[1]University of California, San Francisco, Institute For Neurodegenerative Diseases, Department Of Neurology, Ucsf Weill Institute For Neurosciences, San Francisco, United States of America, [2]University of Colorado Anschutz Medical Campus, University Of Colorado Alzheimer's And Cognition Center, Linda Crnic Institute For Down Syndrome Research, Department Of Neurology, Aurora, United States of America, [3]Fudan University, Department Of Rehabilitation Medicine, Huashan Hospital, State Key Laboratory Of Medical Neurobiology, Institute For Translational Brain Research, Moe Frontiers Center For Brain Science, Shanghai, China, [4]Daiichi Sankyo Co., Ltd., Cns Drug Development, Tokyo, Japan

Aims: Microglia are central to pathogenesis in many neurological conditions and their depletion is one therapeutic strategy. However, drugs targeting colony-stimulating factor-1 receptor (CSF1R) to block microglial proliferation in preclinical disease models have shown mixed outcomes, thus the therapeutic potential of this approach remains unclear. Given the dynamic nature and complexity of microglial activation, the timing of CSF1R inhibition in tauopathy and its translational relevance is still an open question. Thus, the goal of our study was to define a therapeutic window that not only reduced pathological markers, but also led to functional improvement.
Methods: Transgenic B6-Tg(Thy1-MAPT*P301S)2541 mice express the 0N4R isoform of human tau with the P301S mutation. To deplete microglia, mice were dosed with CSF1R inhibitors PLX3397 or PLX5622 in three different dosing paradigms: acute (2−4 months old), chronic (2−7 months old), and terminal (2 months old until death).
Results: CSF1R inhibitors given by multiple dosing paradigms caused a sex-independent reduction in pathogenic tau and reversion of non-microglial gene expression patterns toward a normal wild type signature. Despite greater drug exposure in male mice, only female mice had functional rescue and extended survival. A dose-dependent upregulation of immediate early genes and neurotransmitter dysregulation were observed in the brains of male mice only, indicating that excitotoxicity may preclude functional benefits. Drug-resilient microglia in male mice exhibited morphological and gene expression patterns consistent with increased neuroinflammatory signaling, suggesting a mechanistic basis for sex-specific excitotoxicity.
Conclusions: Complete microglial ablation is neither required nor desirable for neuroprotection and therapeutics targeting microglia must consider sex-dependent effects. Therapeutic modulation of microglial activation by CSF1R inhibitors is a potential approach to treating human tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0785 / #2616

Poster Topic: *Theme B: Taupathies / B02.i. Therapeutic Targets, Mechanisms for Treatment: Other*

DESIGN AND APPLICATION OF A TAU SEED AMPLIFICATION ASSAY AS A NOVEL METHOD FOR THE SCREENING OF SMALL MOLECULE AGGREGATION INHIBITORS

POSTERS: B02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Damian Gorski[1], Fei Wang[2], Tyler Allison[3], Haley Evans[1], Carla Barria[3], Victor Banerjee[4], Danielle Harrison[2], Susana Aznar[5], Jonas Folke[5], Claudio Soto[2]
[1]University of Texas Health Science Center at Houston, Department Of Neurology, Houston, United States of America, [2]University of Texas Health Science Center at Houston, Neurology, Houston, United States of America, [3]UTHealth Science Center at Houston, Neurology, Houston, United States of America, [4]University of Texas Health Science Center at Houston, Neurology, HOUSTON, United States of America, [5]University Hospital Bispebjerg-Frederiksberg, Centre For Neuroscience And Stereology, Copenhagen, Denmark

Aims: Alzheimer's disease (AD) and related tauopathies are characterized by the aberrant accumulation of tau protein aggregates within the brain, resulting in neurodegeneration. Recent research has highlighted the prion-like propagation of disease-associated tau, where pathological forms of tau corrupt normal tau proteins, instigating their misfolding and integration into amyloid fibrils. With no cure currently available, inhibiting tau aggregation offers a promising therapeutic approach.
Methods: The experimental conditions to obtain a highly reproducible and specific tau seed amplification assay (Tau-SAA) were optimized using brain homogenate (BH) from patients affected by AD and other tauopathies. Dilutions of BH between 10^{-4} and 10^{-9} for an average of 10 specimens per group. Tau-SAA signal was read using thioflavinT fluorescence in the presence or absence of known inhibitors of tau aggregation.
Results: Tau-SAA demonstrates remarkable sensitivity, capable of detecting seeding activity at dilutions as extreme as 100 million-fold from AD-afflicted brain samples and displays no seeding activity when exposed to healthy human control brain tissue or specimens from other neurological conditions. We tested a range of established anti-aggregation compounds, distinguishing those with the ability to impede tau aggregation induced by AD brain. Further, we explored the possibility of repurposing drugs by screening a commercially available drug library and identify compounds with the capacity to counteract tau aggregation.
Conclusions: Tau-SAA is a robust and versatile method for the detection of tau aggregates. Additionally, it serves as an effective screening platform for the discovery of small molecules that can inhibit tau seeding when challenged with biologically relevant tau seeds sourced from AD-affected brains. Our findings suggest that Tau-PMCA is a robust technique for both detection of tau aggregates in biological samples and for identification of small molecules able to inhibit tau seeding.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0786 / #205

Poster Topic: *Theme B: Taupathies / B02.i. Therapeutic Targets, Mechanisms for Treatment: Other*

POTENTIAL APPLICATION OF APT20TTMG AS A THERAPY FOR ALZHEIMER´S DISEASE

POSTERS: B02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Rafael Bottos[1], Camila Zimmer[1], Vanessa Sinatti[1], Ericks Soares[1], Britt Poppe[2], Adrien Wiart[2], Xue Chua[2], Ronan Silva[2], Michael Rafii[3], Luc Buee[4], Margaret Magdesian[2], Caio Leal[1]
[1]Aptah Bio Inc., Aptah Bio Inc., San Carlos, United States of America, [2]Ananda Devices Inc., Ananda Devices Inc., Laval, Canada, [3]Alzheimer's Therapeutic Research Institute, University of Southern California, Clinical Neurology, San Diego, United States of America, [4]Lille Neuroscience and Cognition Center, University of Lille, Alzheimer & Tauopathies, Lille, France

Aims: Alzheimer's disease (AD) presents a dysfunction in the U1 small nuclear ribonucleoprotein (snRNP) along with RNA splicing deficiency and mislocalization, which causes cell cycle re-entry and neuronal death. Considering that this dysfunction may precede protein aggregation and enhance spliceosome dysfunction, we aimed to analyze the effects of APT20TTMG, a synthetic single stranded cDNA, in human induced pluripotent stem cells (hiPSCs) derived neurons from healthy (HDC) and AD (ADC) donors and in the senescence-accelerated mouse prone 8 (SAMP8) model.
Methods: Binding of APT20TTMG to U1 snRNP complex and pre-mRNAs was analyzed through protein and qRT-PCR immunoprecipitation, in SK-N-SH neuroblastoma cells. Following treatment with five concentrations of APT20TTMG, mitochondrial activity, glutamate release, apoptosis, morphology, Tau levels, and enrichment analysis of differentially expressed genes (DEGs) were evaluated in hiPSC-derived neurons. Immunofluorescence for amyloid-β (Aβ), total Tau, pTau, and U1-70K was analyzed in cortex and hippocampus of SAMP8 mice, following a 42-day treatment with one concentration of APT20TTMG, via i.c.v.
Results: APT20TTMG selectively bound to U1-70K and U1-C proteins of the U1 complex, U1 snRNA, and Tau and GAPDH pre-mRNAs. Treatment with APT20TTMG did not change mitochondrial activity, glutamate release, or apoptosis in both HDC and ADC neurons. However, it rescued the morphology of ADC neurons, with fiber breadth and branching levels similar to HDC neurons. It also specifically decreased Tau levels in ADC neurons and led to an enrichment of DEGs related to neurogenesis and neuron differentiation. In the SAMP8 model, treatment decreased Aβ in cortex, insoluble pTau in hippocampus, and U1-70K in both cortex and hippocampus.
Conclusions: APT20TTMG is safe to neurons, with significant effects in preventing neurodegeneration and improving axonal functions, suggesting a novel therapeutic approach for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0787 / #2176

Poster Topic: *Theme B: Taupathies / B02.i. Therapeutic Targets, Mechanisms for Treatment: Other*

ND523: A NOVEL PROTEIN-PROTEIN NRF2 INDUCER WITH ANTI-NEUROINFLAMMATORY EFFECTS

POSTERS: B02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Manuela G. Lopez[1], Eric Del Sastre[1], Cristina Fernández-Mendívil[1], Lucia Viqueira[1], Rafael Leon[2], Maria Isabel Rodriguez Franco[2]
[1]Universidad Autonoma de Madrid, Pharmacology, Madrid, Spain, [2]Consejo Superior de Investigaciones Cientificas, Instituto De Química Médica, Madrid, Spain

Aims: Nuclear factor erythroid derived 2-like 2 (NRF2) is a transcription factor that is being proposed as a target for neurodegenerative diseases as it regulates a wide array of genes implicated in regulating cellular redox status and inflammation. Electrophilic NRF2 inducers are highly reactive molecules that can cause off-target effects. Therefore, NRF2-KEAP1 protein-protein inhibitors (PPI) could be a safer alternative. After a drug discovery program, we have identified ND525 as lead compound. Here we studied its mechanism of action and its anti-neuroinflammatory effects.
Methods: The NRF2 inducing mechanism has been evaluated in AREc32 cells, by superficial plasmon resonance, GSH conjugation and lC-IT-MS analysis, and by using WT and NRF2-KO MEFs. The potential anti-neuroinflammatory effect has been evaluated using LPS *in vitro* (BV2 cells and primary glial cultures) and *in vivo*. Sickness behaviour in vivo and cytokines levels were measured by qPCR and multiplex ELISA . Primary cortial neurons transfected with AAV-hTauP301L were used as an *in vitro* tauopathy model.
Results: ND523 is a non-electrophilic compound that induces NRF2 by inhibiting NRF2/KEAP1 interaction. It showed a good anti-neuroinflammatory profile in a microglial murine cell line and in rat primary glial cell cultures; these effects were lost in NRF2 KO cells. The anti-neuroinflammatory effects were corroborated *in vivo* as shown by a reduction of cytokines 4 and 24 h post LPS-injection, reduction in brain microgliosis and improvements in locomotion and cognitive decline. Peliminary data show that ND523 can reduce tauopathy *in vitro* evaluated as a redcution of AT8 staining.
Conclusions: ND523 is a first in class protein-protein inhibitor of NRF2/KEAP1 with potential therapeutic interest in neurodegenerative diseases with neuroinflammation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0788 / #349

Poster Topic: *Theme B: Taupathies / B02.h. Therapeutic Targets, Mechanisms for Treatment: Microglia*

ALZHEIMER'S DISEASE AND TAUOPATHIES: DEVELOPPEMENT OF NEW "THERAGNOSTIC" MOLECULES

POSTERS: B02.H. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Cyann Larralde[1], Lucas Pradeau[1,2], Léo Le Tareau[1,3], Emma Bernard[4], Stacy Alves[5], Frédéric Percevault[1], Sandrine Huclier[6,7], Cyrille Garnier[1,5]
[1]Univ Rennes, Inserm, EHESP, Irset (institut De Recherche En Santé, Environnement Et Travail) – Umr_s 1085, Rennes, France, [2]Institut Pasteur, Polarité Cellulaire, Migration Et Cancer, Paris, France, [3]Centre de Recherche en Biologie de Montpellier (CRBM), Université de Montpellier, Cnrs Umr 5237, Montpellier, France, [4]Univ Rennnes, Inserm, EHESP, Irset (institut De Recherche En Santé, Environnement Et Travail) – Umr_s 1085, Rennes, France, [5]MMDM, University of Montpellier, Ephe, Inserm U 1198, Montpellier, France, [6]Ecole des Mines de Nantes/CNRS/IN2P23/Université de Nantes, Laboratoire De Subatech, Umr 6457, Nantes Cedex, France, [7]ARRONAX GIP, Laboratoire De Subatech, Umr 6457, Nantes Cedex, France

Aims: Our aim is to develop "theranostic" molecules usable in the Alzheimer's disease and Tauopathies. These molecules will i) inhibit Tau fibrillation targeting its nucleation process and ii) be used as a vector coupled to a PET radionuclide in order to perform positron emission tomography (PET) imaging for an early detection of amyloid deposits in brain.
Methods: Chosen molecules are peptides composed of natural "L" amino acids that have the same composition than Tau PHF6 peptide. These peptides have been designed and selected for their therapeutic potential. These peptides have been tested on pathologic hTau.P301S mouse strain and on brain cellular models. Their structures will be modified for optimizing their bioavailability and their potential therapeutic effect.
Results: About fifty peptides have been classified in three groups that are i) amyloid, ii) aggregative and iii) neither amyloid nor aggregative. Peptides belonging to the latter group have been pre-selected and their inhibitory activity was tested on PHF6 *in vitro* self-assembly model. Most of them led to inhibition of the fibrillation rate ranging between 20 and 90%. Peptides exhibiting the highest inhibition were then called "leaders" and were further evaluated. Notably, we demonstrated that selected "leaders" had no effects on SH-SY5Y neuroblastoma cell line growth. Among the leaders, two were chosen for being evaluated as molecular probes for PET imaging. Probes tested on SH-SY5Y cell line had no effects on SH-SY5Y neuroblastoma cell line growth. They will be further tested on our animal model hTau.P301S.
Conclusions: The most promising peptides (patent WO 2023/099560) and probes exhibit the required qualities to become "theranostic" molecules for Alzheimer's disease and Tauopathies therapy and diagnostic.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0789 / #1326

Poster Topic: *Theme B: Taupathies / B02.i. Therapeutic Targets, Mechanisms for Treatment: Other*

FRATERNIN-LIKE PEPTIDES AND THEIR NEUROTOCITY EFFECTS IN PARKINSON'S DISEASE

POSTERS: B02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Leticia Germino Veras[1], Andréia Mayer[2], Henrique Amaral[2], Danilo De Oliveira[2], Gabriel Campos[2], Adolfo Carlos De Souza[2], Anamélia Bocca[2], Solange Rego[2], Raffael De Castro[2], Márcia Renata Mortari[2]
[1]Universidade de Brasília, Intitite Of Biological Sciences Of Unb, Brasilia, Brazil, [2]University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil

Aims: Parkinson's disease (PD) is a neurodegenerative condition characterized by the progressive degeneration of dopaminergic neurons in the Substantia Nigra. With the absence of a specific PD treatment, research into novel therapeutic approaches has gained momentum. One emerging avenue of exploration involves the study of animal venoms, which have demonstrated intriguing interactions with the cardiovascular and nervous systems, opening up new possibilities for treatment development. A candidate in this quest is the natural peptide known as fraternin, sourced from the wasp venom from *Parachatergis fraternus*. To better understand its potential, three analogues—fra-24, fra-14, and fra-10—were synthesized and assessed for their neurotoxic effects using a 6-hydroxydopamine mouse model of PD. To ensure accuracy, all peptides underwent rigorous purity verification exceeding 99%.
Methods: The investigation delved into potential adverse effects, without inducing the 6-OHDA lesion, and encompassed intracerebral ventricular administration at varying doses: 10, 5, and 1 µg/animal for fra-1 and fra-14, and 20, 10, and 5 µg/animal for fra-24. Motor coordination was assessed through behavioral tests, including latency to fall on the rotarod apparatus during treatment and post-treatment temporal evaluations on the rotarod.
Results: revealed that fra-24, administered at 20 µg/animal, exhibited neuromuscular toxicity compared to the SHAM group on the rotarod, potentially impairing motor function. Fra-14, at a dose of 10 µg/animal, induced motor incoordination, while fra-10, administered at all three doses, displayed neuromuscular toxicity, as evidenced by reduced time spent on the rotarod compared to the SHAM group.
Conclusions: Notably, neither fra-14 nor fra-10 demonstrated therapeutic effects, with only minor improvements in motor behavior observed in lesioned groups. Fra-24, at a dose of 20 µg/animal, did not significantly impact animals' motor coordination but displayed toxicity potential, warranting further investigation into its safety and efficacy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0790 / #666

Poster Topic: *Theme B: Taupathies / B02.i. Therapeutic Targets, Mechanisms for Treatment: Other*

NON-INVASIVE PHOTO-OXYGENATION REDUCES INTRACELLULAR TAU AMYLOID IN THE BRAIN OF TAU MODEL MICE

POSTERS: B02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Yukiko Hori[1], Takanobu Suzuki[1], Taka Sawazaki[2], Makoto Higuchi[3], Youhei Sohma[2], Motomu Kanai[4], Taisuke Tomita[1]
[1]Graduate School of Pharmaceutical Sciences, The University of Tokyo, Laboratory Of Neuropathology And Neuroscience, Tokyo, Japan, [2]School of Pharmaceutical Sciences, Wakayama Medical University, Department Of Medicinal Chemistry, Wakayama, Japan, [3]National Institutes for Quantum Science and Technology, Department Of Functional Brain Imaging, Chiba, Japan, [4]Graduate School of Pharmaceutical Sciences, The University of Tokyo, Laboratory Of Synthetic Organic Chemistry, Tokyo, Japan

Aims: Tauopathies, including Frontotemporal dementia and Corticobasal degeneration, are a group of neurodegenerative diseases characterized by the intracellular deposition of tau amyloid. Since tau amyloid is associated with the onset, the efficient clearance of tau amyloid is one of the therapeutic strategies for tauopathies. We have previously developed the amyloid selective *in vivo* photo-oxygenation technology for Aβ, that forms amyloid like tau, using a membrane-impermeable photocatalyst. Moreover, we showed successfully that photo-oxygenated Aβ was cleared from the brain efficiently (Ozawa *et al*., Brain, 2021), suggesting that this technology has potential as therapy. This catalyst was also capable of photo-oxygenating tau, but the effect of photo-oxygenation on intracellular tau amyloid was still unknown due to photocatalyst's membrane-impermeability.
Methods: To access the intracellular tau amyloid, we have developed a novel photocatalyst, CatO, which is permeable to blood brain barrier and cell membranes. The CatO was administered intravenously to 9 months-old tau transgenic mice, and non-invasive *in vivo* photo-oxygenation was performed by light irradiation from outside the skull.
Results: After photo-oxygenation reaction for 10 days, we found in immunohistochemistry and biological analysis that the amount of intracellular tau amyloid was significantly reduced by photo-oxygenation. Furthermore, neuronal cell death in brain was also significantly inhibited, indicating that the photo-oxygenation was able to ameliorate toxicity associated with tau accumulation.
Conclusions: In this study, we have succeeded in non-invasive *in vivo* photo-oxygenation of intracellular tau amyloid using a newly developed cell membrane-permeable photocatalyst, CatO. And we revealed the possibility that photo-oxygenation enhances the degradation of tau amyloid in brain. Clarification of its mechanisms and potential for the therapy against tauopathies are underway.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0791 / #526

Poster Topic: *Theme B: Taupathies / B02.i. Therapeutic Targets, Mechanisms for Treatment: Other*

EFFECTS OF STANDARDIZED GINKGO BILOBA EXTRACT ON BIOENERGETICS IN HUMAN IPSCS

POSTERS: B02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Imane Lejri[1,2], Anne Eckert[1,2]
[1]Neurobiology Lab for Brain Aging and Mental Health, Research Cluster, Molecular & Cognitive Neuroscience, Basel, Switzerland, [2]Universitäre Psychiatrische Kliniken, University Of Basel, Basel, Switzerland

Aims: Protective effects of standardized Ginkgo biloba extract (GBE, LI1370) has been demonstrated on energy metabolism defects in an *in vitro* Alzheimer's disease (AD) model. In this study, we investigated the effect of GBE (OM Pharma support) on bioenergetics in human IPSCs from aged donors.
Methods: First, to characterize the bioenergetics in human iPSCs from aged donors, ATP production (ATP), mitochondrial membrane potential (MMP) and reactive oxygen species (ROS) levels were measured in iPSCs from young and aged donors. Then, the effect of GBE on ATP production, MMP, ROS and mitochondrial respiration were investigated after 24h of treatment in human IPSCs from aged donors.
Results: Our findings demonstrated that in the iPSCs from aged donors, ATP and MMP levels were significantly decreased and mitochondrial ROS (DHR) and mitochondrial superoxide anion (MITOSOX) levels were significantly increased compared to those of the iPSCs from young donors. Low OCR and ECAR levels were reported in the iPSCs from aged donors compared to those from the young donors. GBE treatment (100 ug/ml) exerted significant improvement of ATP production and MMP levels, reduction of the ROS and an amelioration of the mitochondrial respiration.
Conclusions: These findings indicate that GBE seems to be able to improve significantly the age related decline in bioenergetics of the human IPSC from aged donors, through the increase of the ATP production and the improvement of the mitochondrial membrane potential, as well as the reduction of the ROS levels and the amelioration of the mitochondrial respiration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0792 / #712

Poster Topic: *Theme B: Taupathies / B02.i. Therapeutic Targets, Mechanisms for Treatment: Other*

MILD COGNITIVE IMPAIRMENT (MCI) IN PEOPLE WITH PARKINSON'S DISEASE (PD): THE NEED TO CONSIDER THE INDIVIDUAL PROFILE

POSTERS: B02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Sara Rosenblum[1], Sharon Hassin-Baer[2]
[1]University of Haifa, Occupational Therapy, Haifa, Israel, [2]Sheba Medical Centre and Tel Aviv University, Neurology, Ramat Gan, Israel

Aims: In a series of five studies focused on identifying mild cognitive impairment in Parkinson's disease (PD-MCI), we found that subjective self-report standardized questionnaires add important information about patient's daily functional cognitive abilities. Such information was not always in line with their objective global cognitive and the neuropsychological tests results. This presentation illustrates the inter- and intraindividual differences between four people with PD (PwP) suspected for PD-MCI, encompassing objective and subjective self-report tests and questionnaire scores.
Methods: our individuals, all with a Montreal Cognitive Assessment (MoCA) score of 24, were analyzed. Neuropsychological test results and subjective reports about their cognitive abilities, as reflected in real-world daily functioning, were collected. The Movement Disorder Society-Unified Parkinson's Disease Rating Scale cognitive functional score, PD Cognitive Functional Rating Scale (PD-CFRS), Daily Living Questionnaire (DLQ) , Time Organization and Participation (TOPS), and Behavior Rating Inventory of Executive Function-Adult (BRIEF-A) version were also administered and scored. Additionally, their handwriting performance was captured by a computerized system. Each individual's profile was created and will be presented.
Results: All four individuals' global cognitive abilities were similar when measured by the MoCA scores. However, these abilities were completely different as reflected through the neuropsychological battery, the various self-reported daily functional cognitive ability questionnaires, and their handwriting performance. Their individual profiles clearly reflect their personal daily functional challenges.
Conclusions: Characterization of personal profiles of PwP suspected for MCI is essential for providing personalized intervention programs to maintain their cognitive functioning along with their physical state and well-being.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0793 / #2060

Poster Topic: *Theme B: Taupathies / B03.a. Drug Development, Clinical Trials: Immunotherapy*

DESIGN, POPULATION, AND LESSONS LEARNED FROM SCREENING FOR THE PHASE 2 AUTONOMY TRIAL OF POSDINEMAB FOR EARLY SYMPTOMATIC ALZHEIMER'S DISEASE

POSTERS: B03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

David Henley[1,2], Jennifer Bogert[3], Ziad Saad[4], Gallen Triana-Baltzer[5], Hartmuth Kolb[4], Maggie Fedgchin[1]
[1]Janssen Research & Development, LLC, Neurology, Titusville, United States of America, [2]Indiana University School of Medicine, Psychiatry, Indianapolis, United States of America, [3]Janssen Research & Development, LLC, Neurology, Bridgewater, United States of America, [4]Janssen Research & Development, LLC, Neuroscience Biomarkers And Global Imaging, La Jolla, United States of America, [5]Janssen Research & Development, Neuroscience Biomarkers, La Jolla, United States of America

Aims: Autonomy, an ongoing, phase 2, global, multicenter, double-blind, placebo-controlled, randomized, parallel-group study assesses whether the anti-phosphorylated tau monoclonal antibody posdinemab (mid-domain epitope, amino acid 212 and 217) will slow clinical decline in participants with early symptomatic (prodromal/mild dementia) Alzheimer's disease (early AD). The screening period contained several unique features to identify and enroll appropriate participants.
Methods: Adults (55-80) with early AD defined as gradual/progressive subjective decline in cognition over at least 6 months, Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 and memory box score greater or equal to 0.5 at screening and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) delayed memory index score <85. Eligible participants also had plasma p217+tau prescreening for tau PET eligibility and were required to have intermediate levels of tau burden on tau PET (18FMK6240). Participants receive posdinemab (low or high dose) or placebo IV, every 4 weeks. The primary outcome is change from baseline in integrated Alzheimer's Disease Rating Scale (iADRS) Total Score at Week 104. The iADRS composite includes the complete Alzheimer's Disease Assessment Scale Cognitive subscale 13-item (ADAS Cog13) and Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment (ADCS-ADL MCI). Secondary outcomes include change from baseline on ADAS Cog13, RBANS, ADCS-ADL MCI, CDR-SB and tau PET.
Results: Screening began Jan2021 with last participant randomized Aug2023. 522 of 523 participants randomized received at least one dose of blinded treatment. Preliminary baseline characteristics and demographics will be presented.
Conclusions: Autonomy screening period experience is informative for the field, including implementing novel strategies to mitigate cognitive scale learning effects and experience implementing the first trial to use plasma biomarkers as a prescreen for tau PET imaging to enroll the target patient population.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0794 / #1775

Poster Topic: *Theme B: Taupathies / B03.b. Drug Development, Clinical Trials: tau clearance*

OCCUPANCY OF BIIB113, AN INHIBITOR OF THE ENZYME O-GLCNACASE (OGA) IN THE HUMAN BRAIN.

POSTERS: B03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: TAU CLEARANCE

Maciej Kaliszczak[1], Sangram Nag[2], Heike Hering[1], Ben Suttle[3], Flavia C Nery[1], Lori Jones[4], Esin Yesilalan[1], Jaren Landen[1], Lars Farde[2], Per Stenkrona[2], Martin Bolin[2], Anton Forsberg Moren[2], Christer Halldin[2], Laurent Martarello[1]
[1]Biogen, Medical Affairs, Cambridge, United States of America, [2]Karolinska Institutet, Department Of Clinical Neuroscience, Center For Psychiatry Research, Stockholm, Sweden, [3]qPharmetra, Pharmacokinetics, Raleigh, United States of America, [4]Biogen, Medical Affairs, Durham, United States of America

Aims: BIIB113 is an inhibitor of the enzyme O-GlcNAcase (OGA) and developed for the treatment of Alzheimer's disease. OGA inhibition is proposed to increase tau O-GlcNAcylation, resulting in reduced formation of tau. The aim of the present Positron Emission Tomography (PET) study was to describe the relationship between BIIB113 exposure and target engagement in the human brain.
Methods: Single and multiple oral dose studies were conducted in healthy volunteers (HV). 3 to 4 subjects were included per cohort and dosed with BIIB113. Target occupancy (TO) was measured with [^{11}C]BIO-1819578, a PET tracer that binds specifically to OGA. TO was assessed at up to 72 hours (h) post dose. The volumes of distribution (V_T) were estimated using Ichise's Multilinear Analysis (MA1) model with arterial input function. Plasma PK was assessed up to 72 h after BIIB113 administration.
Results: A total of 10 HV participated in the study. A single dose of BIIB113 was able to maintain >90 % TO up to 48 h post treatment. Lowering the dose was needed to obtain lower TO and thereby derive an EC_{50} after a single dose. However, 14 days of treatment with the lower dose of BIIB113 was sufficient to maintain >90% TO up to 48 h post last dose. PK/PD modelling was applied to the totality of data and suggested that the relationship between plasma BIIB113 concentrations and TO was described with an Emax model.
Conclusions: We have demonstrated a high-level of brain TO (>90%) following single and multiple doses of BIIB113 in HV. These results support continued clinical development of BIIB113 in Phase 2 studies and will support the selection of dose regimens.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0795 / #1303

Poster Topic: *Theme B: Taupathies / B03.a. Drug Development, Clinical Trials: Immunotherapy*

PHARMACOKINETICS AND TOLERABILITY OF VY-TAU01, AN ANTI-TAU ANTIBODY FOR THE TREATMENT OF ALZHEIMER'S DISEASE, IN P301S MOUSE AND NONHUMAN PRIMATE

POSTERS: B03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

Wencheng Liu[1], Joydip Kundu[2], Maury Emery[1], Daniel Epling[3], Jeff Thompson[2], Ishan Shah[1], Maneesha Paranjpe[1], Shiron Lee[1], Alison Walsh[4], Matteo Placidi[4], Krishanu Mathur[4], Nancy Everds,[1], Ruth Lightfoot-Dunn[1], John Mondick[3], Sunny Chapel[3], Todd Carter[1], Johnny Yao[2], Chanchal Sadhu[2], Dinah Sah[1]
[1]Voyager Therapeutics, Neuroscience, Cambridge, United States of America, [2]Voyager Therapeutics, Translational Research, Cambridge, United States of America, [3]A2-Ai LLC, Research, Ann Arbor, United States of America, [4]Voyager Therapeutics, Tech Ops, Cambridge, United States of America

Aims: VY-TAU01 is a recombinant humanized IgG4 monoclonal antibody (mAb) directed against pathological tau that is intended to be administered via intravenous (IV) infusion to patients with mild dementia or mild cognitive impairment due to Alzheimer's disease (AD). VY-TAU01 specifically targets an epitope in the C-terminus of tau and is derived from the mouse IgG1 mAb Ab-01. VY-TAU01 binds to pathological tau with high affinity and selectivity over wild-type tau, blocks paired helical filaments seed-induced tau aggregates in vitro, and selectively stains tau tangles in AD and P301S mouse (C57/B6J-Tg[Thy1-MAPT*P301S]2541Godt) brain. Nonclinical studies to support the initiation of the first-in-human study are being conducted in P301S mice and nonhuman primates (NHP). Here we describe the pharmacokinetics (PK) and tolerability of Ab-01 in P301S mice and VY-TAU01 in NHP.
Methods: 1. Characterizing the PK and tolerability of Ab-01 in the P301S mouse after 5 weekly IV doses at 30, 80 or 120 mg/kg. 2. Characterizing the PK and tolerability of VY-TAU01 in NHP after a single IV dose at a high or mid dose level.
Results: No adverse effects were observed in P301S mice or NHP following Ab-01 or VY-TAU01 administration, respectively. The serum PK of 80 mg/kg Ab-01 in the P301S mouse exhibited a profile expected from a mouse IgG1 antibody with a half-life of approximately 12.6 days. Model based PK parameter estimates yielded a clearance rate (C_L) of 0.166 mL/day, and central and peripheral volumes of distribution were 0.839 mL and 1.87 mL, respectively. Additional serum and cerebrospinal fluid PK results will also be presented.
Conclusions: Initial studies demonstrated that Ab-01 and VY-TAU01 are well-tolerated in P301S mice and NHP, respectively, and that the serum PK profile is as expected.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0796 / #2361

Poster Topic: *Theme B: Taupathies / B03.b. Drug Development, Clinical Trials: tau clearance*

HIGH CONTENT SCREENING FOR MODIFIERS OF ENDOGENOUS WILD-TYPE/MUTANT TAU

POSTERS: B03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: TAU CLEARANCE

Maika Itsuno, Sumihiro Maeda, Hideyuki Okano
Keio University, School of Medicine, Physiology, Tokyo, Japan

Aims: To identify human Tau modifiers at multiple levels, such as transcription, translation, and protein degradation, we developed a high-content screening (HCS) assay using human induced pluripotent stem cell (hiPSC)-derived neurons. We fluorescently labeled the endogenous wild-type (WT) tau. In addition, we introduced the hTau A152T mutation or knocked out tau by replacing tau with the fluorescent gene. The hTau A152T mutation is associated with an increased risk of Alzheimer's disease (AD) and frontotemporal dementia spectrum diseases. We aimed to identify modifiers of WT and/or mutant tau by screening existing drug compound libraries.
Methods: First, we fused TagGFP2 to the N-terminus of Tau to monitor endogenous tau in hiPSC-derived neurons, then introduced hTau A152T mutations or replaced Tau with TagGFP2 (KO). We then differentiated the iPSCs into neurons by overexpressing neuron-enriched miRNA 9/9*/124 and a transcription factor, Neurogenin 2. The A152T mutation increased neuronal activity, as measured by Ca^{2+} imaging, mimicking the epileptic phenotype in the hTau-A152T transgenic mouse model. After exposing the hiPSC-derived neurons to small compounds for 10 days, we quantified the TagGFP2 fluorescence intensity using an automated confocal microscope.
Results: We confirmed that the Z', an indicator of assay robustness, was high enough to perform the screens (Z'>0.5). In the initial screen of 1405 compounds, 15 compounds effectively suppressed tau protein levels. While some of these compounds were equally effective in reducing WT and A152T Tau, others were more effective in reducing A152T Tau.
Conclusions: We have developed HCS for Tau modifiers and identified candidate compounds. Interestingly, some compounds have been reported to reduce the risk of neurodegenerative diseases in clinical settings. One of them may do so by reducing oxidative stress by blocking the xanthine dehydrogenase/oxidase pathway.

P0797 / #2350

Poster Topic: *Theme B: Taupathies / B03.c. Drug Development, Clinical Trials: Aggregation inhibitors*

LEVOSIMENDAN INHIBITS DISULFIDE TAU OLIGOMERIZATION AND AMELIORATES TAU PATHOLOGY IN TAUP301L-BIFC MICE.

POSTERS: B03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: AGGREGATION INHIBITORS

Sungsu Lim, Yun Kyung Kim, Ae Nim Pae
Korea Institute of Science and Technology, Brain Research Institute, Seoul, Korea, Republic of

Aims: Accumulation of abnormal tau aggregates is a pathological hallmark of multiple neurodegenerative disorders, collectively called tauopathies. Soluble tau aggregates play a key role in tau pathology as neurotoxic species causing neuronal cell death and also act as prion-like seeds transmitting the disease in the brain. Accordingly, prevention of tau oligomerization or elimination of tau oligomer species became an important therapeutic strategy to halt the disease progression. Here we assessed the potential therapeutic effect of levosimendan as an anti-tau oligomer agent.
Methods: Toward tau-targeted drug discovery, our group has established a tau-BiFC platform to monitor and quantify tau oligomerization in living cells and the mouse brain. By utilizing the tau-BiFC cells, we screened the FDA-approved and passed PhaseI drug library and identified levosimendan as a potent anti-tau agent inhibiting tau oligomerization. By using tau-BiFC mice, we could evaluate the anti-tau oligomerization effects of levosimendan.
Results: Under pathological conditions, most tau exists as a form of disulfide-linked tau oligomers and the treatment of levosimendan prevents the formation of disulfide-linked oligomers by covalently modifying tau cysteines(IC_{50}=2.6±0.1mM). In addition, levosimendan was able to disassemble tau oligomers into monomers, rescuing cells from aggregation states. In comparison, LMTM, the leading tau-targeted drug candidate that is currently on a clinical trial, failed to rescue cells from aggregation states, generating high-molecular-weight tau oligomers instead. Levosimendan displayed robust potency against tau oligomerization and rescued tauopathy-induced cognitive declines in the Tau^{P301L}-BiFC mouse model.
Conclusions: Our data present the potential of levosimendan as a disease-modifying drug for tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0798 / #2051

Poster Topic: *Theme B: Taupathies / B03.c. Drug Development, Clinical Trials: Aggregation inhibitors*

THERAPEUTIC APPROACHES TARGETING 3R/4R TAUOPATHIES FOR THE TREATMENTS OF AD AND PSP

POSTERS: B03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: AGGREGATION INHIBITORS

Ae Nim Pae, Sungsu Lim, Yun Kyung Kim
Korea Institute of Science and Technology, Brain Science Institute, Seoul, Korea, Republic of

Aims: Tauopathies are neurodegenerative disorders characterized by accumulation of tau in neurons or glial cells. Several neuropathologic phenotypes are distinguished based on the distinct anatomic areas and specific isoforms of tau (3R/4R) in pathologic deposits. As tauopathies are strongly linked with neurodegenerative disease, there have been a growing interest in tau-targeted drug discovery. Therefore, we studied and developed novel tau-targeted therapeutic drug candidates for the treatment of AD and PSP by inhibition of tau oligomerization in early stage.
Methods: We performed high-contents screening based on Tau Bi-FC cell-based assay platform and identified novel tau-aggregation inhibitors. Lead optimization was subsequently performed to improve potency and ADME/Tox properties, resulting in the production of lead compounds. *In vivo* efficacy of the lead compound was validated by demonstration of restoring memory impairment and motor dysfunction in transgenic animal models of P301L Tau-BiFC.
Results: The lead compound, **DTC2423** exhibited excellent 4R tau aggregation inhibitory activities (cell-based IC_{50}, 88 nM, in vitro IC_{50}, 40 nM) with good cell viability (MTS IC_{50}, 105 uM). **DTC2423** reduced tau oligomerization and protected neuronal cell death. It restored memory impairment and motor dysfunction in P301L Tau-BiFC Tg mouse models (NOR, Y-maze, Barnes-Maze test, Balance beam and Rotarod test) with reduction of tau pathology. The mode of action of **DTC2423** was confirmed by MALDI-TOF Mass Spectrometric Analysis and TR-2 competition study to show reversible covalent inhibition of disulfide dependent oligomer formation.
Conclusions: Highly potent lead compound was identified having selective inhibition of 4R tau aggregation by using 3R and 4R Tau-BiFC, disease-specific cell-based assay platform and in vivo Tau-BiFC P301L Tg mice model that improved significantly cognitive and motor dysfunction, and reduced tau pathology with good pharmacological properties.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0799 / #433

Poster Topic: *Theme B: Taupathies / B03.e. Drug Development, Clinical Trials: Combination therapy, sex/race, personalized medicines, AI, Other*

A PHASE 2A STUDY OF TPN-101, A NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR, IN PATIENTS WITH PROGRESSIVE SUPRANUCLEAR PALSY

POSTERS: B03.E. DRUG DEVELOPMENT, CLINICAL TRIALS: COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER

Andrew Satlin[1], Michael Cordingley[1], Debbie Liebert[1], Walter Bee[1], Ethan Geier[1], John Sedivy[1], Jay Soto[1], Eckard Weber[1], Adam Boxer[2]
[1]Transposon Therapeutics, Medical, San Diego, United States of America, [2]UCSF Weill Institute of Neurosciences, Memory And Aging Center, San Francisco, United States of America

Aims: To assess the safety, tolerability, pharmacokinetics in plasma and CSF, effect on biomarkers of neuroinflammation and neurodegeneration, and clinical effects of TPN-101, a nucleoside reverse transcriptase inhibitor, in patients with progressive supranuclear palsy (PSP).
Methods: 42 patients with probable PSP meeting Richardson criteria who were symptomatic for less than 5 years were randomly assigned to double-blind treatment with TPN-101 100 mg, 200 mg, 400 mg, or placebo once daily for 24 weeks. Patients who completed the double-blind period of the study were eligible to receive once-daily TPN-101 400 mg in a 24-week open-label treatment period. Patients were assessed for safety, biomarkers, and clinical effects at regular intervals. Lumbar punctures were done at baseline, Week 24, and Week 48 for CSF assessment of PK and biomarkers. The prespecified biomarker of interest was CSF neurofilament light (NfL) at Week 24.
Results: TPN-101 was well-tolerated, with only 2 withdrawals due to adverse events in the TPN-101 treatment groups. Plasma pharmacokinetics were in line with predicted and CSF concentrations exceeded target levels. Compared with baseline values, NfL_{CSF} decreased in the TPN-101 400 mg group and increased in placebo-treated patients (18.4% difference; p=0.158). Interleukin-6 (IL-6), a measure of neuroinflammation that correlates with PSP disease severity, also increased in the CSF in placebo-treated patients and decreased in patients treated with TPN-101. No differences among treatment groups were observed during the 24-week double-blind treatment period on the Progressive Supranuclear Palsy Rating Scale.
Conclusions: All doses of TPN-101 were well-tolerated in patients with PSP. Numerical trends toward reductions in NfL and IL-6 support the potential for a positive effect on neuroinflammation and neurodegeneration. Clinical improvements were not expected due to the size and duration of the study.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0800 / #336

Poster Topic: *Theme B: Taupathies / B04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

LATE-LIFE BODY MASS INDEX HAS A PROTECTIVE EFFECT ON HIPPOCAMPAL VOLUME AND COGNITION IN INDIVIDUALS WITH COGNITIVE IMPAIRMENT

POSTERS: B04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Qin Li, Xiaofeng Li
The Second Affiliated Hospital of Chongqing Medical University, Neurology, Chongqing, China

Aims: To investigate the relationship between body mass index (BMI) and Alzheimer's disease (AD) markers as well as cognition in the elderly with cognitively normal (CN) and cognitive impairment (CI), respectively.
Methods: Participants' data were collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Participants with cognitively normal (CN) were included in the CN group. Participants with mild cognitive impairment and mild dementia were included in the cognitive impairment (CI) group. Linear and logistic regression were used to assess the association between BMI and AD markers as well as cognition.
Results: A total of 330 participants with CI and 84 participants with CN were included in this study. Linear regression showed that BMI was positively associated with baseline hippocampal volume (HV, β=0.04, P<0.001) and negatively associated with p-tau181 (β=-0.005, P=0.044) in participants with CI, whereas in participants with CN, BMI was positively associated with p-tau181 (β=0.012, P=0.013) and not with HV. In the CI group, the interaction effect between APOE ε4 status (or amyloid β positive status) and BMI demonstrated a significant impact on the 2-year Mini-Mental State Examination (MMSE) score, baseline HV, and 2-year HV. Mediation analysis showed that in the CI group, the effect of BMI on HV was partially mediated by diastolic blood pressure (DBP). In the CN group, BMI had a vicious effect on the MMSE score, while the mediating effect of DBP was insignificant.
Conclusions: In the CI participants, BMI may affect HV and cognition via influencing DBP, particularly prominent in APOE ε4 carriers and Aβ positive individuals. Therefore, in clinical practice, we should prioritize the appropriate maintenance of BMI in the elderly with AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0801 / #787

Poster Topic: *Theme B: Taupathies / B04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

MULTIMODAL BRAIN MRI CHARACTERIZATION OF A MOUSE MODEL OF DOWN SYNDROME AND EVALUATION OF A PHARMACOLOGICAL TREATMENT

POSTERS: B04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Julien Caillette[1], Laetitia Degiorgis[1], Marion Sourty[1], Helin Atas-Ozcan[2], Laurent Meijer[3], Yann Herault[2], Laura-Adela Harsan[4]
[1]ICube, Neurosciences, Strasbourg, France, [2]IGBMC, Neurosciences, Illkirch, France, [3]Perha Pharmaceuticals, Neurosciences, Roscoff, France, [4]Icube, Neurosciences, Strasbourg, France

Aims: DYRK1A overexpression is a key player in cognitive impairments observed in Down syndrome (DS) patients and in animal models. Inhibition of this kinase rescues cognitive deficits in the Dp1Yey mouse model of DS. Our aims were to characterize, by multimodal MRI, the brain changes (morphology, microstructure, functional connectivity (FC)) underlying cognitive deficits in the Dp1Yey DS model, and to investigate, via resting state functional MRI (rsfMRI), how brain functional network patterns are remodeled by the Leucettinib-92 DYRK1A inhibitor.
Methods: Dp1Yey mice and wildtype (wt) control mice received either Leucettinib-92 or vehicle. Brain MRI data was acquired on day 11 of the treatment. Anatomical, diffusion and rsfMRI images were preprocessed. Anatomical images were analyzed by Voxel Based Morphometry (VBM). Parametric maps were extracted from the DTI images and parametric diffusion values were compared. RsfMRI data was processed to extract the BOLD time-course from each ROI, and correlation matrices were created. Graph theory was applied to map FC features for each group.
Results: VBM analysis revealed significant brain-wide cortical and subcortical volume alterations in Dp1Yey, involving frontal and sensory cortices and striatal, hippocampic and thalamic regions. Comparison of parametric diffusion maps showed significant changes, suggesting microstructural alterations in Dp1Yey model brain. Graph theory was applied to identify the regions with the most changed functional connections, showing hyperconnectivity in Dp1Yey. Comparing the treated and untreated animals showed that hyperconnectivity to be rescued by Leucettinib-92 treatment in several brain circuitries. The spatio-temporal dynamics of the functional connectivity is also altered in the Dp1Yey model and appears to be partially restored by Leucettinib-92 treatment.
Conclusions: RsfMRI should be further evaluated as a non-invasive tool as a biomarker during clinical trials of DYRK1A inhibitors in DS patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0802 / #1061

Poster Topic: *Theme B: Taupathies / B04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

CLASSIFYING NEUROPATHOLOGICALLY CONFIRMED ALZHEIMER'S DISEASE AND LEWY BODY DEMENTIA ON CLINICAL NEUROIMAGING WITH DEEP LEARNING

POSTERS: B04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Frank Provenzano[1], David Park[2]
[1]Columbia University, Neurology, New York, United States of America, [2]Columbia University, Biomedical Engineering, Manhattan, United States of America

Aims: AD and DLB co-occur frequently, but post-mortem pathology reveals limited ante-mortem accuracy in the clinical diagnosis of AD comorbid with DLB (AD/DLB) against AD alone. We tested whether a single T1-weighted (T1) MRI scan may differentiate AD/DLB and AD using heterogeneously acquired (both research and clinically acquired) neuroimaging, to maximize the amount of pathology-confirmed in-vivo MRIs.
Methods: Datasets consist of mostly clinically-acquired scans from National Alzheimer's Coordinating Center (NACC) and purely research scans from Alzheimer's Disease Neuroimaging Initiative (ADNI). T1 MRI scans are limited to those participants with neuropathology. We examine two groups, an AD with and without LBD pathology. A five-fold cross validation is performed using NACC, while ADNI scans are added in the training dataset. Slice-level 2D Convolutional neural networks (CNN) are trained to differentiate the two groups. From each scan, gray matter is segmented, normalized, smoothed and thresholded and used as input.
Results: On the subject-level, CNN records a classification accuracy of 82% and f1 score of 0.79. Prediction accuracy was higher when the scan date is closer to DOD, with a 100% accuracy recorded within a year from the date-of-death. A Grad-CAM attribution map reveals distinctive cortical patterns for AD and AD/DLB groups.
Conclusions: This study demonstrates how machine learning approaches can help harmonize neuroimaging data from clinical sources to better understand disease diagnosis and progression using a true gold-standard of neuropathological confirmation. The frameworks utilized here can be extended to other diseases that are frequently co-occurring and feasibly extend to single scan diagnostic clinical utility of scans already being acquired.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0803 / #364

Poster Topic: *Theme B: Taupathies / B04.b. Imaging, Biomarkers, Diagnostics: PET - tau*

TOWARDS ROBUST QUANTIFICATION OF LONGITUDINAL [18F]MK-6240 TAU-PET SUVR CHANGES IN CLINICAL STUDIES

POSTERS: B04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

Yuchuan Wang[1], Michal Tomaszewski[1], Richard Baumgartner[2], William Herring[3], Wenping Li[1], Eric Hostetler[1]
[1]Merck Sharp & Dohme, Translational Imaging, Rahway, United States of America, [2]Merck Sharp & Dohme, Biostatistics, Rahway, United States of America, [3]Merck Sharp & Dohme, Clinical Research, Rahway, United States of America

Aims: Longitudinal [18F]MK-6240 tau-PET is increasingly used clinically for monitoring AD progression and/or assessing therapeutic responses. Quantifying standardized uptake value ratio (SUVR) changes in predefined brain regions-of-interests (ROIs) requires analysis-pipeline implementations that often employ distinct methods, leading to differing robustness of study data readouts and statistical power. Our aim is to improve pipeline implementations to achieve more robust longitudinal quantification and to reduce the risk of reporting artificial SUVR-reduction.
Methods: Several historical [18F]MK-6240 tau-PET datasets were investigated using an in-house longitudinal SUVR analysis-pipeline, allowing comparisons of different implementations. Three methods for reference-region SUV estimation were assessed: (1) SUVmean of whole-cerebellar-grey, (2) SUVmean of eroded-cerebellar-grey, and (3) SUVmax-probability of whole-cerebellar-grey. Both (2) and (3) are capable of reference-region decontamination, using empirical erosions and probability-density-functions (PDFs), respectively. Two approaches of ROI-handling were compared: (a) use of “stationary” baseline ROIs to quantify both baseline and follow-up PET, and (b) use of “time-point-matched” ROIs, where quantification of follow-up PET use ROIs generated from follow-up MRI.
Results: Among three methods of quantifying reference-region, method #1 exacerbated artificial SUVR-reductions in target ROIs, especially early Braak regions, due to spill-in contaminations. Both methods #2 and #3 were effective for decontamination, with #3 allowing replicable implementations for all datasets. Between two approaches of ROI-handling, “stationary” approach exacerbated artificial SUVR-reductions when compared to “time-point-matched” approach, especially notable among subjects with higher baseline SUVR. Combining reference-region decontamination and “time-point-matched” ROI-handling enhanced statistical power in detecting longitudinal changes for historical datasets, beneficially impacting sample-size calculations.
Conclusions: Tau-PET quantification robustness is improved by reference-region decontamination and “time-point-matched” ROI-handling. PDF-based decontamination is more consistent/replicable across pipelines/studies. Effective use of longitudinal MRI for PET quantification may be important for future clinical studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0804 / #2456

Poster Topic: *Theme B: Taupathies / B04.b. Imaging, Biomarkers, Diagnostics: PET - tau*

DOES VASCULAR RISK EXPLAIN ACCELERATED TAU ACCUMULATION IN WOMEN COMPARED WITH MEN?

POSTERS: B04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

Melanie Dratva[1], Kenneth Rostowsky[2], Qian Shen[1], Xin Wang[1], Jazmin Diaz[3], Michael Thomas[3], Erin Sundermann[4], Sarah Banks[5]
[1]UCSD, Neurosciences, La Jolla, United States of America, [2]University of Chicago, Neurology, Chicago, United States of America, [3]Colorado State University, Neurosciences, Fort Collins, United States of America, [4]University of California, San Diego, Psychiatry, La Jolla, United States of America, [5]University of California, San Diego, Neurosciences, La Jolla, United States of America

Aims: Across the Alzheimer's Disease spectrum, women have higher rates of tau accumulation compared to men, particularly at the mild cognitive impairment (MCI) stage. Women have been found to have stronger associations between vascular risk and tau than men at single time points. In our earlier work, the Framingham Risk Score (FRS), was found to predict tau PET levels in cognitively normal women but not men. Here, we asked if vascular risk scores explain some of the sex differences seen in tau accumulation in MCI.
Methods: 53 amyloid positive subjects (21 women) with clinical diagnoses of MCI, tau-Positron Emission Tomography (PET) data, and cardiovascular component data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were included in this analysis, which controlled for age, *APOE* status, and education. FRS scores were calculated based on cardiovascular disease points derived from age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, hypertension treatment status, smoking status, and diabetic status. Models were fitted to the data to test (1) whether sex moderated the relationship between FRS and tau accumulation and (2) whether FRS fully mediated the associating between sex and tau accumulation.
Results: Women had lower FRS and accumulated more tau over the 1-2 year period examined in comparison to men in the regions of interest (which spanned Braak regions 3,4, 5 and 6). While FRS was a predictor of higher tau accumulation, it was independent of sex (i.e., not moderated by sex). Moreover, sex predicted higher tau accumulation independent of FRS scores.
Conclusions: While prior research pointed to vascular risk predicting early tau accumulation in women with normal cognition, sex differences in the accumulation of tau during MCI are not explained by vascular risk.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0805 / #2489

Poster Topic: *Theme B: Taupathies / B04.b. Imaging, Biomarkers, Diagnostics: PET - tau*

VENOUS ABNORMALITIES AND BRAIN CLEARANCE

POSTERS: B04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

Lidia Glodzik, Yi Li, Xiuyuan Hugh Wang, Emily Tanzi, Liangdong Zhou, Silky Pahlajani, Tracy Butler, Gloria Chiang, Adrienne Biskaduros, Thomas Maloney, Mony De Leon
Weill Cornell Medicine, Radiology, New York, United States of America

Aims: The concept of glymphatic system proposes that cerebrospinal fluid (CSF) enters the brain parenchyma through spaces surrounding arterioles, passes through interstitial spaces mixing with interstitial fluid and exits the brain through perivenous spaces, facilitating the clearance of metabolic waste. While much attention has been paid to the arterial part of the vascular tree, the role of venous abnormalities remains relatively unexplored. Using our in-house developed PET based method to assess ventricular efflux we examined whether this clearance measure is related to venous density as assessed by deep medullary veins count.
Methods: Data was collected from cognitively impaired and unimpaired research participants enrolled in studies between 2020 and 2023 at the Brain Health Imaging Institute at Weill Cornell Medicine. All participants had their medical history and cognition assessed through standardized clinical interviews. Imaging consisted of 3T MRI scans and 18F-MK6240 PET/CT to estimate brain clearance and tau deposition. The number of DMVs was assessed by visual inspection of minimal intensity projection images (SWI) for veins traversing perpendicularly to the lateral ventricle and defined as the total count of both hemispheres.
Results: We included 32 cognitively impaired subjects (66.1± 12.3 years old, 15 women) and 72 normal individuals (69.8± 7.0, 37 women). Age and sex did not differ between groups. Among subjects with cognitive impairment, but not in normal volunteers, the number of DMVs was positively related to the measure of CSF ventricular efflux (rho=0.43, p=0.01) and inversely associated with tau accumulation in Alzheimer Disease-related composite region (rho=-0.37, p=0.04). The correlation between clearance measure and tau deposition did not reach statistical threshold (rho= -0.28, p=0.10).
Conclusions: Our findings support the notion that healthy venous system plays a role in brain clearance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0806 / #151

Poster Topic: *Theme B: Taupathies / B04.b. Imaging, Biomarkers, Diagnostics: PET - tau*

IDENTIFICATION OF VARIOUS NEUROSYMPTOMATIC DOMAINS AND ASSOCIATED LESIONS IN PROGRESSIVE SUPRANUCLEAR PALSY BY TAU PET.

POSTERS: B04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

Yuko Kataoka[1], Hironobu Endo[1], Kenji Tagai[1], Kiwamu Matsuoka[1], Kousei Hirata[1], Keisuke Takahata[1], Masaki Oya[1], Hideki Matsumoto[1,2], Shin Kurose[1], Masanori Ichihashi[1], Hitoshi Shinotoh[1], Hitoshi Shimada[1], Naomi Kokubo[1], Chie Seki[1], Kazunori Kawamura[1,3], Ming-Rong Zhang[1,3], Takahiko Tokuda[1], Yuhei Takado[4], Makoto Higuchi[1]
[1]National Institutes for Quantum Science and Technology, Department Of Functional Brain Imaging, Chiba-shi, Japan, [2]Tokyo Dental College, Department Of Oral And Maxillofacial Radiology, Tokyo, Japan, [3]National Institutes for Quantum Science and Technology, Department Of Advanced Nuclear Medicine Sciences, Chiba-shi, Japan, [4]National Institutes for Quantum Science and Technology, Quantum Life And Medical Science Directorate, Chiba-shi, Japan

Aims: Progressive supranuclear palsy (PSP) is characterized pathologically by abnormal tau protein depositions and clinically by motor impairments, including vertical oculomotor deficits. This study aimed to identify regional tau accumulations associated with discrete domains of PSP symptoms using PET with [^{18}F]PM-PBB3/florzolotau(18F), a radioligand capable of capturing tau aggregates in primary tauopathies.
Methods: Data were obtained consecutively from February 2018 to August 2021 and included 48 PSP subjects. We performed neurological examinations, including an evaluation of the PSP rating scale, which was sorted into six domains consisting of 'history', 'mentation', 'bulbar', 'ocular motor', 'limb motor', and 'gait and midline' subsections. Correlations of these domain scores with tau accumulations and local atrophy in the brain were evaluated using standard brain-transformed tau PET and T1-weighted MRI images, respectively.
Results: 'Ocular motor' scores were significantly correlated (unc. <0.001) with tau accumulations in the midbrain tegmentum and globus pallidus. By contrast, 'limb motor' and 'gait and midline' scores were significantly correlated (unc. <0.001) with tau depositions in the precentral to supplementary motor cortex and the caudate nucleus, respectively. Volumes of the midbrain tegmentum and globus pallidus were significantly correlated (unc. <0.001) with 'ocular motor' scores, and precuneus volumes were correlated with 'gait and midline' scores.
Conclusions: The present findings have revealed that tau pathologies in distinct brain areas are differentially implicated in individual symptomatic domains in PSP. Tau depositions and local atrophy in the midbrain were associated with oculomotor impairments, indicating that tau-induced, on-site neurotoxicity provokes disrupted eye movements as focal symptoms. Meanwhile, gait and midline deficits may arise from caudate tau accumulations leading to the deterioration of a network involving the precuneus.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0807 / #2559

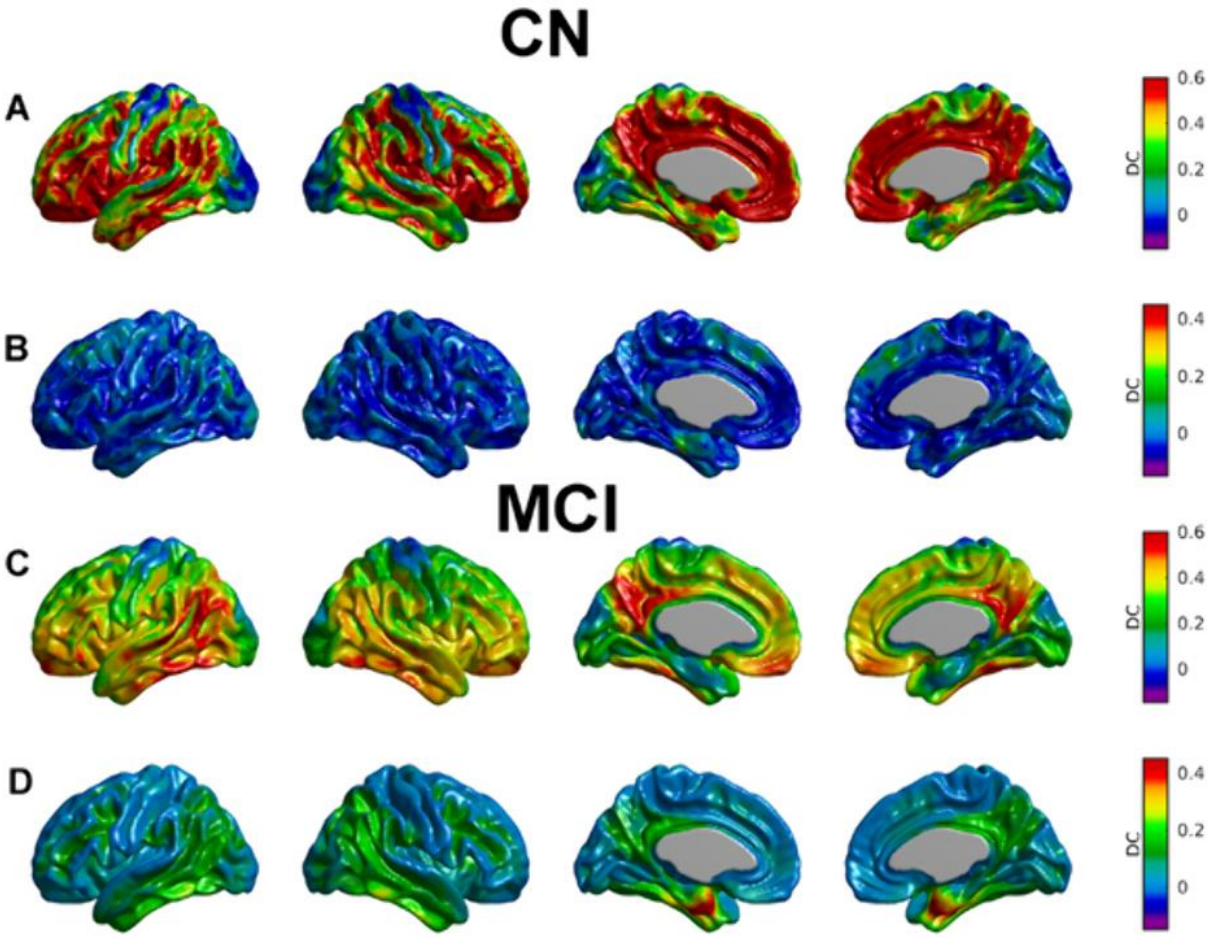
Poster Topic: *Theme B: Taupathies / B04.b. Imaging, Biomarkers, Diagnostics: PET - tau*

SPATIAL ASSOCIATION BETWEEN DISTRIBUTED B-AMYLOID AND TAU VARIES WITH COGNITION

POSTERS: B04.B. IMAGING, BIOMARKERS, DIAGNOSTICS: PET - TAU

Felix Carbonell[1], Carolann Mcnicoll[1], Alex Zijdenbos[2], Barry Bedell[3]
[1]Biospective Inc., Clinical, Montreal, Canada, [2]Biospective Inc., Technology, Montreal, Canada, [3]Biospective Inc., Preclinical, Montreal, Canada

Aims: Most studies exploring the synergistic effect between β-amyloid and tau at early stages of Alzheimer's disease (AD) have only focused on their linear relationship at the local spatial scale. We hypothesize that patterns of spatial association between β-amyloid and tau may be more thoroughly interrogated using alternative association metrics that account for linear as well as more complex, possibly nonlinear, dependencies.
Methods: Our cross-sectional analysis was applied to Tau and Amyloid PET images from cognitively normal (CN) and mild cognitive impairment (MCI) subjects from the ADNI study. We propose a new Canonical Distance-Correlation (CDC) Analysis to uncover spatial patterns in the association between Tau and Amyloid images. Based on the concept of distance-correlation, the CDC approach produces statistically independent components in the distributed-to-distributed organization of the nonlinear association between the two modalities.
Results: The CDC analysis led to scores that were maximally cross-distance-correlated, a sign of an underlying (nonlinear) dependency. The strength and spatial extent of the distance-correlation between the first β-amyloid scores and tau images were stronger in CN than in MCI subjects (Figures 1A, 1C). In contrast, the tau cross-eigenimage carried stronger loads in MCI than in CN subjects, particularly within the entorhinal cortex (Figures 1B, 1D). This pattern of distributed β-amyloid–focal tau dependency could represent an initial indication of cognitive
deterioration.



Conclusions: The CDC analysis can reveal complex patterns in the spatial association between the β-amyloid and tau. Our results suggest that β-amyloid and tau act in a spatially coordinated manner that depends on the cognitive stage. Thus, the CDC analysis may be more accurate than the amyloid or tau SUVR for the enrollment in clinical trials of those individuals on the path of cognitive deterioration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0808 / #928

Poster Topic: *Theme B: Taupathies / B04.d. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

CORRELATIVE MICROSCOPY: SYNCHROTRON XRF IMAGING AND OPTICAL MICROSCOPY FOR THE STUDY OF IRON IN PROGRESSIVE SUPRANUCLEAR PALSY

POSTERS: B04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Natalie Arigundiya[1,2,3], Yunxing Ma[2], Seojin Lee[4,5,6], Naomi Visanji[4,5,6], Kalotina Geraki[3], Joanna Collingwood[2]
[1]University of Warwick, Analytical Science Centre For Doctoral Training, Coventry, United Kingdom, [2]University of Warwick, School Of Engineering, Coventry, United Kingdom, [3]Diamond Light Source, Spectroscopy, Harwell, United Kingdom, [4]University of Toronto, Department Of Laboratory Medicine And Pathobiology, Toronto, Canada, [5]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [6]Toronto Western Hosptial, Krembil Brain Institute, Toronto, Canada

Aims: Iron accumulation is observed in brain regions affected by progressive supranuclear palsy (PSP), a rare tauopathy among the parkinsonism disorders. The influence of iron on amyloid aggregation is well-documented, however, the aetiology of tau aggregation and the role of metals in tauopathies has received less attention. The objective of this work was to facilitate, through a multimodal microscopy approach, a method incorporating synchrotron x-ray fluorescence (SXRF), to investigate the underlying relationship between tau aggregation and iron accumulation. This required a protocol to preserve the metallomics properties of the samples while allowing for cellular-level correlation with neuropathology in the same sections.
Methods: Brain tissue from two age-matched individuals (PSP and control) was prepared and cryo-sectioned with a sapphire blade using a metal-contamination-free protocol. Sections were mounted onto quartz slides etched with finder grids. Regions of interest (ROIs) of 1x1 mm were defined using optical microscopy, and SXRF mapping of elemental distributions in each ROI was performed at Beamline I18 at Diamond Light Source synchrotron. This beamline is distinguished by its microfocus capabilities, with two micron mapping resolution, unambiguous chemical element specificity, and sensitivity to parts-per-million concentrations.
Results: The SXRF chemical element mapping was performed with this label-free technique, and the unique quartz finder grid enabled direct correlation with the light microscope images. PyMCA software was used to derive maps of chemical concentration distribution, by performing spectral fitting to accurately identify elemental peaks and integrate the area beneath each peak.
Conclusions: This method development study has made it possible to correctly identify and evaluate cells and other features in both chemical element and optical microscopy images, creating new scope for direct correlation between iron and tau pathology when the sections are immunostained after SXRF analysis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0809 / #1531

Poster Topic: *Theme B: Taupathies / B04.d. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

DEFAULT MODE NETWORK ALTERATIONS IN FORMER CONTACT SPORT ATHLETES WITH REPETITIVE CONCUSSIONS AND BIOMARKERS OF NEURODEGENERATION

POSTERS: B04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Indira Garcia Cordero[1], Anna Vasilevskaya[1], Foad Taghdiri[1], Mozhgan Khodadadi[2], David Mikulis[2], Apameh Tarazi[2], Asma Mushtaque[2], Neda Anssari[2], Brenda Colella[2], Robin Green[2], Ekaterina Rogaeva[3], Christine Sato[3], Mark Grinberg[3], Danielle Moreno[3], Mohammed Hussain[3], Kaj Blennow[4], Henrik Zetterberg[4], Karen Davis[3], Richard Wennberg[2], Charles Tator[2], Maria Tartaglia[3]
[1]Tanz Centre for Research in Neurodegenerative Diseases, University Of Toronto, Toronto, Canada, [2]Canadian Concussion Centre, Toronto Western Hospital, Toronto, Canada, [3]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: To determine whether biomarker evidence of neurodegeneration in former contact sports athletes (ExPros) with a history of repeated concussion is associated with changes in specific brain structures and functional connectivity networks.
Methods: 41 male former professional athletes with a history of multiple concussions were recruited. The sample was divided into neurodegenerative biomarker positive (N+, n = 16) and negative (N-, n = 25) groups. Classification was based on the positivity in at least one of these biomarkers: plasma and cerebrospinal fluid (CSF) neurofilament light, CSF total tau and plasma phospho-tau181. Ten healthy controls (negative for neurodegenerative biomarkers) were also included. Cognitive and mood/behavior composite scores, whole-brain grey matter volume and functional connectivity (default mode [DMN], salience [SN] and frontoparietal [FPN] networks) were compared across groups. Statistical threshold was set at $p < 0.001$, FWE correction at cluster level ($p < 0.05$). Spearman's rank correlations were performed between network functional connectivity and the number of concussions.
Results: Normal-range mean performance was found in executive function, memory and mood/behavior tests across groups. We found no differences in grey matter volume. The DMN in the N (+) group showed lower connectivity compared to N (-) and healthy controls. No differences were obtained for the SN and FPN. Lower DMN connectivity correlated with a higher number of concussions in the N (+) group ($r = -0.66$, $p = 0.005$), but not in the N (-) group ($r = -0.10$, $p = 0.60$).
Conclusions: DMN functional connectivity may provide sensitive tools to detect asymptomatic ExPros with positive biomarkers of neurodegeneration. Follow-up studies are needed to show whether this alteration is associated with a higher risk of developing dementia after repetitive concussions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0810 / #806

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PERFORMANCE OF A METHOD FOR QUANTIFYING PROGRANULIN AS A TARGET ENGAGEMENT BIOMARKER FOR AZP2006 IN PROGRESSIVE SUPRANUCLEAR PALSY

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Cécilia Estrella[1], Aurélien Blondel[1], Philippe Verwaerde[1], Noëlle Callizot[1], Renaud Jasnowski[2], Audrey Pabiou[2], Aurélie Chene[2], Cendrine Josson[2], Christine Bain[2]
[1]Alzprotect, Clinical Research, Loos, France, [2]Active Biomarkers - Kcas, Bioanalytics, LYON, France

Aims: Progranulin (PGRN) is a neurotrophic factor that plays a key role in the development, survival and maintenance of neurons and microglia. Strategies aiming at restoring PGRN levels in patients with Progressive Supranuclear Palsy (PSP) are investigated as potential therapeutic approaches. In the context of a Phase IIa clinical trial conducted by Alzprotect, evaluating AZP2006 in PSP, Active Biomarkers as the bioanalytical laboratory, quantified PGRN as a target engagement biomarker together with other biomarkers, in plasma and cerebrospinal fluid (CSF) of PSP patients.
Methods: Biotechne and Adipogen PGRN ELISA kits were evaluated in plasma and CSF samples for parallelism and selectivity. Performance of the selected method, including working range and long-term stability at -80°C for up to 52 weeks, was evaluated.
Results: Both PGRN kits were equivalent in terms of selectivity in plasma and CSF and parallelism in plasma. However, Biotechne kit was not sufficiently sensitive to quantify PGRN in CSF. PGRN was then measured both in plasma and CSF by Adipogen kit. Quantification of endogenous PGRN paralleled calibration curve with the recombinant protein. After having determined the minimal required dilution, clinical sample analysis showed that upon AZP2006 treatment, PGRN levels at the end of the treatment were increased in plasma when compared to the baseline. AZP2006 treatment was able to prevent the PGRN decrease observed in CSF of the placebo group. These data were further consolidated by demonstrating acceptable precision of the method across all analytical runs and analysts, and PGRN stability in in-study samples for at least 52 weeks at -80°C.
Conclusions: Quantification of PGRN by a method, qualified according to its context-of-use, generates robust results establishing PGRN as a target engagement biomarker for AZP2006 in PSP.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0811 / #2100

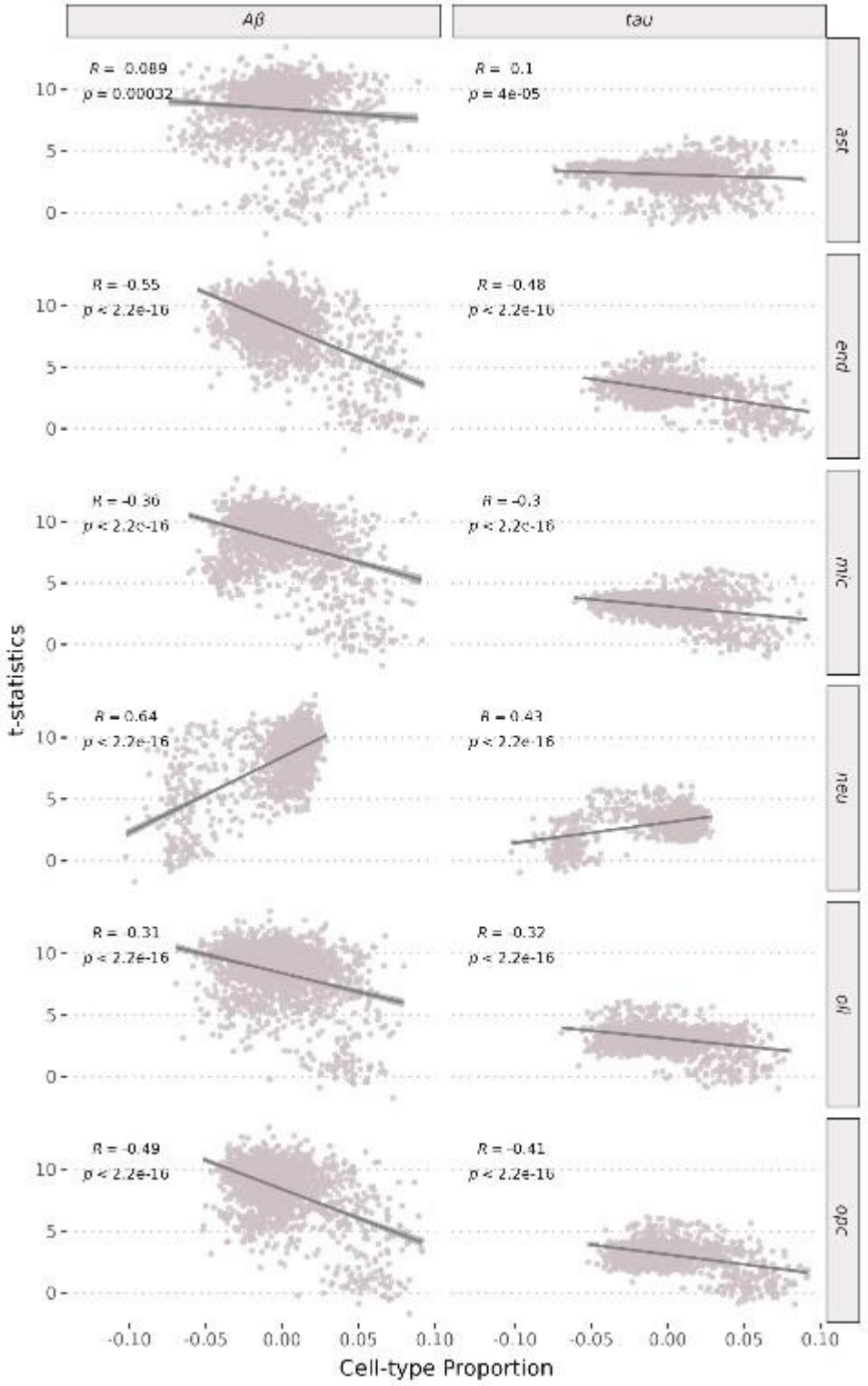
Poster Topic: *Theme B: Taupathies / B04.d. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

MAPPING SIX BRAIN CELL TYPES TO ALZHEIMER'S DISEASE PATHOLOGY.

POSTERS: B04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Min Su Kang[1,2], Julie Ottoy[1,2], Jean-Paul Soucy[3], Gassan Massarweh[3], Sandra Black[2,4], Pedro Rosa-Neto[5,6], Maged Goubran[1]
[1]Sunnybrook Research Institute, The Physical Sciences, Toronto, Canada, [2]Sunnybrook Research Institute, Hurvitz Brain Sciences Program, Toronto, Canada, [3]Montreal Neurological Insitute, Neurology, Montreal, Canada, [4]University of Toronto, Department Of Medicine (neurology), Toronto, Canada, [5]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [6]McGill Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada

Aims: The abnormal amyloid-beta (Aβ) and tau aggregates can be quantified and studied using PET biomarkers. However, the spatial profile of different brain cell types associated with AD pathology at a large-scale imaging level is still unknown.
Methods: A total of 100 participants (67 A-T-, 26 A+T-/+) from the TRIAD cohort underwent T1, ^{18}F-AZD4694, and ^{18}F-MK6240 PET. All T1 and PET images were processed using Freesurfer and PETsurfer, respectively. The DKT atlas was uniformly divided into a high-resolution atlas at 1631 regions. We conducted a group comparison between A- and A+ groups on Aβ or tau PET with age, sex, APOE€4 and education as covariates. The t-statistics from the group contrast were correlated with the six brain cell-type (endothelial, neuron, astrocyte, microglia, oligodendrocyte, oligodendrocyte precursor (OP) cells) spatial proportions maps estimated from cell deconvolution of the Allen Human Brain Atlas in the DKT atlas. The bonferroni correction was applied for the multiple comparisons test.
Results: We showed a significantly greater Aβ or tau PET in the A+ compared to the A- group. Such differences in the Aβ or tau PET were significantly correlated with all six brain cell types (fig1). The proportion of the neuronal cell type was positively correlated with Aβ or tau PET while the other cell types were negatively correlated. The neuronal, endothelial, and OP cell types showed the highest R2 whereas the astrocyte cell type had the lowest R2 with the Aβ or tau PET t-statistics


Aβ
tau
R = 0.089
p = 0.00032
R = 0.1
p = 4e-05
R = -0.55
p < 2.2e-16
R = -0.48
p < 2.2e-16
R = -0.36
p < 2.2e-16
R = -0.3
p < 2.2e-16
R = 0.64
p < 2.2e-16
R = 0.43
p < 2.2e-16
R = 0.31
p < 2.2e-16
R = -0.32
p < 2.2e-16
R = -0.49
p < 2.2e-16
R = -0.41
p < 2.2e-16
ast
end
mic
neu
oli
opc
t-statistics
10
5
0
-0.10
-0.05
0.00
0.05
0.10
Cell-type Proportion

(table1).

PET	Cell Type	R^2	p-val adj.
Aβ	neu	40.6%	5.01×10^{-186}
Aβ	end	29.7%	1.67×10^{-126}
Aβ	opc	24.0%	5.24×10^{-99}
tau	end	23.0%	3.08×10^{-94}
tau	neu	18.3%	1.90×10^{-73}
tau	opc	16.8%	6.77×10^{-67}
Aβ	mic	12.9%	1.09×10^{-50}
tau	oli	10.6%	2.74×10^{-41}
Aβ	oli	9.9%	1.28×10^{-38}
tau	mic	8.9%	1.09×10^{-34}
tau	ast	1.0%	3.98×10^{-5}
Aβ	ast	0.8%	3.15×10^{-4}

Conclusions: This study highlights a significant spatial relationship between the Aβ or tau deposition in AD and the proportion of the six different brain cell-type maps. Notably, the regions with a larger proportion of neuronal cell type were more associated with greater Aβ or tau deposition in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0812 / #2050

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ISOLATION OF SPONTANEOUSLY-RELEASED BRAIN EXTRACELLULAR VESICLES AND ITS IMPLICATIONS FOR STRESS-DRIVEN BRAIN PATHOLOGY

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Patrícia Amorim Gomes[1], Cristian Bodo[2], Carlos Nogueras-Ortiz[3], Martina Samiotaki[4], Minghao Chen[5], Carina Soares-Cunha[1], Joana Silva[1], Bárbara Coimbra[1], George Stamatakis[4], Liliana Santos[1], George Panayotou[4], Foteini Tzouanou[6], Clarissa L. Waites[7], Christos Gatsogiannis[5], Nuno Sousa[1], Dimitrios Kapogiannis[3], Bruno Costa-Silva[2], Ioannis Sotiropoulos[1]
[1]Life and Health Sciences Institute, Neurosciences, Braga, Portugal, [2]Champalimaud Centre for the Unknown, Systems Oncology Group, Lisbon, Portugal, [3]National Institute on Aging, Laboratory Of Clinical Investigation, Baltimore, United States of America, [4]Biomedical Sciences Research Center “Alexander Fleming”, Institute For Bioinnovation, Vari, Greece, [5]Max Planck Institute of Molecular Physiology, Department Of Structural Biochemistry, Dortmund, Germany, [6]Institute of Biosciences & Applications NCSR "Demokritos", Neurosciences, Athens, Greece, [7]Columbia University Medical Center, Department Of Pathology And Cell Biology, New York, United States of America

Aims: Extracellular vesicles (EVs) exhibit great potential for the theragnostics of brain disorders, representing a valuable tool for precision medicine which demands high-quality human biospecimens to unravel individual clinical profiles within pathologically heterogeneous disorders and develop precise patient-tailored treatments. Thus, the collection and characterization of physiologically relevant sEVs are of the utmost importance. However, standard brain EV isolation approaches rely on tissue dissociation, which can contaminate EV fractions. Therefore, we aim to develop a protocol that enriches spontaneously released vesicles and assess their contribution to stress-driven Alzheimer’s disease and depression pathology.
Methods: Based on multiscale analyses (e.g., cryo-EM, label-free proteomics, advanced flow cytometry, ExoView), we characterized the EV fraction isolated with this novel method. Moreover, EV biogenesis was pharmacologically manipulated to assess the validity of the method, while the injection of labelled-EVs into the mouse brain further supported the integrity of the isolated vesicles and their contribution to pathology.
Results: We hereby present an efficient purification method for sEV-enriched population spontaneously released by mouse and human brain tissue. In addition, we tested the significance of the protocol with manipulation of sEVs biogenesis, and under exposure to chronic stress, a clinically relevant precipitant of depression and Alzheimer's disease. Our findings show that the released method monitors the drug-evoked inhibition or enhancement of sEVs secretion while chronic stress induces the secretion of Tau-bearing exosomes accompanied by memory loss and mood deficits suggesting a potential role of sEVs in the brain response to stress and related stress-driven brain pathology.
Conclusions: Overall, the release method offers an isolation method for physiologically-relevant EVs and an ex vivo platform for manipulation of EV biogenesis, which will contribute to the characterization sEVs in brain function and pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0813 / #309

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

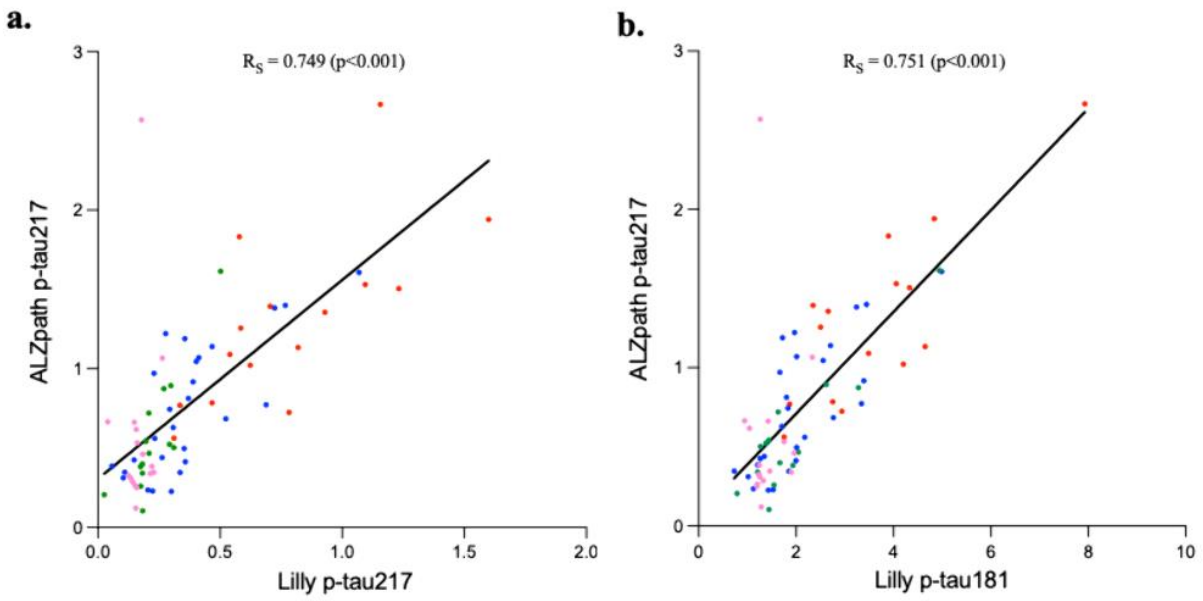
COMPARISON OF PLASMA ALZPATH P-TAU217 WITH LILLY P-TAU217 AND P-TAU181

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Divya Bali[1], Shorena Janelidze[1], Gemma Salvadó[1], Geidy Serrano[2], Thomas Beach[2], Andreas Jeromin[3], Oskar Hansson[1]
[1]Lund University, Clinical Memory Research Unit, Lund, Sweden, [2]Banner Sun Health Research Institute, Brain And Body Donation Program, Sun City, United States of America, [3]ALZPath, Inc, Alzpath, Inc, Carlsbad, United States of America

Aims: There is an urgent need for accurate and validated methods to measure plasma phosphorylated tau (p-Tau) biomarkers in Alzheimer´s disease (AD). Here we compare the performance of newly developed plasma ALZpath p-Tau217 assay to other established p-Tau assays such as Lilly p-Tau217 and Lilly p-Tau181.
Methods: We included 72 participants from the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) cohort, where we analysed antemortem collected plasma samples with ALZpath p-Tau217 as well as Lilly p-Tau217 and p-Tau181. The plasma biomarkers were compared with relevant post-mortem neuropathological measures.
Results: We found that ALZpath p-Tau217 correlated significantly with Lilly p-Tau217 and Lilly p-Tau181 (Figure1). ALZpath p-Tau217, Lilly p-Tau217 and Lilly p-Tau181 were found to be significantly associated with plaque load (ρ=0.53, ρ=0.73 and 0.59 $p<0.001$), when adjusting for tangle load (Table1). However, only Lilly p-Tau217 was significantly associated with tau tangle load (ρ=0.32, p=0.007), when adjusting for plaques. The correlations of ALZpath p-Tau217 and Lilly p-Tau181 with plaque load were comparable but Lilly p-Tau217 exhibited significantly higher correlations with plaques (ρ_{diff} =0.20; p=0.015) and tangles (ρ_{diff} =0.29; p=0.003) than ALZpath p-Tau217. ALZpath p-Tau217 and Lilly p-Tau181 predicted the elevated levels of ADNC, tangle, and amyloid pathology with similar accuracy (AUCrange, 0.74-0.79) but the AUC´s of Lilly p-Tau217 were significantly higher in comparison to ALZpath p-Tau217 (ADNC, AUC_{diff}=0.12, p_{diff}=0.021; Braak, AUC_{diff}=0.08, p_{diff}=0.021; CERAD, AUC_{diff}=0.11, p_{diff}=0.024) (Figure5) (Figure 2-4).

Figure 1



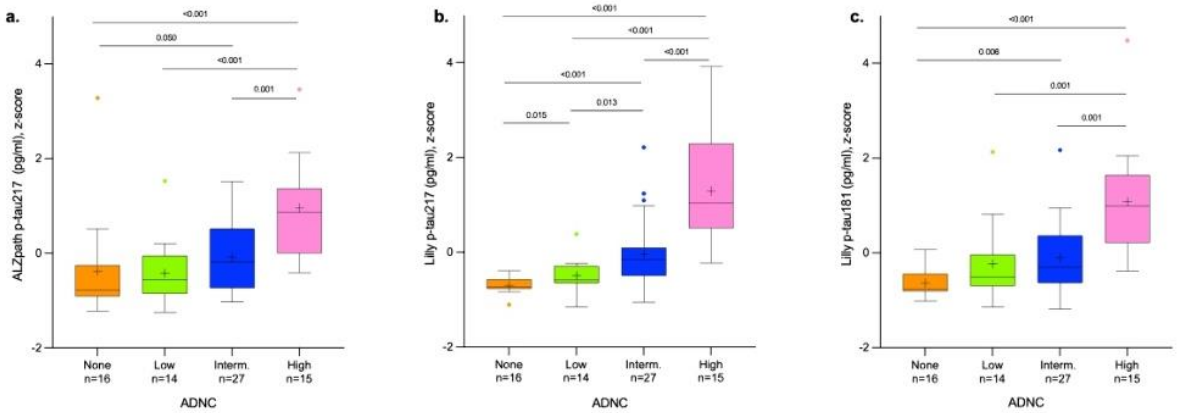
Correlation analysis between different plasma biomarkers
Spearman correlation analysis was used to assess the association between a) ALZpath p-tau217 and Lilly p-tau217 b) Alzpath p-tau217 and Lilly p-tau181.

Table1: Association between ALZpath p-tau217and Lilly p-tau181 or Lilly p-tau217 with amyloid or tangle load

Adjusted for covariates (age, sex and PMI) and pathology (tangles or plaques)			
	ρ	**p-value**	**p-value comp.**
Tangles			
ALZpath p-tau217	0.03	0.82	Ref.
Lilly p-tau181	0.15	0.21	0.29
Lilly p-tau217	0.32	0.007	0.003
Plaques			
ALZpath p-tau217	0.53	**<0.001**	Ref.
Lilly p-tau181	0.59	**<0.001**	0.491
Lilly p-tau217	0.73	**<0.001**	0.015

Partial correlation analysis was used to assess the association of ALZpath p-tau217 and Lilly p-tau181 or Lilly p-tau217 with amyloid or tangle load, adjusting for covariates such as age, sex and time between blood drawn and death (PMI) as well as other pathology (i.e., when looking at tangles adjusting for plaques and conversely). Bootstrapping was used to measure the significant differences between the correlation coefficients. Abbreviations: p-tau, phosphorylated tau.

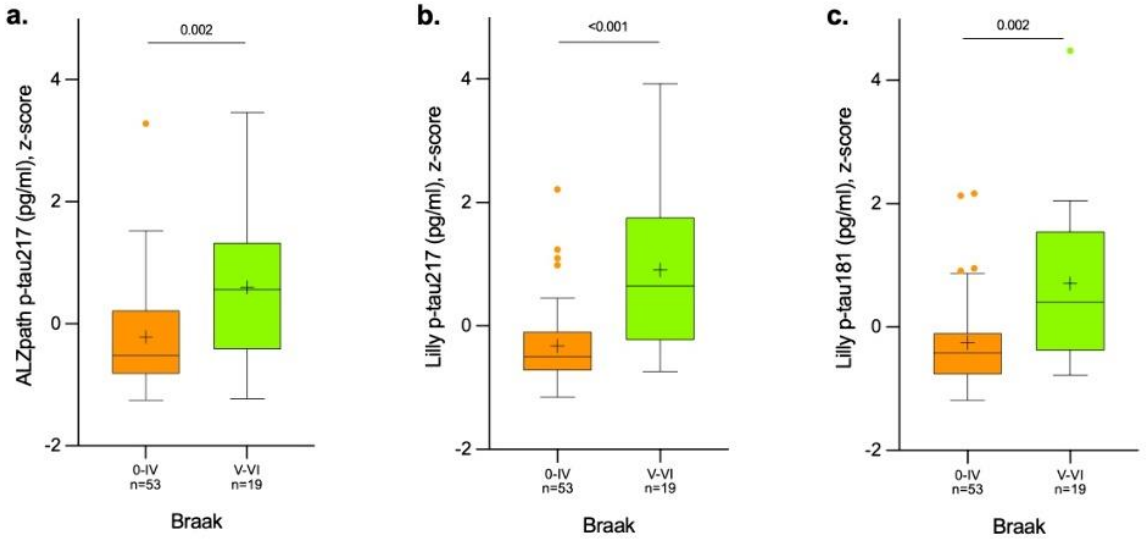
Figure 2



Levels of plasma biomarkers by ADNC classification

Plasma levels of a) ALZpath p-tau217 b) Lilly p-tau217 c) Lilly p-tau181 by ADNC classification. Overall group differences were assessed using Kruskal Wallis test and within group differences were measured using Mann-U-Whitney test (p-value). Boxes show interquartile range, the horizontal lines are the medians, and the whiskers are plotted using Tukey method. Abbreviations: ADNC, Alzheimer´s disease neuropathologic change; p-tau, phosphorylated tau.

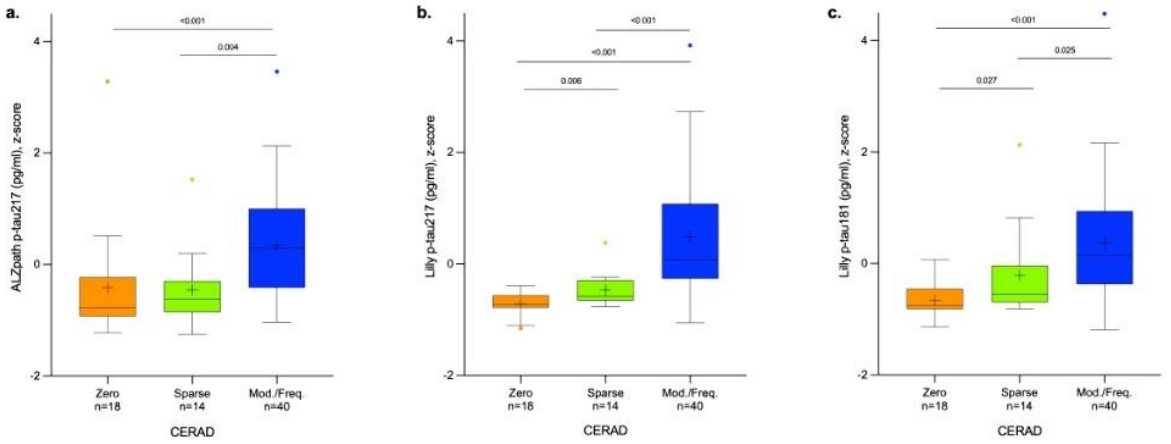
Figure 3



Levels of plasma biomarkers by Braak Staging

Plasma levels of a) ALZpath p-tau217 b) Lilly p-tau217 c) Lilly p-tau181 by Braak Staging. Overall group differences were assessed using Kruskal Wallis test and within group differences were measured using Mann-U-Whitney test (p-value). Boxes show interquartile range, the horizontal lines are the medians, and the whiskers are plotted using Tukey method. Abbreviations: p-tau, phosphorylated tau.

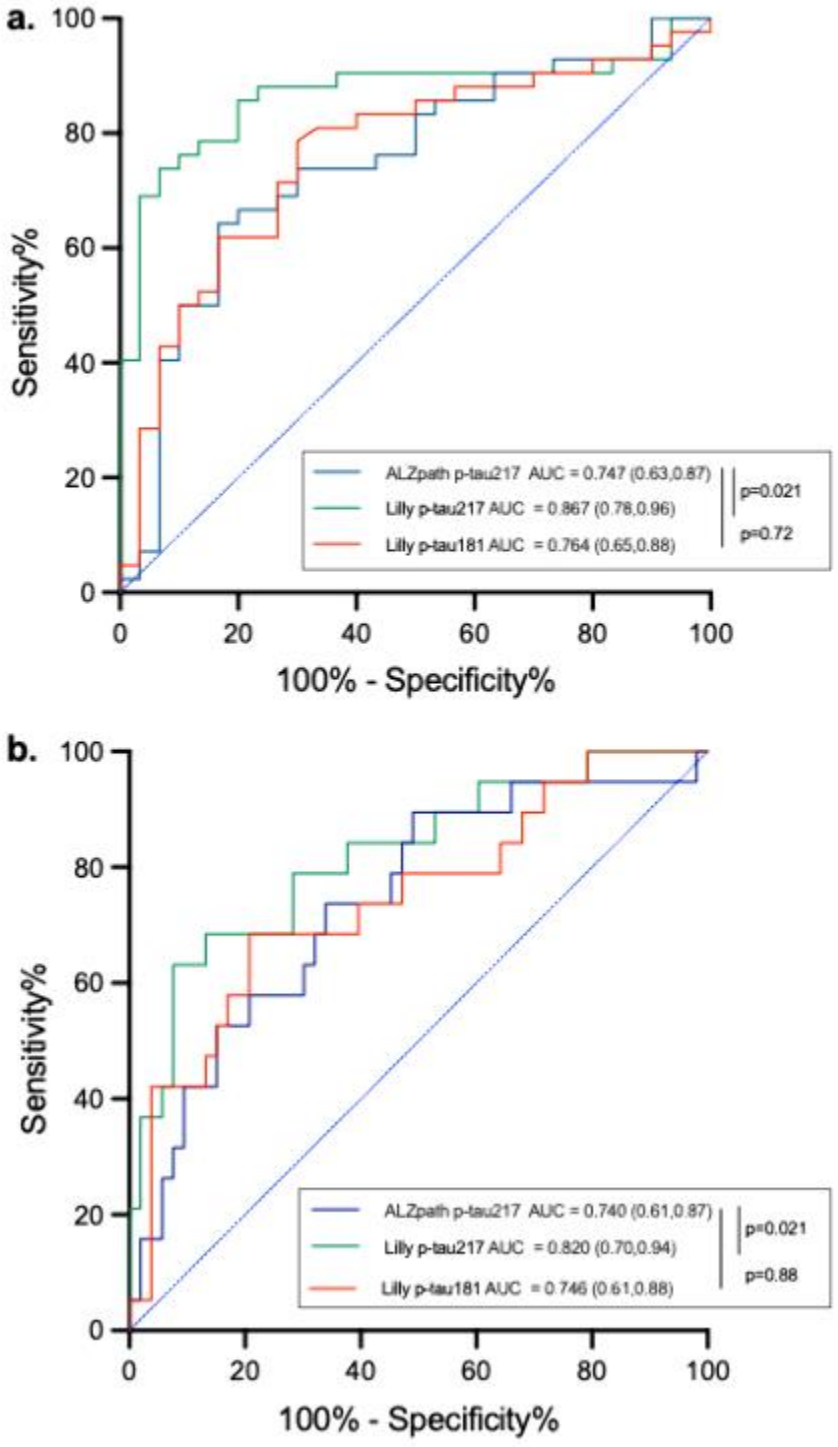
Figure 4

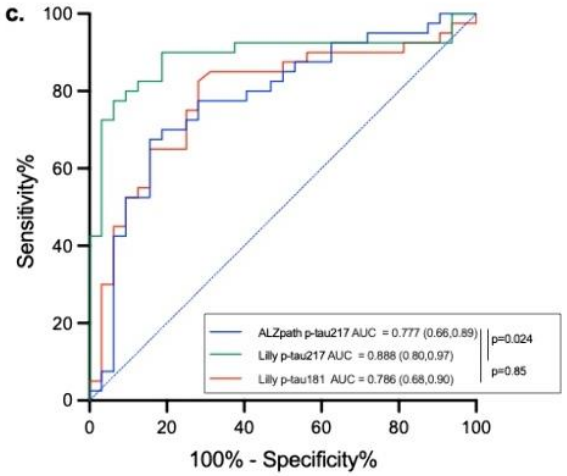


Levels of plasma biomarkers by CERAD classification

Plasma levels of a) ALZpath p-tau217 b) Lilly p-tau217 c) Lilly p-tau181 by CERAD classification. Overall group differences were assessed using Kruskal Wallis test and within group differences were measured using Mann-U-Whitney test (p-value). Boxes show interquartile range, the horizontal lines are the medians, and the whiskers are plotted using Tukey method. Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer´s Disease; p-tau, phosphorylated tau.

Figure 5


a.
Sensitivity%
100% - Specificity%
ALZpath p-tau217 AUC = 0.747 (0.63,0.87)
Lilly p-tau217 AUC = 0.867 (0.78,0.96)
Lilly p-tau181 AUC = 0.764 (0.65,0.88)
p=0.021
p=0.72
b.
Sensitivity%
100% - Specificity%
ALZpath p-tau217 AUC = 0.740 (0.61,0.87)
Lilly p-tau217 AUC = 0.820 (0.70,0.94)
Lilly p-tau181 AUC = 0.746 (0.61,0.88)
p=0.021
p=0.88



Predicting neuropathological scales classification

ROC curves analysis for predicting a) ADNC b) Braak c) CERAD classification. ADNC was dichotomized as negative (none/low) or positive (intermediate/high), CERAD was dichotomized as negative (low/sparse) or positive (moderate/frequent) and Braak stages were also dichotomized as negative (0-IV) or positive (V-VI). The DeLong test was used to determine whether the area under the curve (AUC) of two ROC curves was statistically different. Abbreviations: ADNC, Alzheimer´s disease neuropathologic change; AUC, Area under the curve; CI, confidence interval; CERAD, Consortium to Establish a Registry for Alzheimer´s Disease; p-tau, phosphorylated tau; ROC, receiver-operating characteristic.

Conclusions: ALZpath p-Tau217 exhibited similar performance as Lilly p-Tau181, but in this cohort associations between ALZpath p-Tau217 and the core measures of AD pathology were significantly lower in comparison with Lilly p-Tau217. These findings will need to be replicated in larger independent cohorts.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0814 / #147

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

IDENTIFICATION OF BIOMARKER PANELS USING SIMOA PLATFORM FOCUSING ON AD AND FTD

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Athanasia Chatziefstathiou[1], Sezgi Canaslan[2], Eirini Kanata[3], Kostas Vekrellis[4], Vasilios C. Constantinides[5], Elisabeth Kapaki[5], Matthias Schmitz[2], Inga Zerr[2], Timea Gombos[6], Konstantinos Xanthopoulos[3], Theodoros Sklaviadis[3], Dimitra Dafou[1]
[1]Aristotle University of Thessaloniki, Department Of Genetics, Developmental And Molecular Biology, Thessaloniki, Greece, [2]University Medical Center and the German Center for Neurodegenerative Diseases (DZNE), Department Of Neurology, Göttingen, Germany, [3]Aristotle University of Thessaloniki, School Of Pharmacy, Thessaloniki, Greece, [4]Biomedical Research Foundation of the Academy of Athens, Division Of Basic Neurosceiences, Athens, Greece, [5]School of Medicine, National and Kapodistrian University of Athens, Eginition Hospital, First Department Of Neurology, Athens, Greece, [6]Accelsiors AG, Management And Technical Position, Baar, Switzerland

Aims: Dementia is one of the leading causes of impaired ability in elderly people, affecting approximately 50 million people worldwide. Alzheimer's disease (AD) is the most common form of dementia representing almost 70% of cases, followed by frontotemporal dementia (FTD). The main goal of the current study is the identification of a suitable combination of biomarkers in cerebrospinal fluid (CSF) allowing differential diagnosis of AD from FTD patients and from healthy controls.
Methods: A multiplex panel of four biomarker candidates, namely glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), total tau (TAU) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) have been analyzed using the ultrasensitive single-molecule array (SIMOA) assay. To identify biomarker differences between CSF samples from a cohort of 43 AD, 33 FTD and 60 Control patients, Principal of sparse Partial Least Squares – Discriminant Analysis (sPLS-DA) was used.
Results: We observed that in CSF samples all four biomarkers were significantly elevated in AD patients compared to control samples. Receiver operating characteristic (ROC) curve analysis resulted in a very good diagnostic accuracy as indicated by the area under the curve (AUC) values of 0.71-0.94 & $p \leq 0.0003$. We also observed that CSF-NfL, CSF-TAU & CSF-UCH-L1 were significantly elevated in FTD patients compared to controls, with an AUC of 0.72-0.91 & $p \leq 0.0006$. Finally, we also noticed an increase on CSF-GFAP and CSF-TAU in AD compared to FTD patients, with an AUC of 0.7- 0.8 and $p \leq 0.004$.
Conclusions: Our study suggests that NfL, TAU and UCH-L1 could evolve into useful biomarkers to discriminate between AD or FTD and healthy individuals, while GFAP and TAU could be used for differential diagnosis between AD and FTD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0815 / #2264

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA PHOSPHORYLATED TAU 217 AS AN EARLY BIOMARKER FOR ALZHEIMER'S DISEASE

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Maciej Dulewicz[1], Fernando Gonzalez-Ortiz[1], Przemyslaw Kac[1], Agnieszka Kulczńska-Przybik[2], Barbara Mroczko[2], Thomas Karikari[1], Michael Turton[3], Peter Harrison[3], Johannes Kornhuber[4], Jörg Hanrieder[1], Henrik Zetterberg[1], Kaj Blennow[1], Piotr Lewczuk[4]
[1]University of Gothenburg, Psychiatry And Neurochemistry, Mölndal, Sweden, [2]Faculty of Medicine, Neurodegeneration Diagnostics, Białystok, Poland, [3]Bioventix, Plc, Farnham, United Kingdom, [4]Universitätsklinikum Erlangen and Friedrich-Alexander Universität Erlangen-Nürnberg, Psychiatry And Psychotherapy, Erlangen, Germany

Aims: The primary goal of this study is to investigate the diagnostic utility of measuring plasma and cerebrospinal fluid (CSF) pTau217 levels in identifying possible AD cases. This study intends to evaluate how effectively the concentrations of pTau217 in the blood and CSF can differentiate individuals with possible AD in comparison to the control group.
Methods: Plasma and CSF concentrations of pTau217 were measured by an in-house single molecule array (Simoa) developed at the University of Gothenburg (UGOT pTau217). The quantitative assessment of classical biomarkers (Aβ-42, Aβ-42/Aβ-40, Tau, and pTau181) in the CSF of patients with possible AD according to the Erlangen Score algorithm (ER 2 and 3) and controls (ER 0) were performed by Lumipulse.
Results: Significantly higher CSF and plasma concentrations of pTau217 were noticed in possible AD patients compared to controls. The levels of CSF pTau217 correlated positively with pTau217 in plasma and pTau181 and negatively with CSF Aβ1-42 and Aβ ratio. Similar results were observed for plasma levels of pTau217.
Conclusions: As new anti-Aβ therapies become available for AD, blood biomarker could be used to screen patients for treatment eligibility and monitoring. The results of the present study indicate that plasma pTau217 could be potentially a valuable blood biomarker for detecting early AD pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0816 / #872

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

MALDI-MS METHOD DEVELOPMENT TO DETECT PHOSPHORYLATED TAU FRAGMENTS IN CEREBROSPINAL FLUID

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Yusaku Hioki, Rie Yamamoto, Sadanori Sekiya, Shinichi Iwamoto, Koichi Tanaka
Shimadzu Corporation, Koichi Tanaka Mass Spectrometry Research Laboratory, Kyoto, Japan

Aims: Tau pathology in brain and increased total and phosphorylated tau concentrations in CSF are hallmarks of Alzheimer's disease (AD). In recent years, analytical methods that utilize mass spectrometry, which can measure multiple regions or phosphorylation site occupancies in tau, have been developed, and their performance as biomarker for AD has been reported. This study aims to develop a simple, robust, and reliable analytical method for tau and p-tau in CSF, taking advantage of the features of MALDI-MS.
Methods: Immunoprecipitation was carried out using monoclonal antibody HT7 or a combination of HT7 and BT2 to capture the mid-region of tau. Isolated and enriched tau fragments were then analyzed by MALDI-MS under matrix conditions that facilitate the detection of a hydrophilic group of peptides in the mid-domain.
Results: More than a dozen tau fragments were detected in 0.5 mL of CSF, including fragment that appeared to be multi-phosphorylated. In the case of additional trypsin digestion, MS/MS analysis of a possibly phosphorylated fragment showed a -98 peak, suggesting that it was phosphorylated. Further evaluation, including identification of fragments, is warranted.
Conclusions: Our simple analytical workflow combining immunoprecipitation with high recovery and MALDI-MS could be applicable to the analysis of tau fragments including phosphorylation in CSF.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0817 / #2458

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

NEW SITE-SPECIFIC PHOSPHO-TAU BIOMARKERS FOR ALZHEIMER'S EARLY DETECTION

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Bin Xu[1], Shih-Hsiu Wang[2], Ling Wu[2], Nailya Gilyazova[1], John Ervin[3]
[1]BRITE Research Institute of North Carolina Central University, Pharmaceutical Sciences, Durham, United States of America, [2]Duke University Medical Center, Pathology, Durham, United States of America, [3]Duke University Medical Center, Neurology, Durham, United States of America

Aims: Currently reliable biomarkers are lacking for detecting mild cognitive impairment (MCI), an early stage of Alzheimer's disease.
Methods: We developed a site-specific phospho-tau (p-tau) antibody screening approach that targets high-molecular-weight misfolded p-tau aggregates in brain. We screened a comprehensive set of p-tau epitopes targeting all major phosphorylation sites with high AD patient frequencies.
Results: Using postmortem AD dementia, MCI, and normal controls brains, we identified multiple new phospho-tau epitopes including p-tau396 and p-tau422 as new epitopes for differential detection of AD dementia and MCI. From quantitative ELISA, p-tau396 and p-tau422 were not only able to differentiate subjects with AD dementia from controls (AUC=0.983, $p<0.0001$ for p-tau396; AUC=1.000, $p<0.001$ for p-tau422), but was also able to differentiate subjects with MCI from controls with diagnostic performance (AUC=0.83, $p<0.05$ for p-tau396; AUC=0.91, $p<0.01$ for p-tau422) that are more sensitive/selective than comparison biomarkers p-tau181 (AUC=0.72, $p<0.05$), p-tau217 (AUC=0.75, $p<0.01$) and p-tau231 (AUC=0.58, $p=0.26$) in our study. We further validated our findigns with immunohistochemical staining of postmortem brain tissues with p-tau396 and p-tau422 antibodies. Both epitopes showed increased neurofibrillary tangle pathology in the hippocampus and temporal cortex of subjects with MCI. Image analysis using machine-learning algorithms reliably detected more severe tau burden in MCI brains versus cognitively normal controls, even among subjects with the same Braak stages.
Conclusions: Brain p-tau396 and p-tau422 levels strongly correlate with cognitive status in early AD. Our findings provide potential targets for MCI neuropathological staging and for developing novel fluid-based biomarker tests for early AD diagnosis.

P0818 / #2615

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

BRAIN-DERIVED TAU OLIGOMERS IN PLASMA BRAIN-DERIVED EXTRACELLULAR VESICLES AS A POTENTIAL PREDICTIVE BIOMARKER FOR ALZHEIMER'S DISEASE.

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Michela Marcatti, Wen-Ru Zang, Rakez Kayed, Giulio Taglialatela
University of Texas Medical Branch, Neurology, Galveston, United States of America

Aims: Alzheimer's disease (AD) represents a pressing global healthcare issue; therefore, it is necessary to establish reliable predictive biomarkers to identify individuals at a high risk of developing AD, enabling the potential initiation of treatments during the preclinical stage. Our aim is to address this imperative by investigating plasma brain-derived extracellular vesicles (pl-BDEVs) and brain-derived tau oligomers (BDTOs) as potential biomarkers for early AD detection.
Methods: In this study, we employed plasma samples longitudinally collected from participants enrolled in the Texas Alzheimer's Research and Care Consortium (TARCC), who were initially cognitively normal or displayed mild cognitive impairment (MCI), and later either progressed to AD (termed "converters") or remained cognitively normal/MCI (termed "non-converters"). We enriched pl-BDEVs from central nervous system (CNS) cell types, including neurons, microglia, astrocytes, and oligodendrocytes. These isolated pl-BDEVs were subject to comprehensive analyses, such as nanoparticle tracking analysis for size, number, and distribution assessments, and western blotting to evaluate the expression of extracellular vesicles markers (CD63, CD9, CD81) and CNS cell type markers (L1CAM, TMEM119). Western blotting was also employed to detect the presence of BDTOs in pl-BDEVs.
Results: We successfully detected BDTOs in pl-BDEVs derived from MCI plasma samples and identified differences between converters (individuals who progressed to AD) and non-convertrs (individuals who remained cognitively stable).
Conclusions: Our study highlights BDTOs as potential indicators of AD pathology in plasma samples, underscoring their significance as a novel class of biomarkers. By exploring previously uncharted BDTO conformers in pl-BDEVs, we contribute to the quest for predictive AD biomarkers. Discovering distinct BDTOs conformers in peripheral BDEVs holds promise for enhancing preclinical forecasting and advancing early-stage AD treatments.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0819 / #1990

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DEVELOPMENT OF NULISA™ CNS DISEASE PANEL FOR COMPREHENSIVE PROTEOMIC PROFILING OF NEURODEGENERATIVE DISEASES

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Xiao-Jun Ma, Shweta Iyengar, Shalaka Deshmukh, Sean Kim, Xiaomei Xu, Wei Feng, Xiaolei Qiu, Bingqing Zhang, Yuling Luo
Alamar Biosciences, LLC, Research And Development, Fremont, United States of America

Aims: Objectives: The pursuit of blood biomarkers for neurodegenerative diseases (NDDs) has been hampered by the lack of a proteomic tool with the required sensitivity to detect exceedingly low levels of brain-derived proteins in blood. We recently developed a novel proteomic technology called NULISA™ with attomolar sensitivity and high multiplexing in a fully automated system. In this study, we developed the NULISA CNS disease panel, a highly multiplexed assay designed to characterize key hallmarks of NDDs in blood and cerebrospinal fluid (CSF). We evaluated the performance of this panel in plasma and CSF samples from NDD patients and healthy controls.
Methods: Methods: A 120-plex NULISA including known disease markers such as neurofilament light, synuclein A and phosphorylated Tau (p-Tau181, p-Tau217, and p-Tau231) was developed and used to analyze plasma (n=38) and CSF (n=29) samples from NDD patients and age-matched controls. Target detectability and assay precision were assessed, and linear regression analysis was performed for each target for differential abundance between disease and controls.
Results: Results: We developed a CNS disease panel of 120 targets implicated in various pathways and processes characteristic of NDDs. Using 10 mL plasma or CSF, NULISA demonstrated high sensitivity detecting ~95% of the targets in plasma and ~80% in CSF and high precision with a median CV of ~6.0%. Linear regression analysis identified both known and novel proteins with significant differences in abundance between disease and age-matched controls.
Conclusions: Conclusion: We developed a comprehensive CNS disease-targeted panel for the NULISA platform to address the growing demand for blood-based biomarker discovery and validation. This study demonstrated the potential of the NULISA CNS disease panel to advance research in blood-based biomarkers for early neurodegenerative disease detection and monitoring and eventually therapeutic intervention.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0820 / #1989

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

STRATIFICATION OF PARKINSON SYNDROMES BY EXOSOME TAU PROTEIN PROFILING

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Mojtaba Nemati, Günter Höglinger, Franziska Hopfner
LMU hospital, Department Of Neurology, München, Germany

Aims: We aimed to explore the molecular profile of neuronal exosomes from different Parkinson's syndromes regarding their Tau protein profile.
Methods: Exosomes of neuronal origin were enriched through immunoprecipitation using the cell surface marker L1CAM. The Tau protein contents of the purified exosomes were then examined using ultrasensitive SIngle MOlecule Array (SIMOA) assays.
Results: The exosomes captured using L1CAM were confirmed to be positive for the neuronal markers.
The total Tau protein and Phosphorylated Tau protein contents of each exosome population were then compared to generate molecular profiles for the different Parkinson's syndromes.
Conclusions: Here we characterize the Tau protein and phosphorylated Tau protein contents of blood-derived exosomes from neuronal exosomes providing molecular profiles of different Parkinson's syndromes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0821 / #2445

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ALZHEIMER'S DISEASE BIOLOGICAL AND CLINICAL STAGES CORRELATION IN A REAL-WORLD MEMORY CLINIC POPULATION

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Marina Scop Medeiros[1], Pamela Lukasewicz Ferreira[2], Bruna Bellaver[2], Hussein Zalzale[2], Guilherme Povala[2], Guilherme Negrini[2], Francieli Rohden[2], Markley Silva Oliveira Junior[3], Sarah Abbas[4], Firoza Lussier[5], Helmet Karim[2], Chang Hyung Hong[6], Hyun Rho[6], Sang Son[6], Tharick A Pascoal[7]
[1]University of Pittsburgh, Psychiatry, Pittsburgh, Brazil, [2]University of Pittsburgh, Psychiatry, PITTSBURGH, United States of America, [3]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America, [4]3501 Forbes Avenue, Psychiatry, Pittsburgh, United States of America, [5]University of Pittsburgh, Psychiatry, Pittsburgh, United States of America, [6]Ajou University School of Medicine, Psychiatry, Suwon, Korea, Republic of, [7]Department of Neurology and Psychiatry, University Of Pittsburgh School Of Medicine, Pittsburgh, United States of America

Aims: To investigate whether a 4-level biological staging system involving amyloid-beta (AB) PET, plasma GFAP, plasma p-tau217 and plasma NfL correlates with clinical stages as measured by Global Deterioration Scale (GDS) in patients with Alzheimer's Disease (AD) from South Korean memory clinics.
Methods: We assessed data from BICWALTZS, a cohort composed of multiple memory clinics. Biological stages were defined as exclusively AB PET positive (stage 1), additional presence of elevated plasma GFAP (stage 2), additional elevated plasma p-tau-217 (stage 3) and additional elevated plasma NfL (stage 4). Classification and cut-off points are shown in Table1. For clinical staging, we used the GDS, ranging from 1 (Preclinical) to 7 (very severe cognitive decline), as described in Table2.

Biological Stages	1	2	3	4
Biomarker	Aβ PET only	Additional Plasma GFAP	Additional Plasma P-tau217	Additional NFL
Cut-off	Visual interpretation	192.68pg/mL *	0.23pg/mL*	36pg/mL *

Table1. Classification criteria for biological stages. * Cut-off points were determined as two standard deviations (SD) above the mean of cognitively unimpaired AB-negative individuals.

1	2	3	4	5	6	7
No cognitive decline	Very mild cognitive decline	Mild cognitive decline	Moderate cognitive decline	Moderately severe cognitive decline	Severe cognitive decline	Very severe cognitive decline

Table2. Classification criteria for clinical stages according to Global Deterioration Scale (GDS).

Results: Of the total clinical population (N=1359), 230 patients were AB-PET positive and clinically diagnosed with subjective memory decline or MCI (n=109) or AD (n=121). The distribution of clinical cases across biological stages is represented in Figure 1. The figure demonstrates an increase in later clinical stages (mainly stages 4 and 5) in later biological stages. Biological stages were able to predict clinical stages, even controlling for age, sex, APOE status and years of education (R=0.2486, P=< 2e-16).

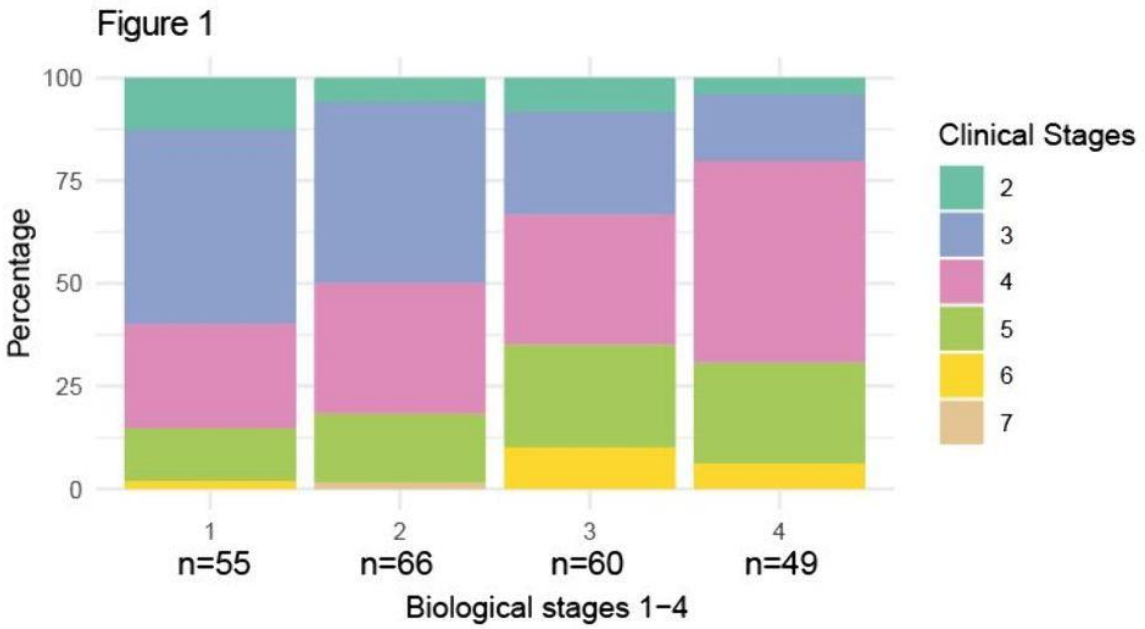


Figure1. Distribution in percentages of clinical stages across biological stages in the BICWALTZS memory clinic cohort. Biological and clinical stages are described in Table1 and Table2.

Conclusions: Fluid biomarkers may serve as proxy of higher clinical burden of AD pathology, even in the absence of Tau PET for biological staging, which is less accessible although required in the latest NIA-AA criteria (as of July 2023 – draft). Importantly, we demonstrated that creating a biological staging system based on fluid biomarkers may better characterize the disease in real-world large populations. More studies are needed to assess the prognostic value of these fluid biomarkers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0822 / #143

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

A PERIPHERAL CANDIDATE MICRORNA PROFILE FOR EARLY DIAGNOSIS OF SPORADIC ALZHEIMER'S DISEASE

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Maria Tsamou[1], Faidra Kalligerou[2], Eva Ntanasi[2], Nikolaos Scarmeas[2], Susanna Skalicky[3], Matthias Hackl[3], Erwin Roggen[1]
[1]ToxGenSolutions, Toxgensolutions, Maastricht, Netherlands, [2]Aiginition Hospital, 1st Neurology, National And Kapodistrian University Of Athens, Athens, Greece, [3]TamiRNA, Tamirna, Vienna, Austria

Aims: Late-onset or sporadic Alzheimer's disease (sAD) is a progressive, neurodegenerative, and age-related disease, leading to irreversible brain damage along with cognitive impairment and memory loss. The underlying pathological changes take place several years prior to the appearance of the first clinical symptoms, however, due to the disease's complexity, the diagnosis of sAD at the preclinical stage remains poor and inaccurate. The aim was to identify changes in circulating microRNA (miR) expression to detect early biomarkers of underlying sAD pathology.
Methods: A set of candidate miRs, earlier detected in biofluids from subjects at early stage of sAD compared to cognitively healthy controls, was retrieved from available publicly data, and was linked to processes described by the recently proposed Tau-driven adverse outcome pathway (AOP) for memory loss. Quantitative RT-PCR was used to measure the relative expression of the selected miRs in serum samples of 12 cases (mild cognitive impairment (MCI)) and 29 healthy controls (HC), recruited within the ongoing Aiginition Longitudinal Biomarker Investigation Of Neurodegeneration (ALBION) cohort study. Data on the protein levels of amyloid-β ($A\beta_{42}$), total and phosphorylated Tau (t-tau and p-tau), in cerebrospinal fluid (CSF) as well as the cognitive z-scores of the participants were also retrieved.
Results: Each doubling in the relative expression of 13 miRs in serum was associated with changes in the odds of having MCI (vs HC) or having pathological proteins ($A\beta_{42}$, t-tau and p-tau) in their CSF, or with the global composite z-score.
Conclusions: These candidate human circulating miRs may be of great importance in early diagnosis of sAD. There is an urgent need for confirming these proposed early predictive biomarkers for sAD, which can further contribute not only to societal but also to economic benefits.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0823 / #1502

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EXPLORING INFLAMMATORY EXTRACELLULAR VESICLE SURFACE ANTIGENS AS BIOMARKERS FOR ALZHEIMER'S DISEASE

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Elena Vacchi[1,2], Carlotta Cimiotti[1], Sara Bolis[3], Emanuele Pravatà[1,4], Sandra Pinton[2], Stefania Rossi[4], Lucio Barile[1,3], Alain Kaelin Lang[1,4], Paolo Paganetti[1,5], Leonardo Sacco[4], Giorgia Melli[1,2,4]
[1]Università della Svizzera Italiana, Faculty Of Biomedical Sciences, Lugano, Switzerland, [2]Laboratories for Translational Research, EOC, Neurodegenerative Diseases Group, Bellinzona, Switzerland, [3]Laboratories for Translational Research, EOC, Cardiovascular Theranostic Group, Bellinzona, Switzerland, [4]Ente Ospedaliero Cantonale, Neurocenter Of Southern Switzerland, Lugano, Switzerland, [5]Laboratories for Translational Research, EOC, Aging Disorders Group, Bellinzona, Switzerland

Aims: Alzheimer's disease (AD) is the most common irreversible neurodegenerative disorder of the elderly. Its clinical diagnosis can be confirmed with expensive and invasive laboratory exams. Thus, new biomarkers and diagnostic tools to facilitate the proper management of patients are required. With the aim to identify new biomarkers for AD, we characterized the expression of multiple plasmatic Extracellular Vesicles (EVs) surface markers, related to immune response and inflammation. Indeed, emerging evidence suggests a central role of inflammation in the development and pathogenesis of AD.
Methods: Thirty confirmed AD patients, among which 7 with mild cognitive impairment (MCI) and 23 with moderate-severe dementia, and 20 healthy controls (HC) were enrolled. Patients underwent clinical evaluation, cerebrospinal fluid Aβ and Tau analysis, and magnetic resonance imaging (MRI). All subjects underwent blood collection. Plasma-derived EVs were analyzed by flow cytometry to measure the expression of 37 EV surface markers.
Results: AD-derived EVs showed higher CD62P and lower CD2 expression compared to those from HC. CD62P was associated with AD diagnosis, displaying good diagnostic performance, correlating with cognitive impairment, and showing higher expression in AD patients with pathological levels of Aβ42 in the CSF. These results were re-confirmed considering the moderate-severe patients only. In addition, CD41b was found increased in MCI subjects compared to both HC and severe AD showing reliable diagnostic performance for the MCI group.
Conclusions: Plasmatic EV surface markers characterization reinforces the role of EVs as promising biomarkers for AD, opening the possibility of developing non-invasive diagnostic tools.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0824 / #2855

Poster Topic: *Theme B: Taupathies / B04.e. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

INCREASING PLASMA ABETA42/40 ACCURACY BY COMBINING P-TAU181 LEVELS THAT ARE MEASURED BY FULLY AUTOMATED IMMUNOASSAY PLATFORM

POSTERS: B04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Kazuya Matsumoto[1], Shun Murakami[1], Kengo Ishiki[1], Kazuto Yamashita[1], Masahiro Miura[1], Shigeki Iwanaga[2], Toshiyuki Sato[1], Atsushi Iwata[3]
[1]Sysmex Corporation, Central Research Laboratories, Kobe, Japan, [2]Sysmex Corporation, Technology Strategy, Kobe, Japan, [3]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Department Of Neurology, Tokyo, Japan

Aims: Confirming amyloid pathology in the brain is necessary for determining the eligibility for Alzheimer's disease treatment with disease-modifying therapeutics. Blood-based biomarkers have attracted attention for invasiveness and accessibility, including the plasma β-amyloid1-40, 1-42 ratio (Aβ42/40) and phosphorylated tau (p-tau). We have previously shown that plasma Aβ42/40 measured by an Automated Immunoassay System HISCL™-5000 / HISCL-800 can predict amyloid pathology with high accuracy. In this study, clinical performance was evaluated in combination with prototype p-tau181 assay to investigate the additional potential of blood biomarkers in predicting amyloid pathology.
Methods: Plasma Aβ42/40 and p-tau181 were measured in 25 samples collected at Tokyo Metropolitan Geriatric Hospital and Institute of gerontology to assess their ability to predict amyloid pathology. Amyloid pathology in the brain was determined by amyloid PET scans as assessed by visual read method. The distribution of each biomarker level in the PET-positive and PET-negative groups was compared by Mann-Whitney U test. The predictive performance of amyloid pathology was evaluated by ROC analysis.
Results: The samples were classified into 8 amyloid PET positive and 17 negative groups. Both Aβ42/40 and p-tau181 showed significant differences between two groups ($p<0.005$, $p<0.05$, respectively). Furthermore, ROC analysis showed that the area under the curve (AUC) value was increased when combining p-tau181 with Aβ42/40 (AUC: 0.890) compared to Aβ42/40 alone (AUC: 0.857).
Conclusions: Our study has demonstrated that the plasma p-tau181 assay increased the predictive accuracy of plasma Aβ42/40 for amyloid PET status. In the future, we would increase the number of clinical samples to confirm the reliability of this specific combination. Through the expanding of our research, our goal is to contribute to the advancement of AD diagnosis using blood-based biomarkers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0825 / #2043

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

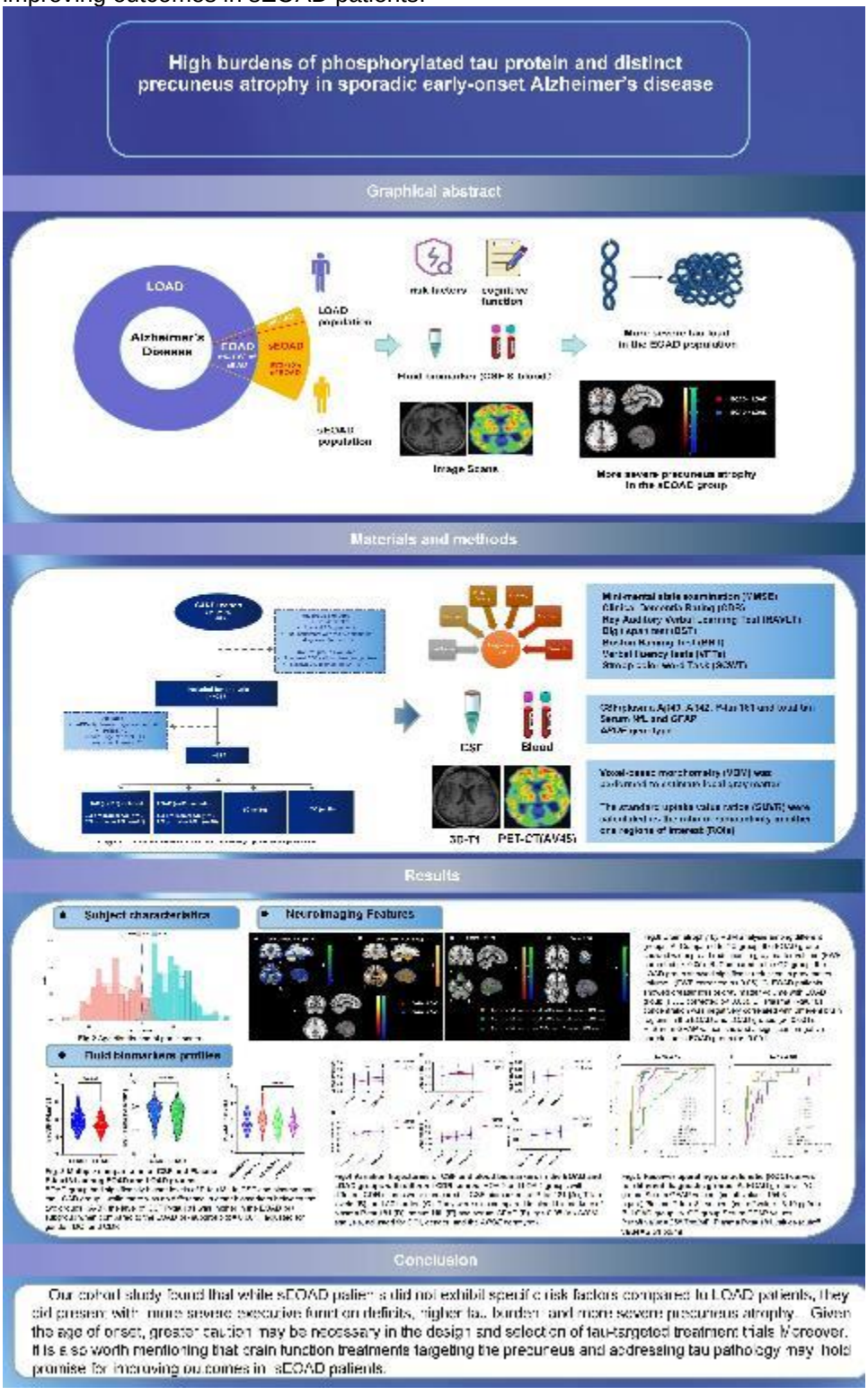
HIGH BURDENS OF PHOSPHORYLATED TAU PROTEIN AND DISTINCT PRECUNEUS ATROPHY IN SPORADIC EARLY-ONSET ALZHEIMER'S DISEASE

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Xinyi Lv[1], Yong Shen[1], Jiong Shi[2]
[1]The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, Department Of Neurology, Hefei, China, [2]The FirsAffiliated Hospital of USTC, Department Of Neurology, HeiFei, China

Aims: Early onset Alzheimer's disease (EOAD) is a rare but devastating sub-classification of AD. We selected patients who had an age of onset younger than 65 years. Most of these patients did not have a family history of dementia.The objective of this study was to gather additional evidence regarding the clinical characteristics and potential underlying mechanisms of sEOAD within the population.
Methods: sEOAD (n=110), late onset AD (LOAD, n=89), young controls (YC, n= 50), and old controls (OC, n=25). Fluid biomarkers were measured with single molecule array, including cerebrospinal fluid (CSF) and plasma Aβ42, Aβ40, P-tau181, T-tau, serum NfL, and GFAP.
Results: We found sEOAD patients exhibited more severe executive function impairment and bilateral precuneus atrophy (p< 0.05, FWE corrected) compared with LOAD patients. sEOAD patients showed elevated CSF and plasma P-tau181 levels (153 ±81.2 pg/ml, p= 0.002; 6.08± 2.26 pg/ml, p= 0.046 respectively). Furthermore, a significant correlation was observed between precuneus atrophy and serum GFAP levels in the sEOAD group (p< 0.001). Serum GFAP levels (AUC= 96.0%, cutoff value= 154.3 pg/ml) showed excellent diagnostic value in distinguishing sEOAD patients from the control group. These preliminary findings highlighted the crucial role of tau protein phosphorylation in the pathogenesis and progression of sEOAD.
Conclusions: Our cohort study found that while sEOAD patients did not exhibit specific risk factors compared to LOAD patients, they did present with more severe executive function deficits, higher tau burden, and more severe precuneus atrophy. Given the age of onset, greater caution may be necessary in the design and selection of tau-targeted treatment trials.Moreover, it is also worth mentioning that brain function treatments targeting the precuneus and addressing tau pathology may hold promise for

improving outcomes in sEOAD patients.



AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0826 / #1680

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

INVESTIGATION OF METAL ACCUMULATION IN THE HUMAN BRAIN USING HIGH RESOLUTION SECONDARY ION MASS SPECTROMETRY (SIMS) IMAGING TECHNIQUES

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Zahraa Berro[1], Maria Angels Subirana[2], Clementine Warres[3], Tatjana Taubitz[4], Jean Audinot[1], Fabio A. Zucca[5], Luigi Zecca[5], Michel Mittelbronn[6], Felix Borgmann[6], Antje Biesemeier[7]
[1]Advanced Instrumentation for Nano-Analytics, Materials Research and Technology Department, Luxembourg Institute of Science and Technology, 41 Rue Du Brill, Esch-Belval Belvaux Sanem, Luxembourg, [2]Institut des Sciences Analytiques et de Physico-Chimie pour l'Environnement et les Matériaux (IPREM), UMR 5254, Cnrs, Université De Pau Et Des Pays De L'adour, E2s Uppa, Pau, France, [3]University of Tübingen, Nmi Natural And Medical Sciences Institute At The University Of Tübingen, Tubingen, Germany, [4]Max Planck Institute of Molecular Physiology, Department Of Structural Biochemistry, Dortmund, Germany, [5]National Research Council of Italy, Institute Of Biomedical Technologies, Segrate, Italy, [6]Laboratoire National de Santé, Luxembourg Center Of Neuropathology, Dudelange, Luxembourg, [7]Luxembourg Institute of Science and Technology, Advanced Instrumentation For Nano-analytics, Materials Research And Technology Department, Esch-Belval Belvaux Sanem, Luxembourg

Aims: One characteristic hallmark observed in the brain during aging and Parkinson's disease (PD) is the neuronal accumulation of iron and other toxic metals in substantia nigra (SN) and locus coeruleus (LC), e.g., in the Neuromelanin (NM) organelle (having melanin, lipid and protein-based partitions of less than 100 nm). However, few studies attempted high lateral resolution subcellular (re)distribution analyses of these metals. Therefore, this work aims to study metal distributions in NM of LC using novel analytical approaches based on secondary ion mass spectrometry (SIMS) and to correlate the changes with the onset of PD.
Methods: Epon-embedded or fresh frozen human LC from elderly and PD patients were investigated by light, fluorescence and electron microscopy for high resolution imaging and immunohistochemistry, and the chemical analysis was performed by analytical electron microscopy and mass spectrometric imaging (MSI).
Results: We present first results for the chemical identification of sub-organellar NM metal storage sites in LC. The semi-quantitative SIMS data shows higher accumulation of iron in NM in comparison to the cytoplasmic and other cellular compartments, without accumulation of copper or zinc in LC as compared to previous analysis on SN NM. Additional immunohistochemistry shows the molecular profiling of LC NM with a comparison between PD and non-PD patients.
Conclusions: We analysed the sub-cellular localization of metals in elderly patients using novel high-resolution chemical and structural imaging techniques in addition to the molecular profiling. Continued work will be done on fresh frozen samples of PD specimen for a better close to native analysis of PD pathophysiology also including molecular MSI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0827 / #1545

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

COMPARISON OF THE DIAGNOSTIC ACCURACY OF RESTING-STATE FMRI DRIVEN MACHINE LEARNING ALGORITHMS IN THE DETECTION OF MILD COGNITIVE IMPAIRMENT

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Gergő Bolla[1], Dalida Berente[2], Anita Andrassy[3], Janos Zsuffa[3], Anita Kamondi[3], Mate Kiss[4], Andras Horvath[3]
[1]Semmelweis University, Neurosciences ("jÁnos SzentÁgothai"), Budapest, Hungary, [2]Semmelweis University, School Of Phd Studies, Budapest, Hungary, [3]National Institute of Mental Health, Neurology and Neurosurgery, Neurocognitive Research Center, Budapest, Hungary, [4]Siemens Healthcare, Siemens Healthcare, Budapest, Hungary

Aims: Mild cognitive impairment (MCI) is a potential therapeutic window in the prevention of dementia; however, automated detection of early cognitive deterioration is an unresolved issue. The aim of our study was to compare various classification approaches to differentiate MCI patients from healthy controls, based on rs-fMRI data, using machine learning algorithms.
Methods: A local database was used from two independent institutions. Three fMRI parameters were used in five feature selection algorithms: Local Correlation, Intrinsic Connectivity, and Fractional Amplitude of Low Frequency Fluctuations. Support Vector Machine (SVM) and Random Forrest (RF) methods were applied for classification. Intracalcarine cortex, Superior Parietal lobule, Superior Frontal gyrus, Supracalcarine Cortex, Inferior Temporal gyrus and Precentral Gyrus were identified via feature selection algorithms as the most relevant features.
Results: We achieved a relatively wide range of 78-87% accuracy for the various feature selection methods with SVM combining the three rs-fMRI parameters. RF provided a more harmonized result among the feature selection algorithms with 80-84% accuracy.
Conclusions: Our results suggest that the combination of various fMRI parameters is needed for precise automated detection of MCI. Since feature selection algorithms can highly influence the final accuracy of the detection algorithm, RF classification method seems to be superior. Our results highlight the potential of ML- based fMRI applications for automated diagnostic techniques to distinguish MCI patients from healthy subjects.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0828 / #2356

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

VISUALIZING TAU PROTEIN NEUROFIBRILLARY TANGLES IN HIPSC-DERIVED RETINAL NEURONS AND POSTMORTEM SAMPLES OF AD PATIENT'S RETINA USING BODIBY-BASED FLUORESCENT LIGANDS.

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Ylenia Gigante[1], Lorenza Mautone[2], Silvia Ghirga[1], Lorenzo Barolo[3], Paola Baiocco[3], Alberto Boffi[4], Silvia Di Angelantonio[3]
[1]D-TAILS, D-tails, Roma, Italy, [2]CLN2S-IIT (Italian Institute of technology), Iit (italian Institute Of Technology) Rome, Viale regina Elena, Italy, [3]SAPIENZA UNIVERSITY OF ROME, Department Of Physiology And Pharmacology "v.erspamer", ROME, Italy, [4]SAPIENZA UNIVERSITY OF ROME, Department Of Biochemicalsciences "alessandro Rossi Farnelli", ROME, Italy

Aims: Alzheimer's disease (AD) is a neurodegenerative disease characterized by the progressive impairment of behavioral and cognitive functions. Neurofibrillary tangles (NFTs), composed of hyperphosphorylated tau protein, are established hall-marks of the pathology and Alzheimer's disease progression. Developing a therapeutic strategy based on the selective detection of NFTs in the retina is a promising diagnostic tool for early detection of AD. In this study we describe development of highly specific tau fluorophores, such as BT-1, for selective detection of pathological forms of tau protein and the use of cell permeant peptides (CPP) nanocage to deliver BT-1 to hiPSC-derived retinal neurons and in and postmortem samples of AD patients' retina.
Methods: BT-1 fluorophore (Soloperto et al., 2021) is a BODIPY-based fluorescent probe developed to bind hyperphorylated and oligomeric tau. The fluorescent probe BT-1 was delivered to retinal cells and in retinal tissues using CCP, natural nanocages capable of encapsulating small molecules.
Results: The results showed the effective internalization of the Nanocage-BT-1 complex into living retinal neurons, exhibited low toxicity. Moreover, has been shown the ability of NC-BT-1 complex to bind hyperphosphorylated and oligomeric tau in iPSC derived retinal cells as well as in postmortem retina of AD patients.
Conclusions: We demonstrated the ability of CPP nanocages loaded with the fluorescent probe BT-1 to detect NFTs in hiPSC derived retinal cells and AD retinal slices, developed a promising method for the early diagnosis of AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0829 / #895

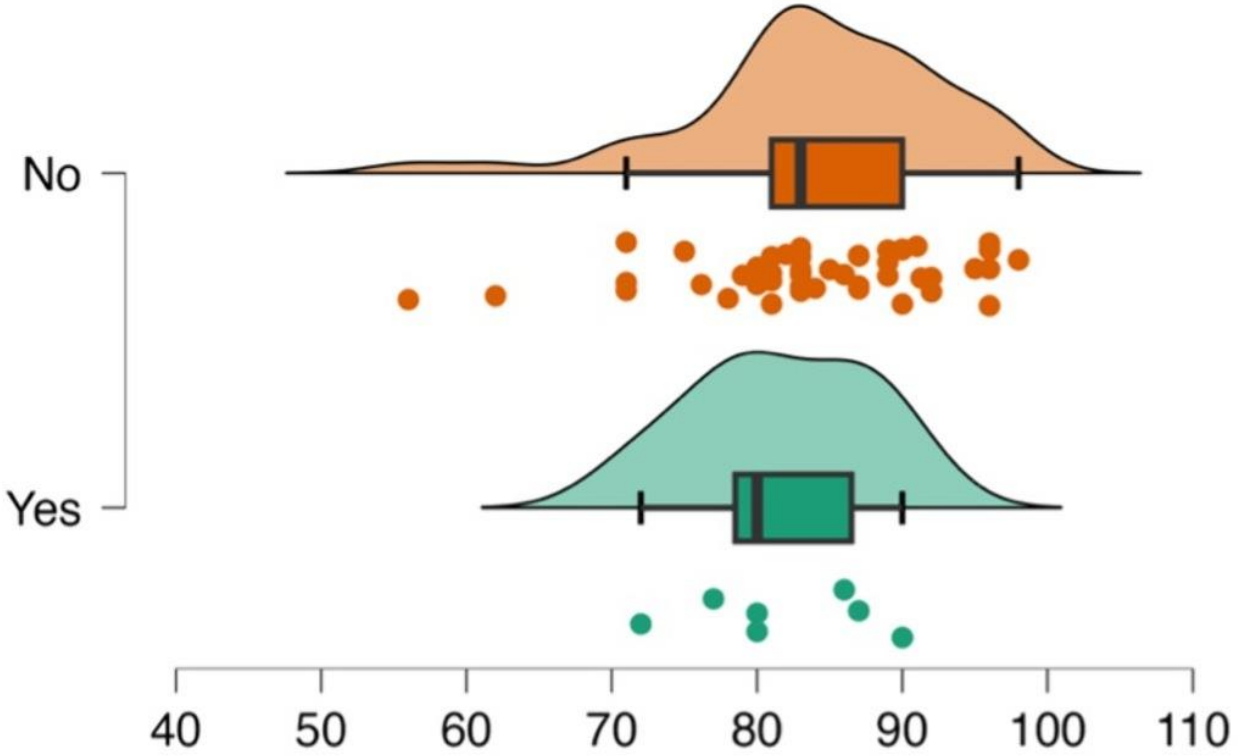
Poster Topic: *Theme B: Taupathies / B04.g. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric & behavioral tests, Digital endpoints, remote testing*

MOVEMENT DISORDER (MD) IN FRONTOTEMPORAL LOBAR DEGENERATION (FTLD) DUE TO TAUOPATHY

POSTERS: B04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING

Manisha Narasimhan[1], David Foxe[1,2], Rebekah Ahmed[1,3], Olivier Piguet[1,2]
[1]Brain and Mind Centre, The University Of Sydney, Sydney, Australia, [2]School of Psychology, The University Of Sydney, Sydney, Australia, [3]Sydney Medical School, The University Of Sydney, Sydney, Australia

Aims: Frontotemporal Lobar Degenerations (FTLDs) are clinically, pathologically and genetically heterogenous disorders involving frontal and temporal lobes and causing a wide range of clinical disease. Movement disorder (MD) phenomenology in FTLD due to Tauopathy is reported but not well understood. We studied the prevalence and neuropsychological profile of MD on initial presentation of behavioural-variant Frontotemporal Dementia (bvFTD), Progressive Supranuclear Palsy (PSP), Corticobasal Syndrome (CBS) and Progressive Non-Fluent Aphasia (PNFA).
Methods: A total of 273 patients were included from the FRONTIER Research Clinic database between 2008 and 2020. Patients underwent comprehensive neurological and neuropsychological assessment. Presence of MD was recorded on initial presentation. Patients were assessed on the Addenbrooke's Cognitive Examination (ACE) and seven cognitive domains of attention, verbal memory, visual memory, language, visuospatial function, executive function and social cognition. Composite measures were developed.
Results: Of 273 patients, 78 (29%) had MD on initial presentation. Movement disorder was noted in 15/150 (10%) of bvFTD, 7/45 (15.56%) of PNFA, 16/25 (64%) of PSP, 36/41 (87.8%) of CBS and 4/12 (33.33%) of CBS-PNFA patients. Total ACE scores were higher in the group without MD *(p=0.05)* as depicted in **Figure 1**. Patients with MD had lower scores across all cognitive domains, significantly for attention *(p=0.02)* and visuospatial function *(p=0.02*). **Figure 1 Total ACE scores in FTLD-MD vs FTLD-noMD**



Conclusions: This study demonstrates overlap between cognitive, language and motor FTLD-phenotypes. On initial presentation, patients with behavioural and language syndromes had MD, seen in 10% of bvFTD and 15.6% of PNFA. Conversely 36% of PSP and 12.2% of CBS patients did not present with MD. Identification of MD may be important in early disease identification and predicting prognosis. Neuropsychological testing may provide an effective way of profiling clinical FTLD subtypes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0830 / #2343

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

A NOVEL DIAGNOSTIC METHOD FOR ALZHEIMER TAU PATHOLOGY BASED ON SEEDED AMPLIFICATION AND ULTRA-SENSITIVE QUANTIFICATION OF IN VIVO AGGREGATES.

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Md Tohidul Islam, Thomas Karikari, Kaj Blennow
University of Gothenburg, Psychiatry And Neurochemistry, Göteborg, Sweden

Aims: Aggregated tau is a crucial pathophysiological indicator in various neurodegenerative diseases, but accurately quantifying tau aggregates remains challenging due to low abundance. Our research aims to pioneer a novel approach for the amplification and quantification of minute amounts of aggregated human tau protein, focusing on a specific domain crucial for disease pathology.
Methods: Our innovation incorporates cutting-edge methodologies and customized reagents to selectively amplify aggregated tau protein, specifically targeting the pathological domain. The amplification step covers generating recombinant tau aggregates using monomeric recombinant tau proteins, which enhances the detection sensitivity of tau aggregates, allowing for their precise quantification. Following amplification, we employ Single Molecule Array (Simoa)assay, an immunoassay employing high-affinity antibodies to quantify tau aggregates in CSF samples, ensuring accuracy and reliability. The immunoassay is designed to be adaptable for the evaluation of blood plasma and serum, thus broadening its clinical utility.
Results: Our initial findings are exceptionally promising, demonstrating the successful amplification of minute amounts of aggregated tau protein. This has led to a substantial enhancement in the detectability of tau aggregates, offering enhanced sensitivity compared to existing techniques. Moreover, the immunoassay has demonstrated exceptional precision and specificity in quantifying tau aggregates in CSF samples. These preliminary findings verify the potential of our approach as a revolutionary tool for early neurodegenerative disease diagnosis and monitoring. In the current application, we propose to perform further analytical and clinical validation of the assay towards establishing its context of use.
Conclusions: The proposed method offers clinical significance by pioneering a novel approach to sensitively amplify and quantify aggregated human tau protein, targeting a critical disease-related domain. This approach holds immense value for clinical studies and clinical trials, allowing for the precise monitoring of treatment responses.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0831 / #1341

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

IMPAIRED MELANOPSIN ACTIVITY IN PARKINSON'S VS. ALZHEIMER'S DISEASE

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Oliver Steiner[1], Jan De Zeeuw[2]
[1]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Campus Benjamin Franklin (CBF), 3. motor And Cognition Group, Department Of Neurology, Berlin, Germany, [2]Charité –Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Sleep Research & Clinical Chronobiology, Institute Of Physiology, Berlin, Germany

Aims: The eye, as an extension of the brain, provides a window into neurodegenerative processes. Yet, neurodegenerative diseases exhibit shared retinal abnormalities, for example, in the retinal ganglion cells (RGCs). Chromatic pupillometry enables in vivo evaluation of the functional integrity of melanopsin-expressing RGCs. This meta-analysis examines chromatic pupillometry data from Alzheimer's disease (AD) and Parkinson's disease (PD) to assess the functional state of mRGCs across neurodegeneration.
Methods: We conducted a literature search on PubMed and Scopus spanning 1991 to August 2023. We analyzed chromatic pupillometry parameters including baseline pupil size (BPS), transient peak amplitude (showcasing rods and cones' activity), and post-illumination pupil response (PIPR) from red and blue light stimuli—with blue PIPR denoting melanopsin function. Using fixed and random effects models, these parameters were compared across AD patients (n = 42; 2 studies), PD (n = 66; 3 studies), and healthy controls (n = 91).
Results: Relative to controls, PD patients demonstrated a marked decrease in melanopsin-mediated blue PIPR (weighted mean difference (WMD) = -9.14, 95% CI: -14.19 to -4.08, $p < 0.001$). For both blue and red light stimuli, no significant differences were observed in BPS or transient peak amplitude in PD patients ($p>0.05$). For AD patients, neither the PIPR nor transient peak amplitude for blue or red light revealed significant deviations when compared to controls.
Conclusions: The results delineate disease-specific photoreceptor dysfunctions in neurodegeneration: While the rods and cones system seem intact in both conditions, the integrity of the melanopsin system might be in specific relation to PD pathology. Thus, functional analysis is a promising strategy to increase the discriminative validity of structural retinal modeling and might help to tailor interventional strategies targeting the melanopsin system.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0832 / #1644

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

FWD IS MORE STRONGLY RELATED TO ASTROGLIOSIS THAN NEURO-AXONAL DAMAGE

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Vishaal Sumra[1,2], Mohsen Hadian[2], Allison Dilliott[3,4], Andrew Frank[5], Anthony Lang[6], Angela Roberts[3,7], Angela Troyer[8], Stephen Arnott[8], Brian Tan[8], Corinne Fischer[9], Connie Marras[9], Donna Kwan[10], David Tang-Wai[2], Elizabeth Finger[11], Ekaterina Rogaeva[2], Joel Ramirez[12], Kelly Sunderland[13], Lorne Zinman[12], Malcolm Binns[13], Michael Borrie[4], Morris Freedman[13,14], Miracle Ozzoude[12], Robert Bartha[3,4], Richard Swartz[12,14], Douglas Munoz[15], Mario Masellis[12,14], Henrik Zetterberg[16], Maria Tartaglia[17,18]
[1]University of Toronto, Institute Of Medical Science, Toronto, Canada, [2]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [3]Western University, Robarts Research Institute, London, Canada, [4]Western University, Schulich School Of Medicine And Dentistry, London, Canada, [5]University of Ottawa, Department Of Medicine, Ottawa, Canada, [6]Toronto Western Hospital, Edmond J Safra Program In Parkinson's Disease, Toronto, Canada, [7]Canadian Centre for Activity and Aging, Canadian Centre For Activity And Aging, London, Canada, [8]Baycrest Health Sciences, Baycrest Health Sciences Centre, Toronto, Canada, [9]St. Michael's Hospital, Li Ka Shing Knowledge Institute, Toronto, Canada, [10]Queen's University, Department Of Medicine, Kingston, Canada, [11]London Health Sciences Centre, Lawson Health Research Institute, London, Canada, [12]Sunnybrook Research Institute, Hurvitz Brain Sciences Program, Toronto, Canada, [13]Baycrest Health Sciences, Rotman Research Institute, Toronto, Canada, [14]University of Toronto, Department Of Medicine (neurology), Toronto, Canada, [15]Queen's University, Department Of Medecine, Kingston, Canada, [16]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Göteborg, Sweden, [17]University of Toronto, Tanz Centre For Research In Neurodegenerative Disease, Toronto, Canada, [18]Toronto Western Hospital, Krembil Research Institute, Toronto, Canada

Aims: Free-water diffusion (FWD), a diffusion MRI metric, is a non-specific marker of neuroinflammation. Given previous research implicating neuroinflammation in the pathogenesis of neurodegenerative diseases (NDs), we examined the relationship between FWD and biofluid markers for neuroinflammation and neurodegeneration across NDs.
Methods: We generated FWD maps in 367 subjects (108 AD/MCI, 37 ALS, 42 FTD, 122 PD, 58 VCI) using diffusion and structural MRI data from the ONDRI cohort. Plasma glial fibrillary acidic protein (GFAP) and neurofilament light (NfL) concentrations were measured using Simoa Human N4PE assay. Recursive Feature Elimination (RFE) was implemented on regional FWD to identify which ROIs are the most important features in relation to GFAP or NfL, and utilized a deep learning model to determine if selected features better predict GFAP or NfL.
Results: Across NDs, FWD is correlated with GFAP (Left Cortical-GM; R=0.2, p=0.0001, Right Cortical-GM; R=0.18, p=0.0002) but not NfL. RFE revealed that the middle frontal, superior temporal and parahippocampal gyri, temporal pole, and lateral occipital cortex are the most important features to predict GFAP, whereas the frontal pole, superior parietal lobule, and left cerebral white matter are the most important features to predict NfL. A deep learning model was used to predict GFAP or NfL concentration using selected features along with group, plasma-pTau^{181}, age, sex, and ethnicity. A data split of 80% for training and 20% for testing were employed to develop/evaluate our model. The selected features predict GFAP (R_{train}=0.89, R_{test}=0.83) more strongly that NfL (R_{train}=0.72, R_{test}=0.42).
Conclusions: FWD is more related to astrogliosis than neuro-axonal damage. RFE allowed for the generation of a model including regional FWD, demographic and AD biomarkers, that predicted GFAP better than NfL. FWD may be a useful neuroinflammatory marker in NDs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0833 / #1778

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

DEVELOPMENT OF A "REAL-TIME QUAKING-INDUCED CONVERSION" (RT-QUIC) ASSAY FOR DETECTION OF MISFOLDED TAU PROTEIN AFTER IMMUNOPRECIPITATION-ENRICHMENT FROM PATIENT PLASMA

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Samuel Uhlig[1], Max Holzer[2], Isabel Hilbrich[2], Jens Stieler[2], Ingolf Lachmann[3], Thomas Arendt[2], Katharina Waniek[3], Jakob Hasler[1]
[1]Paul-Flechsig-Institut für Hirnforschung, Neuropathologie, Leipzig, Germany, [2]Paul Flechsig Institut, Ag Holzer, Leipzig, Germany, [3]Roboscreen GmbH, Roboscreen Gmbh, Leipzig, Germany

Aims: Alzheimer's disease and related tauopathies are characterized by the presence of abnormal tau protein aggregates in the central nervous system. Detecting misfolded tau protein before symptomatic onset is crucial for effective intervention. Currently, diagnosis relies on PET-Scan or invasive procedures like cerebrospinal fluid analysis, which are only feasible when cognitive symptoms are manifest. Our research aims to adapt the "real-time quaking-induced conversion" (RT-QuIC) assay, initially designed for brain and cerebrospinal fluid samples, to detect tau aggregates in blood plasma.
Methods: In our study, we determined the influence of various buffer ions following the Hofmeister series to enhance RT-QuIC sensitivity. Furthermore, different Tau fragments were assessed for their suitability as seeding agents.
Immunoprecipitation (IP) was employed to enrich tau protein in patient sera and to eliminate matrix effects from blood proteins. Two IP elution methods, boiling and pH adjustment, were tested for efficient recovery of tau fragments, addressing the challenge of low picogram per milliliter (pg/ml) tau content in blood.
Results: Standardized conditions were developed to enhance assay sensitivity and reliability for the early detection of tau aggregates such as sodium citrate buffer and dextran sulfate. Currently, we are using the recombinant tau protein fragment K12CFh for RT-QuIC assay, offering more sensitivity than the dGAE tau fragment. Preliminary results show a significant inverse correlation between lag time of seeded aggregation using plasma samples and the corresponding CSF tau concentration.
Conclusions: In summary, our work focused on refining the RT-QuIC assay for the early detection of tau aggregates in blood plasma. Through standardization and the use of recombinant tau protein fragment K12CFh, our goal is to enable a less invasive means of diagnosing tauopathies prior to symptomatic presentation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0834 / #223

Poster Topic: *Theme B: Taupathies / B04.h. Imaging, Biomarkers, Diagnostics: Other*

ACOUSTIC AND OTHER CORRELATES OF REDUCED WORDS PER BREATH GROUP IN PRIMARY PROGRESSIVE APRAXIA OF SPEECH

POSTERS: B04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Rene Utianski, Joseph Duffy, Gabriela Meade, Heather Clark, Kennedy Josephs, Hugo Botha, Jennifer Whitwell, Keith Josephs
Mayo Clinic, Neurology, Rochester, United States of America

Aims: Primary Progressive Apraxia of Speech (PPAOS) is a neurodegenerative syndrome that manifests as disruptions of motor speech planning/programming. In connected speech, some patients produce fewer syllables per breath than might be expected from their observed respiratory support. To date, no investigations have explored the relationship between this subjectively identified feature and acoustic measurements of syllables per breath group, which is the goal of this study.
Methods: Data were collected from 46 patients with PPAOS. As a part of the speech evaluation, alternating motion rates (AMRs) were recorded to evaluate the ability to perform rapid and accurate repetitions of sounds ("puh," "tuh," and "kuh") on a single breath. The Apraxia of Speech Rating Scale (ASRS-3), which indexes the presence and severity of speech characteristics, including articulatory (sound distortions, distorted sound additions and substitutions) and prosodic (sound prolongations, between and within word segmentation, and slow rate) disruptions, was also scored. Spearman correlations, with adjusted values, were calculated between a subjective ratings of syllables per breath group (where 0=8+ and 4=1-2) and 1) other ASRS features and 2) the mean number of syllables produced in one breath across the AMR tasks.
Results: Reduced words per breath group ratings were inversely associated with the mean number of syllables produced in the AMR task (-0.61) and positively with the overall severity of ASRS (.55), with a trend for the prosodic speech features.
Conclusions: These results suggest subjective judgments of reduced words per breath group in conversation track with acoustic measurements of this feature in AMRs, either of which may serve as a biomarker of PPAOS and facilitate earlier identification. Future studies will explore data-driven analysis of this feature and the sensitivity and specificity of subjective versus objective measures.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0835 / #422

Poster Topic: *Theme B: Taupathies / B05.i. Genetics, Epidemiology: Other*

MAPT EXPRESSION IS MEDIATED BY LONG-RANGE INTERACTIONS WITH CIS-REGULATORY ELEMENTS

POSTERS: B05.I. GENETICS, EPIDEMIOLOGY: OTHER

Brianne Rogers[1], Ashlyn Anderson[2], Shelby Lauzon[1], Natalie Davis[2], Rebecca Hauser[1], Sydney Roberts[1], Ivan Rodriguez-Nunez[2], Katie Trausch-Lowther[2], Erin Barinaga[1], Paige Hall[2], Jared Taylor[1], Mark Mackiewicz[2], Brian Roberts[2], Sara Cooper[3], Lindsay Rizzardi[2], Richard Myers[2], J. Nicholas Cochran[1]
[1]HudsonAlpha Institute for Biotechnology, Cochran Lab, Huntsville, United States of America, [2]HudsonAlpha Institute for Biotechnology, Myers Lab, Huntsville, United States of America, [3]HudsonAlpha Institute for Biotechnology, S. Cooper Lab, Huntsville, United States of America

Aims: *MAPT* expression is absent in neural progenitor cells (NPCs) and increases during differentiation. This temporally dynamic expression pattern suggests that *MAPT* expression is controlled by transcription factors and *cis*-regulatory elements specific to differentiated cell types. Given the relevance of *MAPT* expression to neurodegeneration pathogenesis, identification of such elements is relevant to understanding disease risk and pathogenesis.
Methods: We performed HiC, chromatin conformation capture (Capture-C), single-nucleus multiomics (RNA-seq+ATAC-seq), bulk ATAC-seq, and ChIP-seq for H3K27Ac and CTCF in NPCs and neurons differentiated from human iPSC cultures. We nominated candidate *cis*-regulatory elements (cCREs) for *MAPT* in human NPCs, differentiated neurons, and pure cultures of inhibitory and excitatory neurons. We then assayed these cCREs using luciferase assays and CRISPR interference (CRISPRi) experiments to measure their effects on *MAPT* expression. Finally, we integrated cCRE annotations into an analysis of genetic variation in AD cases and controls.
Results: We nominated 94 cCREs for *MAPT*, including the identification of cCREs specifically active in differentiated neurons. Eleven regions enhanced reporter gene transcription in luciferase assays. Using CRISPRi, 5 of the 94 regions tested were identified as necessary for *MAPT* expression. Rare and predicted damaging genetic variation in both nominated and confirmed CREs was depleted in AD cases relative to controls, consistent with the hypothesis that variants that disrupt *MAPT* enhancer activity, and thereby reduce *MAPT* expression, may be protective against neurodegenerative disease.
Conclusions: We identified both proximal and distal regulatory elements for *MAPT* and confirmed the regulatory function for several regions, including three regions centromeric to *MAPT* beyond the well-described H1/H2 haplotype inversion breakpoint. This study provides compelling evidence for pursuing detailed knowledge of CREs for genes of interest to permit better understanding of disease risk.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0836 / #830

Poster Topic: *Theme B: Taupathies / B05.i. Genetics, Epidemiology: Other*

KLOTHO KL-VS GENOTYPE MODIFIES THE RELATIONSHIP BETWEEN VO2 MAX AND TAU IN AT-RISK COHORT

POSTERS: B05.I. GENETICS, EPIDEMIOLOGY: OTHER

Noah Cook[1], Ira Driscoll[1,2], Sarah Lose[1,2], Brianne Breidenbach[1,2], Mackenzie Jarchow[1], Catherine Gallagher[3,4], Sterling Johnson[1,2,3], Sanjay Asthana[1,2,3], Bruce Hermann[1,2,3], Mark Sager[1,2], Kaj Blennow[5,6], Henrik Zetterberg[5,6,7,8], Cynthia Carlsson[1,2,3], Gwendlyn Kollmorgen[9], Margherita Carboni[10], Dane Cook[3,11], Dena Dubal[12], Ozioma Okonkwo[1,2,3]
[1]University of Wisconsin-Madison, Wisconsin Alzheimer's Disease Research Center, Madison, United States of America, [2]University of Wisconsin-Madison, Wisconsin Alzheimer's Institute, Madison, United States of America, [3]William S. Middleton VA Hospital, Geriatric Research Education And Clinical Center, Madison, United States of America, [4]University of Wisconsin School of Medicine and Public Health, Department Of Neurology, Madison, United States of America, [5]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg, Mölndal, Sweden, Molndal, Sweden, [6]University of Gothenburg, Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, Molndal, Sweden, [7]UK Dementia Research Institute, Ucl Institute Of Neurology, London, United Kingdom, [8]UCL London, Uk Dementia Research Institute, London, United Kingdom, [9]Roche, Roche Diagnostics Gmbh, Penzberg, Germany, [10]Roche, Roche Diagnostics International Ltd, Rotkreuz, Switzerland, [11]University of Wisconsin-Madiosn, Department Of Kinesiology, School Of Education, Madison, United States of America, [12]University of California-San Francisco, Department Of Neurology And Weill Institute For Neurosciences, San Francisco, United States of America

Aims: Increasing evidence indicates that physical activity may delay or prevent the onset of Alzheimer's disease (AD). *KLOTHO* KL-VS heterozygosity (KL-VS$_{HET}$) has also been associated with resilience against AD pathology. We examine whether there is a potential for synergy between the functionally advantageous KL-VS$_{HET}$ variant and aerobic fitness (measured via VO_2 max) on core cerebrospinal fluid (CSF) biomarkers for AD in a cognitively unimpaired, adult cohort enriched for AD risk.
Methods: Middle-aged and older adults (N=131; Mean$_{AGE}$=63) from the Wisconsin Registry for Alzheimer's Prevention and Wisconsin Alzheimer's Disease Research Center who were genotyped for *KLOTHO* and *APOE*, underwent CSF sampling, and had available VO_2 max data were included in analyses. General linear models, covarying for sex, age, parental history of AD, and *APOE*, examined whether *KLOTHO* modified the relationship between VO_2 max and core CSF biomarker levels (pTau, tTau, $A\beta_{42}/A\beta_{40}$, pTau/$A\beta_{42}$).
Results: For KL-VS non-carriers (KL-VS$_{NC}$) (N=89), CSF biomarker levels were similar across the range of VO_2 max values (p's>0.54). For KL-VS$_{HET}$ (N=42) however, those with higher VO_2 max had significantly lower levels of CSF tTau (p=0.03) and pTau (p=0.04) but not $A\beta_{42}/A\beta_{40}$ or pTau/$A\beta_{42}$ (p's>0.13).
Conclusions: Our present results suggest a synergistic benefit of being aerobically fit and heterozygous for KL-VS in relation to tau accumulation, suggesting potentially shared underlying biological mechanisms that need to be further investigated and elucidated.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0837 / #727

Poster Topic: *Theme B: Taupathies / B05.i. Genetics, Epidemiology: Other*

ASSOCIATION TESTING REVEALS POSSIBLE CONTRIBUTION OF GENETIC VARIATION IN APH1B TO DISTINCT NEUROPATHOLOGICAL LESIONS OBSERVED IN ALZHEIMER'S DISEASE

POSTERS: B05.I. GENETICS, EPIDEMIOLOGY: OTHER

Celeste Laureyssen[1,2], Klara Gawor[3], Jasper Van Dongen[1,2], Fahri Küçükali[1,2], Marta Koper[3], Markus Otto[4], Christine Von Arnim[5], Philip Van Damme[6,7], Rik Vandenberghe[8], Dietmar Thal[3,9], Kristel Sleegers[1,2]
[1]VIB Center for Molecular Neurology, Complex Genetics Of Alzheimer's Disease Group, Wilrijk, Belgium, [2]University of Antwerp, Department Of Biomedical Sciences, Wilrijk, Belgium, [3]KU Leuven, Laboratory For Neuropathology, Department Of Imaging And Pathology, And Leuven Brain Institute, Leuven, Belgium, [4]Martin-Luther-University Halle-Wittenberg, Department Of Neurology, Halle (Saale), Germany, [5]University Medical Center Göttingen, Devision Of Geriatrics, Göttingen, Germany, [6]VIB-KU Leuven, Laboratory For Neurobiology, Leuven, Belgium, [7]UZ Leuven, Department Of Neurology, Leuven, Belgium, [8]KU Leuven, Experimentele Neurologie, Leuven, Belgium, [9]University Hospital Leuven, Department Of Pathology, Leuven, Belgium

Aims: Alzheimer's disease is the leading cause of dementia worldwide. Besides neurofibrillary tangles and amyloid beta plaques, a wide range of co-morbid neuropathological features can be observed. Since AD has a very strong genetic background and displays a wide phenotypic heterogeneity, this study aims at investigating the genetic underpinnings of co-morbid and hallmark neuropathological lesions.
Methods: DNA was extracted from fresh frozen brain material of 351 individuals aged 55 or older. Genotyping data was collected for 49 single nucleotide polymorphisms (SNPs) known to be associated with AD using an in-house designed long read sequencing multiplex assay (Oxford Nanopore Technologies). Variants were tested for association with Braak NFT stage, TDP-LATE stage, Thal amyloid phase, CAA severity, Granulovacuolar degeneration stage, CERAD, NIA-AA score and Braak PD stage. Association testing was done using PLINK linear regression. Replication of significant associations was performed in the ROSMAP cohort for overlapping neuropathological phenotypes.
Results: Association testing revealed several nominally significant associations, but besides *APOE*, a SNP in exon 1 of *APH1B* was strongly associated with Braak NFT stages ($p=3.15*10^{-7}$), GVD stage ($p=0.0003$), CERAD score ($p=0.0002$), Thal amyloid phase ($p=0.0002$) and NIA-AA score ($p=1.48*10^{-5}$), all passing Bonferroni multiple testing correction. The SNP was also nominally associated with CAA severity ($p=0.005$). Association signals were corrected for age and sex and were independent of *APOE* genotype. These results were independently replicated in the ROSMAP cohort (n=1141) for Braak NFT score ($p=0.02$) and CERAD score ($p=0.004$).
Conclusions: Our results highlight the role of *APH1B* in several neuropathological phenotypes observed in AD. *APH1B* encodes a subunit of gamma-secretase, making it especially interesting that we find strong association with tangle-related pathologies. Future perspectives include functional validation to further unravel the downstream effects of the mutation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0838 / #531

Poster Topic: *Theme B: Taupathies / B06.a. Cell, Molecular and Systems Biology: Tau, tau isoforms*

EFFECTS OF THE AIS PROTEINS ANKYRIN G AND TRIM46 ON TAU SORTING

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

Daniel Adam[1], Michael Bell-Simons[1,2], Helen Breuer[1], Hans Zempel[1]
[1]Institute of Human Genetics, University Hospital Cologne, Center For Molecular Medicine Cologne (cmmc), Cologne, Germany, [2]Max-Planck-Gesellschaft, Max-planck-institute For Biology Of Ageing, Cologne, Germany

Aims: The somatodendritic, pathophysiological missorting of the axonal, microtubule-associated protein TAUau is one of the main hallmarks of Alzheimer's Disease. However, the main mechanism behind physiological, axonal sorting of TAUau remains elusive. The axon initial segment (AIS) and two of its major components, i.e., Ankyrin G (ANKG) and Tripartite motif-containing protein 46 (TRIM46) have been postulated as constituents of a physiological Tau diffusion barrier (TDB) located at the AIS in rodent *in-vitro* cell models, but human neurons is elusive.
Methods: Here we investigated the development of the AIS in human iPSC-derived neurons (iNs) and *MAPT*-KO iNs using western blot, qPCR and immunofluorescence. We established the knockdown of ANKG and TRIM46 in iNs using lentiviral transduction, expressed dendra2-tagged Tau in *MAPT*-KO iNs for pulse-chase life-tracking of TAU trafficking, and expressed BirA-fused to several deletion constructs of TAU to identify AIS-based interactors via mass-spectrometry.
Results: Our time course revealed accumulation of ANKG and TRIM46 to occur between days 5 and 21 after neuronal differentiation, serving as a baseline for knockdown to study TAU localization. We visualised Tau diffusion using photoconvertible dendra2, albeit poorly due to low brightness. Our BirA-Tau fusion proteins sort correctly, and biotinylation was demonstrated via WB and IF, pending proteomic analysis.
Conclusions: Our system allows tracking the TAU-diffusion, in future, we will employ mEosEM as photoconvertible tag. Knockdown of ANKG and TRIM46 will reveal if these proteins impact Tau sorting human neurons. The establishment of our BirA-Tau constructs will reveal new Tau interaction partners within the AIS when coupled with laser microdissection-assisted proteomic analysis of the AIS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0839 / #1411

Poster Topic: *Theme B: Taupathies / B06.a. Cell, Molecular and Systems Biology: Tau, tau isoforms*

DEVELOPMENT OF A HUMAN IPSC-BASED FTD MODEL SHOWING ADVANCED TAUOPATHY PHENOTYPES

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

Angelika Dannert[1,2], Lea Knez[2], Martina Fetting[3,4], Dominik Paquet[2,4]
[1]LMU Munich, Graduate School For Systemic Neurosciences, Planegg-Martinsried, Germany, [2]University Hospital LMU Munich, Institute For Stroke And Dementia Research, Munich, Germany, [3]German Center for Neurodegenerative Diseases, Dzne Munich, Munich, Germany, [4]Munich Cluster for Systems Neurology, Synergy, Munich, Germany

Aims: Malfunction of the protein Tau is a hallmark of neurodegenerative Tauopathies such as Alzheimer's disease and Frontotemporal Dementia (FTD). In the healthy human brain, Tau expression and splicing are highly regulated and dys-regulation of the ratio between 3-repeat (3R) and 4R splice isoforms leads to FTD. To understand the relevance of Tau isoforms for disease, we aimed to create one of the first models that reproduces the adult human 1:1 splice ratio of 3R and 4R Tau and use it to recreate endogenous development of molecular Tauopathy hallmarks.
Methods: For this purpose, we developed a novel iPSC-based cortical neuron model that, as a default, expresses 3R and 4R Tau in the 1:1 ratio found in adult human neurons using a multi-step CRISPR/Cas9 genome editing strategy that alters endogenous Tau isoform expression from the genomic MAPT locus. To create a disease model, we further included disease-causing Tau mutations.
Results: 4R Tau expression in these cortical neurons was required to elicit strong and robust formation of late-stage Tau pathology in the presence of Tau mutations. In particular, these neurons endogenously accumulated seeding-competent, misfolded, fibrillar Tau in tangle-like structures inside the somata of affected neurons. Exclusive expression of mutant 4R Tau in the absence of 3R Tau disproportionately intensified pathology, resulting in abundant Tau misfolding and aggregation.
Conclusions: The generated human iPSC-derived neuronal model recapitulates the adult human 3R/4R Tau ratio and develops endogenous late-stage Tau pathology. We further demonstrated modulability of the phenotypes in a proof-of-principle drug screen. The presented model will thus provide a valuable experimental platform to study mechanistic disease processes and to complement drug screening efforts.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0840 / #1201

Poster Topic: *Theme B: Taupathies / B06.a. Cell, Molecular and Systems Biology: Tau, tau isoforms*

INTRON RETENTION AS A PRODUCTIVE MECHANISM IN HUMAN MAPT: RNA SPECIES GENERATED BY RETENTION OF INTRON 3

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

Vega García-Escudero[1], Daniel Ruiz-Gabarre[2], Laura Vallés Saiz[2], Almudena Carnero-Espejo[1], Isidro Ferrer[3], Félix Hernández[4], Ramón García-Escudero[5], Jesús Ávila[4]
[1]Universidad Autónoma de Madrid, Anatomy, Histology And Neuroscience, Madrid, Spain, [2]CBM Severo Ochoa, Molecular Neuropahtology, Madrid, Spain, [3]University of Barcelona, Department Of Pathology And Experimental Therapeutics, Barcelona, Spain, [4]Centro de Biología Molecular Severo Ochoa, Molecular Neuropathology, Madrid, Spain, [5]CIEMAT, Biomedical Oncology Unit, Madrid, Spain

Aims: Tau is a microtubule-binding protein encoded by the *MAPT* gen. Tau is essential for several physiological functions and associated with pathological processes, including Alzheimer's disease. Six tau isoforms are typically described in the central nervous system, but current research paints a more diverse landscape and a more nuanced balance between isoforms. Recent work has described tau isoforms generated by intron 11 and intron 12 retention. This work adds to that evidence, proving the existence of *MAPT* transcripts retaining intron 3. Our aim is to demonstrate the existence of mature *MAPT* RNA species that retain intron 3 in human brain samples and to study its correlation with Alzheimer's disease across different regions.
Methods: First evidence of intron-3-retaining *MAPT* species come from analysis of RNA-seq databases. We further demonstrate the existence of these mature RNA species in human neuroepithelioma cells and human brain samples by qPCR. We also use digital droplet PCR to demonstrate the existence of RNA species that retain either intron 3, intron 12 or both introns.
Results: Intron-3-retaining species are even more prominently present that intron-12-retaining ones. We show the presence of *MAPT* transcripts that retain both introns 3 and 12. Relative abundance of intron-3- or intron-12-retaining MAPT species are increased with respect to double-retaining species in patients with Alzheimer's disease, especially in hippocampal samples. Moreover, we find a significant increase in intron-3- or intron-12-retaining species and its relative abundance with respect to double-retaining *MAPT* species in cerebellum in contrast to frontal lateral cortex and hippocampus in individuals with no signs of dementia.
Conclusions: Intron retention constitutes a potential mechanism to generate Tau isoforms whose mature RNA expression levels correlate with Alzheimer's pathology showing its potential as a biomarker associated to the disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0841 / #305

Poster Topic: *Theme B: Taupathies / B06.a. Cell, Molecular and Systems Biology: Tau, tau isoforms*

NUCLEAR LAMINA ALTERATIONS IN NEURONS AND GLIAL CELLS IN ALZHEIMER'S DISEASE

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

Mauro Montalbano[1], Zachary Walton[2], Rakez Kayed[1]
[1]The University Of Texas Medical Branch, Neurology, Galveston, United States of America, [2]The University Of Texas Medical Branch, School Of Medicine, Galveston, United States of America

Aims: The nuclear lamina (NL) is a structural determinant of the nuclear envelope. The NL is a meshwork of four Lamin proteins (Lamins A, B1, B2, and C) along the nuclear margin of eucaryotic cells that provides nuclear structural support and regulates chromatin organization. Cytoplasmic aggregation of misfolded tau is associated with Alzheimer's Disease (AD). With emerging evidence indicating that tau protein aggregation profoundly impacts nuclear structure and function, we hypothesize that tau aggregates induce maladaptive nuclear lamina structure and affects chromatin organization.
Methods: Using cell fractioning, biochemical assays, co-immunofluorescence, high-resolution airyscan microscopy and comprehensive high-throughput image analysis, we identified and quantified structural lamin alterations (tickness and integrity) in neurons and glia cells of aged-matched non-demented and AD brains.
Results: We found that tau, particularly in its oligomeric form, triggers NL maladaptive structures and deep reorganization of chromatin. Additionally, our in vivo observations revealed that the pathogenic P301S mutant tau exacerbates age-related NL alterations, specifically impacting Lamin A cellular localization and protein levels.
Conclusions: Our data suggest that in AD brains, the NL is morphologically and structurally altered as characterized by defective lamins expression and cellular mislocalization. Addittionally, tau aggregates drive NL structural impairments, which determine a deep re-organization of chromatin suggesting additional molecular insights of tau-induced toxicity in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0842 / #1797

Poster Topic: *Theme B: Taupathies / B06.a. Cell, Molecular and Systems Biology: Tau, tau isoforms*

RT-QUIC IN THE DETECTION OF 4R TAU SEEDS ACROSS NEURODEGENERATIVE DISEASES AND BRAIN REGIONS

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

Heidi Standke[1], David Coughlin[2], Matteo Manca[1], Mikayla Huntley[1], Olivia Thomas[1], Caitlin Swanberg[1], Yongya Kim[2], Thea Andreasson[2], Varun Rachakonda[3], Douglas Galasko[4], Annie Hiniker[4], Allison Kraus[1]
[1]Case Western Reserve University School of Medicine, Department Of Pathology, Cleveland, United States of America, [2]University of California, San Diego, Department Of Neurosciences, San Diego, United States of America, [3]Nova Southeastern University, Kiran C. Patel College Of Allopathic Medicine, Fort Lauderdale, United States of America, [4]University of California, San Diego, Department Of Neurology, San Diego, United States of America

Aims: It is unknown how self-replicating misfolded proteins, or protein seeds, co-occur in other neurodegenerative diseases. Here, we utilize the ultrasensitive real-time quaking induced conversion (RT-QuIC) assay to selectively detect 3R/4R and 4R tau protein seeds across neurodegenerative diseases and brain regions to examine tau seeding activity as it relates to neuropathological characteristics and varies across brain regions.
Methods: The 4R RT-QuIC assay was used to evaluate neuropathologically characterized brain tissue samples (n=67) to explore 4R tau seeding in frontal cortex samples across a variety of neurodegenerative diseases including PSP and CBD. We further examined the topographic differences of 3R/4R and 4R tau seeds through the analysis of 3R/4R and 4R RT-QuIC seeding activity from hippocampus, frontal cortex, and basal ganglia samples in a subset of cases with AD (n=11), PSP (n =13), mixed AD and PSP pathology (n=7), and control cases (n=4).
Results: 4R RT-QuIC identified all 4R tauopathy cases, with 4R seeding activities being 10,000-fold higher than age-comparable controls. 4R tau seeds were detected, albeit in lower quantities, in other neurodegenerative diseases. Additionally, the 4R RT-QuIC assay could discriminate PSP and CBD with differing characteristic 4R tau amyloid structures based on ThT amplitude readout, with electron microscopy indicating distinct ultrastructures of disease-specific seeded amyloids. The 3R/4R RT-QuIC assay was also neuroanatomically selective in tau seeding in cases of AD, PSP, and mixed tau pathologies.
Conclusions: 4R tau seeds are a prevalent co-occurrence across neurodegenerative diseases. RT-QuIC assays can determine the neuroanatomic distribution of tau seeds, even in cases of mixed tau pathology, and can be used to infer amyloid core structural differences.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0843 / #482

Poster Topic: *Theme B: Taupathies / B06.a. Cell, Molecular and Systems Biology: Tau, tau isoforms*

STUDY THE CELLULAR EFFECT OF NEW TAU ISOFORMS OVER EXPRESSION GENERATED BY INTRON RETENTION.

POSTERS: B06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: TAU, TAU ISOFORMS

Francisco Vallejo-Bedia[1], Daniel Ruiz-Gabarre[2], Anastasia Stoliarov-Radushinskaya[1], Mar Pérez-Martínez[3], Félix Hernández[4], Jesús Ávila[4], Vega García-Escudero[3]
[1]CBM Severo Ochoa, Molecular Neuropathology, Madrid, Spain, [2]CBM Severo Ochoa, Molecular Neuropahtology, Madrid, Spain, [3]Universidad Autónoma de Madrid, Anatomy, Histology And Neuroscience, Madrid, Spain, [4]Centro de Biología Molecular Severo Ochoa, Molecular Neuropathology, Madrid, Spain

Aims: Truncated by intron retention CW-Tau isoform could have protective Alzheimer's disease functions on a cellular level. To prove this, will be studying its subcellular localization compared to other canonical Tau isoforms, analyzing its role in mitochondrial morphology and microtubule function, and characterizing its effect on vesicle trafficking, with special emphasis on the autophagic flux and vesicles exportation.
Methods: SH-SY5Y cells were infected with pWPI lentiviral vectors containing T30 canonic tau, TIR-30 CW-Tau and GFP as control before carrying out immunoflourencent assays againts mitochondria, microtubules and vesicles involved in the autophagic flux. In addition, cells were subcellular fragmented to analyze the nuclear presence of CW-Tau. Concurrently, HEK293T cells were transfected with psG5 eucaryotic expression plasmids with different Tau isoforms and were treated with cccp and Bafilomicine A1 to analyze in detail the autophagic flux and the vesicle exportation in different tau conditions.
Results: We first validated the specifity of a new antiody against CW-Tau performing immunofluorescence. Once the specifitiy of the transduction was confirmed, we saw that CW-Tau shows homogeneous localization throughout the cell, with high nuclear representation, comparing with canonic Tau isoforms, with a lack of presence on the nucleous. We further demonstrated that CW-Tau overexpression does not affect the microtubule net area, and neither affect the mitochondrial morphological conditions. Finally, CW-Tau overexpression showed an increased endocytosis EEA1 clusters, a mainteined autophagic flux with LC3 and p62 synthesis and degradation ratios, differing on the overexpression of canonic tau isoforms, which had unbalanced synthesis and degradation ratios.
Conclusions: The results obtained point out that CW-Tau could ameliorate or at least mantain cell funcion in Alzheimer's disease, and could be proposed as a therapeutic target and genic therapy strategy against this dementia and other tauopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0844 / #1830

Poster Topic: *Theme B: Taupathies / B06.c. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

LINKING SINGLE-NUCLEUS-ATAC/RNA-SEQ WITH NEUROPATHOLOGICAL TRAITS IN PRIMARY TAUOPATHIES

POSTERS: B06.C. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

Nils Briel[1,2], Viktoria Ruf[2], Paul Feyen[3], Felix Stübing[2,3], Günter Höglinger[4,5], Jochen Herms[2,3,5]
[1]University Hospital Zurich, Neurology, Zurich, Switzerland, [2]University of Munich, Center For Neuropathology And Prion Research, Faculty Of Medicine, Munich, Germany, [3]German Center for Neurodegenerative Diseases, Translational Brain Research, Munich, Germany, [4]LMU hospital, Department Of Neurology, München, Germany, [5]Munich Cluster for Systems Neurology, Synergy, Munich, Germany

Aims: Our previous work [1] highlighted distinct astrocyte signatures in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). In this study, we aimed to investigate network-based gene-expression/gene-activity patterns and their molecular function in these diseases. We also aimed to link network activity with neuropathological (NP) traits.
Methods: We performed unpaired single-nucleus ATAC/RNA-seq on postmortem frontal cortex samples from N=8 PSP, N=8 CBD, and N=8 control cases. After preprocessing and QC, we recovered more than 93,000 (ATAC) and 112,000 (RNA) high-quality nuclei. Using *Seurat&hdWGCNA* we determined cell type identity, constructed weighted gene co-expression networks on meta cells, and assessed gene ontologies. Associations between networks and manually quantified NP traits (ie, tufted astrocytes, TA; FFPE, contralateral cortex) were tested with *glm* (adjusted for age and postmortem-interval).
Results: In PSP, our analysis revealed dysregulated gene activity modules in astrocytes. Specifically, we found a gene network “turquoise” enriched with synaptic terms downregulated in PSP astrocytes. Another network “blue” reminiscent of tangle-positive cells was upregulated in PSP astrocytes and associated with TA counts. Network “blue” core regulators were involved in mRNA processing, astrocyte, and B cell differentiation.
In CBD, the gene expression module "yellow" with its core regulator *PPARGC1A* was enriched with neuroinflammatory terms and downregulated in Parvalbumin+ inhibitory neurons.
Conclusions: Our analysis demonstrates a) cell type-resolved dysregulated gene-networks in primary Tauopathien, b) specific hub genes (eg, *C1orf61*, astrocytic DEG in AD [2]; *PPARGC1A*, implicated in inhibitory neurons in AD [3]), and c) a possible systems biology approach to identify therapeutic targets. Further studies are needed to validate outlined alterations and their role in tangle-bearing cells themselves or their microenvironment. References:
1. Briel et al. Acta Neuropathologica. 2022
2. Sadick et al. Neuron. 2022
3. Weiping et al. JAMA Neurology. 2009

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0845 / #1911

Poster Topic: *Theme B: Taupathies / B06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

COMPARISON OF SPATIAL TRANSCRIPTOMIC PLATFORMS IN THE RECOVERY OF NEOCORTICAL CELL SUBTYPES FOR TOPOLOGICAL ANALYSES

POSTERS: B06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Philip De Jager, Mariko Taga, Hans-Ulrich Klein, Vilas Menon, Ya Zhang
Columbia University Irving Medical Center, Center For Translational And Computational Neuroimmunology, Department Of Neurology And Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York, United States of America

Aims: We defined 92 neocortical (glial, neuronal, endothelial,..) cell subtypes in 1.6 million transcriptomes from the prefrontal cortex of 424 participants in the ROSMAP cohorts. Here, we attempted to recover these cell subtypes in spatial transcriptomic data generated from the same 4 tissue blocks profiled using 4 different platforms and to map their topological relationships. This is part of the NIH-funded Brain-MAAP project.
Methods: After careful evaluation, we selected 4 participants with prefrontal cortex frozen samples with RIN>7; 2 participants who do not fulfill a pathologic diagnosis of Alzheimer disease (AD) and have minimal amyloid and Tau proteinopathies, as well as 2 participants who fulfil a pathologic diagnosis of AD. For each participant, a section of the frozen tissue was cut and profiled with the visium platform from 10X Genomics. A sister section was profiled with a targeted 500 gene panel using the Vizgene Merscope platform. The next section was profiled the Xenium platform from 10x Genomics, and a fourth section is being profiled using Stereoseq from STOmics. Following data preprocessing, data will be made available through the AD Knowledge Portal, and results will be uploaded as well.
Results: Data quality for the first three platforms tested were excellent; Stereoseq data is being generated currently. We are currently analyzing these data and will present final results at the conference, along with a comparison of the platforms. Preliminary results using the Merscope data suggest that we were able to recover 9 of our 12 subtypes of microglia in these ST data.
Conclusions: Our results will help to guide platform selection by the community by presenting data collected from sister sections from same 4 brain samples using 4 distinct platforms representing both RNA capture and targeted multiplexed FISH.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0846 / #1177

Poster Topic: *Theme B: Taupathies / B06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

BEYOND THE ROLE OF PLCG2 IN MICROGLIA IN ALZHEIMER'S DISEASE

POSTERS: B06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Hongjun (Harry) Fu[1], Tae Yeon Kim[1], Diana Acosta[1], Nicholas Sweeney[1], Qi Guo[2], Yuzhou Chang[1], Shuo Chen[1], Geidy Serrano[3], Douglas Scharre[1], Qin Ma[2], Thomas Beach[3]
[1]The Ohio State University Wexner Medical Center, Neuroscience, Columbus, United States of America, [2]The Ohio State University Wexner Medical Center, Biomedical Informatics, Columbus, United States of America, [3]Banner Sun Health Research Institute, Brain And Body Donation Program, Sun City, United States of America

Aims: Recent Genome Wide Association Studies have identified novel rare coding variants in immune genes associated with late onset Alzheimer's disease (LOAD) including the gene encoding the enzyme phospholipase-C-γ2 (PLCG2), which is associated with both reduced (P522R variant) and increased (M28L variant) risk of AD. The role of PLCG2 in AD has been largely investigated in microglia and responses to amyloid β (Aβ) pathology. We aim to investigate the cell autonomous role of PLCG2 in neurons in AD.
Methods: 10x Genomics single nucleus RNA-seq, ATAC-Seq, and Visium spatial transcriptomics were employed to characterize the cell-type-specific and region-specific changes of PLCG2 in the middle temporal gyrus of human AD compared to the control. The immunostaining and WB assay were used to measure the localization and protein levels of PLCG2, p-tau, and p62 in human AD and PS19 tau mice. The PLCG2 and FUW-mCherry-GFP-LC3 were utilized to measure the change of autophagy dynamics induced by PLCG2.
Results: Here we report that PLCG2 mRNA is significantly increased in AD not only in microglia, but also in neurons and astrocytes of human AD compared to the control. The protein level of PLCG2 is also significantly increased in tau transgenic mice and human AD compared to controls. It should be noted that the expression of PLCG2 protein is significantly lower in neurons with tau pathology than those cells without tau pathology. The effect of PLCG2 on autophagy dynamics is under investigation.
Conclusions: These results suggest that repression or dysfunction of PLCG2 may contribute to tau pathology in neurons in AD, probably via the regulation of autophagy pathway. Our findings provide a novel role of PLCG2 in neurons, beyond microglia, in AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0847 / #1382

Poster Topic: *Theme B: Taupathies / B06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

ANALYSIS OF THE LOCUS COERULEUS CIRCADIAN TRANSCRIPTOME IN P301S TAU TRANSGENIC MICE

POSTERS: B06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Eun Young Kim[1], Eui-Beom Jeong[1], Do-Yun Koo[2], Jae Hyung Lee[2]
[1]Ajou University, School of Medicine, Department Of Biomedical Sciences, Suwon, Korea, Republic of, [2]School of Dentistry, Kyung Hee University, Department Of Oral Microbiology, Seoul, Korea, Republic of

Aims: Circadian clock system regulates the physiology and behavior of organisms to manifest about 24hr rhythm. Disruptions in circadian rhythms and sleep disturbance frequently occur in neurodegenerative diseases including Alzheimer's disease, Parkinson's disease etc. Furthermore, circadian rhythm disruption is a potential risk factor that may accelerate pathological processes of neurodegenerative diseases. However, the mechanistic link between circadian clock and neurodegeneration remains incompletely understood. The Locus coeruleus (LC) is the norepinephrine (NE)-containing nucleus in the brainstem and innervates into widespread brain regions including the cerebral cortex, hippocampus, and hypothalamus. The LC-NE system plays an important role in a variety of brain functions, including attention, emotion, cognition, and the sleep-wake cycle. Intriguingly, the LC is an initial site of neurofibrillary tangles (NFTs), a neuropathological hallmark of Alzheimer's disease. In this study, we aimed to understand how circadian clock might influence tauopathy pathology in the LC. Specifically, we sought to identify daily rhythmic oscillating genes in cell-type specific manner.
Methods: Briefly, 3-month-old B6C3F1(wild-type) and P301S Tau transgenic male mice were entrained under 12:12 light:dark (LD) cycle for 2 weeks and transferred to constant dark (DD) condition. Mice were scarified at every 4hrs during 2 days of DD and locus coeruleus containing brain region were processed for RNA sequencing.
Results: We identified total 638 oscillating genes in wild-type mice and total 376 oscillating genes in P301S Tau transgenic mice. The rhythmic genes were not completely overlapped and the phase distribution of rhythmic genes were delayed in P301S Tau transgenic mice.
Conclusions: We are currently analyzing the characteristics of circadian rhythmic oscillating genes in LC and will discuss the potential significance of those genes in the pathogenesis of P301S Tau transgenic mice.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0848 / #841

Poster Topic: *Theme B: Taupathies / B06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

CELL TYPE-SPECIFIC ASSOCIATIONS WITH ALZHEIMER'S NEUROPATHOLOGY AND COGNITIVE IMPAIRMENT CONSERVED ACROSS RACIAL AND ETHNIC GROUPS

POSTERS: B06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Vilas Menon[1], Tain Luquez[1], Rebecca Chiu[1], Jonathan Algoo[1], Jason Mares[1], Lin Wang[1], Archana Yadav[1], Matti Lam[1], Ivy Kosater[1], Pallavi Gaur[1], Philip De Jager[2], David Marquez[3,4], Lisa Barnes[4], Ya Zhang[1], David Bennett[4]
[1]Columbia University Irving Medical Center, Center For Translational And Computational Neuroimmunology, Department Of Neurology, New York, United States of America, [2]Columbia University Irving Medical Center, Center For Translational And Computational Neuroimmunology, Department Of Neurology And Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York, United States of America, [3]University of Illinois at Chicago, Kinesiology & Nutrition, Chicago, United States of America, [4]Rush University Medical Center, Rush Alzheimer's Disease Center, Chicago, United States of America

Aims: Objectives: To identify cell type-specific transcriptomic and epigenetic changes in brain tissue associated with clinical and pathological hallmarks of Alzheimer's Disease (AD). We focus on those found consistently across individuals of different races and ethnicities, to ensure that proposed cell type target signatures are broadly applicable to wider sections of the population.
Methods: We generated joint single-nucleus RNA/ATAC-seq data (Multiome) on post-mortem brain tissue from 3 regions – dorsolateral prefrontal cortex, superior temporal gyrus, and anterior caudate – from 160 individuals from one of five cohort studies (ROSMAP, MARS, AACore and LATC) from the Rush Alzheimer's Disease Center. Roughly one-third of these individuals self-identified as non-Latino White, one-third as non-Latino African American, and one-third as Latino. With median ~4000 nuclei post-QC from each decedent in each brain region, we investigated associations of cell type signatures – clusters, gene expression modules, and open chromatin regions – with Braak stage, CERAD score, and dementia status.
Results: Our three sets of analyses revealed consistent signatures across all three racial and ethnic groups. These included a higher frequency of GPNB+ microglia in cortical regions but not in the anterior caudate in individuals with greater pathology and dementia. In astrocytes, levels of SERPINH1 expression showed associations with pathology and dementia in multiple brain regions. Among cortical neurons, we find lower proportions of one SST+ subtype and higher proportions of two RORB+ subtypes in decedents at later Braak stages and in those with dementia.
Conclusions: We identify a set of cell types, genes, and open chromatin regions that show differences across AD pathology and clinical diagnosis. Importantly for selecting targets with broadest possible applicability, we highlight patterns that are found consistently in three different racial and ethnic groups.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0849 / #1798

Poster Topic: *Theme B: Taupathies / B06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

FTD-MAPT HUMAN BRAIN PROTEOMICS: EXTENSIVE DYSREGULATION OF METABOLIC PATHWAYS

POSTERS: B06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Suzanne Miedema, Leon Balthaus, Remco Klaassen, Berna Özer, Guus Smit
Vrije Universiteit Amsterdam, Molecular & Cellular Neurobiology, Amsterdam, Netherlands

Aims: Frontotemporal dementia (FTD) is a major cause of lethal early-onset dementia. FTD is hereditary in 30% of cases, mainly induced by mutations in the C9orf72 (FTD-C9), progranulin (FTD-GRN), and microtubule-associated protein tau (FTD-MAPT) genes. The remaining 70% (sporadic FTD) can be conceived as a complex trait disorder. Our research aims to determine key cell types and disease mechanisms for hereditary FTD and to construct a disease framework to enable molecular profiling of sporadic cases.
Methods: We re-investigated our FTD-MAPT cohort using a state-of-the-art mass spectrometry-based quantitative approach. Laser-dissected temporal cortex tissues from FTD-MAPT (n=15) and non-demented controls (n=7) were analysed by LC-MS/MS using the timsTOF Pro2 running in dia-PASEF mode. Raw peptide data was analysed with DIA-NN followed by processing in the MS-DAP pipeline. Biological interpretation was inferred with Gene Ontology and cell type enrichment analyses (EWCE).
Results: We were able to deeply measure the FTD-MAPT proteome, detecting 38,489 peptides in 6,306 proteins with reliable quality. Differential abundance analysis (q<0.01) revealed major protein regulation in FTD-MAPT (n=1,011). We observed extensive involvement of metabolic pathways, related to e.g. RNA and amino acids (previously identified), fatty acid oxidation, and glutathione synthesis. In addition, specialized cell-ECM interactions, such as focal adhesion and integrin-mediated signalling, were strongly enriched. Cell type analysis this time showed additional enrichment for microglia, indicating we improved the detection of proteins of this cell type.
Conclusions: Our results demonstrate a heavy involvement of dysregulated metabolic processes in the FTD-MAPT subtype. Proteomic profiling of sporadic FTD cases is currently ongoing. With our efforts, we aim to build a resource that can be used to explore potential mechanisms of disease and to pave the way for the development of disease subtype-specific treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0850 / #1539

Poster Topic: *Theme B: Taupathies / B07.a. Animal Models: Transgenic rodents*

CHARACTERIZATION OF TAU LEVELS, INCLUDING PTHR217 IN THE PS19 ALZHEIMER´S DISEASE MOUSE MODEL

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Benedikt Kien, Roland Rabl, Livia Breznik, Magdalena Daurer, Tina Loeffler, Stefanie Flunkert, Manuela Prokesch
QPS Austria GmbH, Neuropharmacology, Grambach, Austria

Aims: The microtubule-associated protein tau is a primary component of neurofibrillary tangles – one of the major pathological hallmarks of Alzheimer´s disease. PS19 transgenic mice overexpressing the disease-associated P301S tau mutation, are reported to present a strong tauopathy-related brain pathology. However, not all relevant phosphorylation sites were already evaluated in these mice. Recent studies highlight phosphorylated tau at residue threonine 217 (pThr217) as a new promising plasma biomarker for pathological changes implicated in Alzheimer's disease (AD) and it therefore gained attention as possible target in AD therapeutics. Here, we thus performed a detailed biochemical characterization of the soluble and insoluble brain fraction of PS19 mice at different ages, analyzing levels of total tau and different ptau species, including pThr231 and pThr217.
Methods: PS19 mice were sacrificed at the age of 2, 4, 6, and 8 months and cortical and hippocampal soluble and insoluble protein fractions were generated. Those fractions were analyzed for total tau and different ptau species, including pThr231 and pSer217, using different immunosorbent assays and automated western blotting.
Results: Analyses are still in progress, but results will provide an extensive characterization of PS19 mice across different ages including the new emerging marker tau pThr217.
Conclusions: Together with already published data, our results will further support the value of PS19 mice as a valid animal model to investigate the deleterious effects of increased mutant tau and to test novel drug agents.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0851 / #1677

Poster Topic: *Theme B: Taupathies / B06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

INTEGRATED NEUROPATHOLOGIC AND SINGLE CELL TRANSCRIPTOMIC ANALYSIS REVEALS EIF2 ABNORMALITIES IN PROGRESSIVE SUPRANUCLEAR PALSY

POSTERS: B06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Kristen Whitney[1], Won-Min Song[2], Abhijeet Sharma[3], Diana Dangoor[1], Margaret Krassner[1], Kurt Farrell[1], Thomas Christie[1], Hadley Walsh[1], Bin Zhang[4], Ana Pereira[3], John Crary[1]
[1]Icahn School of Medicine at Mount Sinai, Department Of Pathology, Friedman Brain Institute, Ronald M. Loeb Center For Alzheimer's Disease, New York, United States of America, [2]Icahn School of Medicine at Mount Sinai, Genetics And Genomic Sciences, New York, United States of America, [3]Icahn School of Medicine at Mount Sinai, Neuroscience And Neurology, New York, United States of America, [4]Icahn School of Medicine at Mount Sinai, Genetics And Genomic Sciences, And Pharmacological Sciences, New York, United States of America

Aims: Progressive supranuclear palsy (PSP) is the most common primary tauopathy characterized by a constellation of neuropathologic features including 4R-tau positive neurofibrillary tangles and glial tau inclusions. Most PSP cases are sporadic and associated with common structural variation in the 17q21.31 *MAPT* locus as well as other risk loci, including *EIF2AK3* which is critical for the unfolded protein response (UPR). Despite these known genetic risk associations, mechanisms underlying disease pathogenesis and selective vulnerability of different cell types are unclear.
Methods: To investigate transcriptomic changes in vulnerable cell populations, we performed single-nucleus RNA sequencing (snRNA-seq) in the subthalamic nucleus and adjacent regions from human post-mortem PSP brains with variable disease severity compared to clinically normal controls. Transcriptional differences were validated by immunohistochemistry on brain regions either selectively vulnerable or protected in PSP using antibodies for activated EIF2α (pEIF2α), phosphorylated tau (p-tau, AT8), and other cell-type specific markers.
Results: Differential gene expression and pathway analysis identified EIF2 signaling, a target of the UPR, as the top activated pathway in vulnerable cell types. Histological validation showed pEIF2α+ cells in 100% of PSP cases and no pEIF2α+ cells in controls. Vulnerable brain regions had the highest frequency of pEIF2α+ cells, while none were detected in protected regions. The number of pEIF2α+ cells positively correlated with tau burden, and pEIF2α+ granules localized to p-tau$^+$ neurons and astrocytes.
Conclusions: These data show EIF2 activation positively associates with tau burden in vulnerable brain regions and cell types in PSP, providing a potential mechanistic link with *EIF2AK3* genetic risk and the UPR.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0852 / #1564

Poster Topic: *Theme B: Taupathies / B07.a. Animal Models: Transgenic rodents*

CHARACTERIZATION OF A TRANSGENIC MOUSE MODEL OF TAUOPATHY USING QUANTITATIVE EEG: DO TAU-INDUCED DEFICITS LEAD TO DISRUPTED EEG SPECTRA

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Venceslas Duveau[1], Frank Menniti[2], Alexis Evrard[3], Betty Mandé-Niedergang[3], Corinne Roucard[1], Yann Roche[1], Katie Dunton[2]
[1]SYNAPCELL SAS, Sales, Saint-Ismier, France, [2]MindImmune Therapeutics, Pharmacology, Kingston, United States of America, [3]SYNAPCELL SAS, Operations, Saint-Ismier, France

Aims: Alzheimer's disease (AD), the most common form of dementia, is associated with two pathological hallmarks: beta amyloid deposition and neurofibrillary tau tangles. However, lack of understanding of how these primary pathologies result in cognitive deficits remains a hurdle to the development of meaningful therapeutics. We studied changes in electroencephalography (EEG) characteristics with age in the P301L tauopathy mouse model. P301L mice overexpress the 4R/2N isoform of human tau under control of the CaMKIIα promoter on a C57BL/6 background. In this experiment, C57BL/6 will be used as controls and their EEG profile will be compared to the transgenic P301L to evidence a potential EEG biomarker related to the P301L mutation, or the lack thereof.
Methods: In P301L mice and WT controls, monopolar electrodes were implanted bilaterally over the frontal cortex and over parietal cortex on one side. A depth electrode was also implanted in the hippocampus, with a reference electrode over the cerebellum. A Fast Fourier Transform (FFT) was performed on EEG signal from each electrode for frequencies ranging from 1 to 140Hz.
Results: In P301L mice up to 9 months of age, we observed a decrease of power in all classical frequency bands (from Delta to Epsilon) in the hippocampus as compared to WT. There was a persistent trend for an increase in high Delta in frontal cortex, and for a decrease in Theta in parietal cortex. Interestingly, this general pattern of change was evident from 4 months of age.
Conclusions: This study highlights the utility of EEG to identify subtle and persistent changes in brain function in response to AD-relevant tau pathology. Further characterization of the model, including study of the potential pharmaco-sensitivity of the phenotype to therapeutic intervention is ongoing.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0853 / #1723

Poster Topic: *Theme B: Taupathies / B07.a. Animal Models: Transgenic rodents*

OPTIMIZATION OF TAU EXTRACTION FROM HUMAN POST-MORTEM PROGRESSIVE SUPRANUCLEAR PALSY BRAIN FOR MODELLING TAU PATHOLOGY IN VIVO

POSTERS: B07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Hania Qamar[1], Rodylyn Ferry[1], Alison Mao[1], Ivan Martinez-Valbuena[1], Naomi Visanji[1,2,3]
[1]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [2]University of Toronto, Department Of Laboratory Medicine And Pathobiology, Toronto, Canada, [3]Toronto Western Hosptial, Krembil Brain Institute, Toronto, Canada

Aims: To develop an animal model that replicates the anatomical and cytopathologic hallmarks, spatiotemporal spread of pathology and progressive neurodegeneration that characterize Progressive Supranuclear Palsy (PSP) using human brain derived tau. Here we compare the effects of five different tau extraction methods from human PSP brain inoculated in mice that express all six isoforms of human tau.
Methods: Whole brain extracts, PBS soluble extracts as well as 0.1%, 1% and 2% sarkosyl insoluble (SI) tau extracts were prepared from human PSP brain. The tau yield from each preparation was analyzed using ELISA. 6hTau mice were each inoculated in three key nuclei implicated in early stages of PSP (substantia nigra, globus pallidus and caudate putamen). Locomotor behaviour was assessed and tau cytopathologies were examined at 3- and 6-months post inoculation (mpi) using immunohistochemistry (IHC) for phosphorylated tau (AT8).
Results: The PSP whole brain extract yielded the greatest amount of total tau, followed by the PBS soluble extract, 0.1% SI, 1% SI and 2% SI extract, which had the lowest total tau yield. The brains of PBS soluble tau inoculated animals were negative for AT8 IHC at 3 and 6 mpi. 2% SI tau inoculation resulted in AT8 positive neurons and neurites at 3 mpi. Analysis of additional timepoints and extract preparations are ongoing.
Conclusions: Although PBS soluble tau extraction yielded the highest amount of total tau, inoculation in animals did not result in pathology. Conversely, inoculation with 2% SI tau, which had the lowest yield, induced abnormal neuronal tau deposition reminiscent of early pathology in PSP. These data demonstrate the importance of determining the optimal tau extraction method from human brain as a first step in developing an animal model of PSP pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0854 / #1754

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

IMPACT ON LONGEVITY AND REDUCTION OF A-SYNUCLEIN AGGREGATION IN THE NL5901 STRAIN OF CAENORHABDITIS ELEGANS TREATED WITH CANNABIDIOL.

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Ruth Melida Sanchez Mora[1], Alejandra Mantilla Galindo[2], Rodrigo Gonzalez Reyes[2]
[1]Universidad Colegio Mayor de Cundinamarca, Bogota, Bogotá, D.C., Colombia, [2]Universidad del Rosario, Bogota, Bogotá, D.C., Colombia

Aims: Aims: To assess the impact of CBD on the NL5901 strain of Caenorhabditis elegans.
Methods: Materials and Methods: Nematodes were placed on Petri dishes, where the effect of CBD at various doses on lifespan and alpha-synuclein aggregation in the NL5901 strain was evaluated. The N2 strain was used as a control. They were fed with E. coli.
Results: : CBD treatment increased the lifespan in the N2 strain with a median of 32 days, 95% CI (0.2189 - 1.6) vs. CBD 3 µM with a median of 53 days, 95% CI (0.6 - 4.5), vs. CBD 30 µM with a median of 53 days, 95% CI (0.5 - 4.7). Similarly, in the NL5901 strain, the median lifespan was 23 days (0.1 - 1.1), vs. CBD 0.3 µM with a mean of 58 days, CI (0.8 - 7.5), vs. CBD 3 µM with a mean of 40 days, CI (0.6 - 5.2), vs. CBD 30 µM with a mean of 50 days, CI (0.8 - 5.8). CBD treatment also reduced alpha-synuclein aggregates compared to the control group (mean fluorescence intensity (IF) 88.84 ± 38.46) vs. 0.3 µM CBD (IF 32.56 ± 12.25), vs. 3 µM CBD (IF 36.32 ± 11.36), vs. 30 µM CBD (IF 24.89 ± 6.6).
Conclusions: Conclusion: CBD treatment in NL5901 nematodes demonstrated an increase in lifespan and a decrease in alpha-synuclein aggregation in vivo.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0855 / #641

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

SRCD AND SAXS ANALYSIS OF (PYROGLUTAMATE) ALPHA-SYNUCLEIN – DIMERIC STATE AS A SIGNIFICANT INTERMEDIATE IN OLIGOMERISATION?

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Alexandra Bluhm[1], Anja Schulze[2], Wei Xiang[3], Maike Hartlage-Rübsamen[1], Stephan Schilling[2], Philippe Bénas[4], Aurélien Thureau[5], Frank Wien[6], Steffen Roßner[1], Claude Sauter[4]
[1]University of Leipzig, Paul Flechsig Institute For Brain Research, Leipzig, Germany, [2]Fraunhofer Institute for Cell Therapy and Immunology, Department Of Molecular Drug Design And Target Validation, Halle, Germany, [3]University Hospital Erlangen, Molecular Neurology, Erlangen, Germany, [4]University of Strasbourg, Molecular And Cellular Biology Institute, Strasbourg, France, [5]Synchrotron SOLEIL, Swing, Gif-sur-Yvette, France, [6]Synchrotron SOLEIL, Disco, Gif-sur-Yvette, France

Aims: Alpha-synuclein (aSyn) aggregation represents a key event in the neurodegenerative cascade of synucleinopathies. Here, we present new insights into structural characteristics of aggregated full-length (FL-) aSyn and, for the first time, of recently discovered pathological pyroglutamate (pGlu-) aSyn variants of different lengths. The generation of pGlu-aSyn post-translational modification (PTM) requires two enzymatic activities for: (i) N-terminal truncation of aSyn and (ii) the subsequent cyclisation of the resultant N-terminal glutamine to pGlu by glutaminyl cyclase (QC).
Methods: To initiate aggregation, recombinant FL- and pGlu-aSyn variants were agitated with 900 rpm, at 37°C for 5 h. To gain insights into structural properties of monomeric and oligomeric states, synchrotron radiation circular dichroism (SRCD) and size exclusion chromatography coupled small angle X-ray scattering (SEC-SAXS) were performed at SOLEIL synchrotron (France).
Results: SRCD analyses showed that soluble pGlu-aSyn variants are intrinsically disordered proteins, consistent with the known intrinsically disordered nature of FL-aSyn. In order to emulate a lipid environment, SDS micelles were added and the chameleon-like properties of aSyn became evident as the proteins adopted an alpha-helical fold, depending on the length of the pGlu-aSyn variants. An amyloid pore, which was described for the FL-aSyn, could be detected using SEC-SAXS data analyses. Furthermore, shapes of oligomeric pGlu-aSyn variants were bioinformatically modeled. Surprisingly, data suggest the formation of a dimeric state for all proteins studied.
Conclusions: Understanding the complexity and the influence of PTMs on protein aggregation is important for developing disease-modifying interventions. We here investigated the 3D-shape of the dimeric state as a key intermediate in the aggregation/oligomerisation process. Additionally, our results suggest a role of QC as aSyn-modifying enzyme and highlight it as a potential target for treatment of synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0856 / #1714

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

FROM LOCAL TO GLOBAL: INDUCING PARKINSON'S DISEASE-LIKE PATHOLOGY FROM LOCUS COERULEUS TO OTHER BRAIN REGIONS

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Weilin Chen, Carolin Klaus, Pan Gao, Paul Feyen, Thomas Köglsperger, Lars Paeger, Jochen Herms
Deutsches Zentrum für Neurodegenerative Erkrankungen, Translational Brain Research, München, Germany

Aims: Parkinson's Disease (PD) is pathologically characterized by misfolded and abnormally aggregated α-synuclein (α-Syn) in neurons, called Lewy body. Current diagnostic criteria based on PD motor symptoms are not practical enough to distinguish early PD, so it is significant to understand the mechanisms and development of prodromal PD non-motor syndromes. Interestingly, locus coeruleus (LC), is also related with non-motor syndromes like hyposmia, sleep disorder, dementia and depression. Thus, we speculate that there may be potential relationships between LC and PD prodromal syndromes. To investigate that, we start from seeding the α-Syn preformed fibrils (PFFs) in LC of mouse, as animal model to simulate the premotor syndromes and development of prodromal PD.
Methods: C57BL/6J mice were injected with α -synuclein pre-formed fibrils (PFF) in locus coeruleus unilaterally. Mice were sacrificed at the time period of 1, 3 and 6 months after injection, and the propagation of phosphate-129 α -synuclein (Ps129), as well as the density of noradrenergic fibres in LC and other brain region were examined by immunofluorescence staining.
Results: Ps129 pathology appeared early in 1 month after injection, and mainly propagated to median prefrontal cortex, hypothalamus, amygdala and periaqueductal grey, which are also main input areas of LC. In 3 months and 6 months after injection, Ps129 keep aggregating morphologically. Degeneration of noradrenergic fibers were observed in amygdala after 3 months of injection.
Conclusions: Our data indicate that α-Syn pathology could be induced by PFF injection in LC and appeared in areas that innervate LC, hints that propagation of pathology may obey a retrograde neuroanatomical way. Furthermore, we assume that under α-Syn pathological status, brain regions like amygdala may suffer from noradrenergic degenerations, which may be one of the mechanisms of prodromal PD syndromes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0857 / #2211

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

CHARACTERISING ALPHA SYNUCLEIN AGGREGATES FROM MOUSE MODELS AND HUMAN BRAIN SAMPLES USING DNA-PAINT

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Emre Fertan, John Danial, Jeff Lam, David Klenerman
University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom

Aims: Alpha synuclein (aSyn) is a major component of the Lewy bodies found in the brains of Parkinson's disease (PD) patients. However, the toxicity mechanisms of aSyn and the relationship between the morphological and geometric structure of the aggregates and the damage they cause has not been well understood. Moreover, while mouse models expressing human aSyn are often used to study PD, the aSyn aggregates produced by the mice has not been well characterised and compared with the aggregates from human brain samples. Lastly, the impact of the extraction method used to harvest the aggregates on the specific types of aggregates acquired is not well understood.
Methods: We first soaked and homogenised the brains of Line 61 mice as well as post-mortem brain samples from PD patients. Then the homogenised samples were further extracted with sarkosyl and triton-x. We characterised the aSyn aggregates in these samples using single-molecule pulldown (SiMPull) and DNA-PAINT using the epitope-specific 4B12 antibody.
Results: Our results show clear size and shape differences, as well as their numbers, between the mice at different ages, human PD samples and controls, and human and mouse PD samples. Moreover, the method of extraction also provides aggregates with statistically different sizes and shapes.
Conclusions: Since the geometric and structural characteristics of aggregates correlate with heir toxicity and involvement in different disease mechanisms, understanding how the method used to harvest these aggregates effects these properties is crucial. Here we provide a super-resolution characterisation of aSyn aggregates from a well validated mouse model as well as human samples, and show how using different methods of harvesting and imaging these aggregates can provide different results.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0858 / #1454

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

SUBCELLULAR AND BIOCHEMICAL CHARACTERIZATION OF THE NOVEL A30G A-SYNUCLEIN MUTANT IN PARKINSON'S DISEASE

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Vasilina Zafeira Gavra[1,2], Ronald Melki[3], Christina Kyrousi[4], Leonidas Stefanis[1,4], Marina Pantazopoulou[1,2]
[1]Biomedical Research Foundation, Academy of Athens, Clinical- Experimental Surgery & Translational Research, Athens, Greece, [2]National and Kapodistrian University of Athens, School Of Medicine, Athens, Greece, [3]Institut Francois Jacob (MIRCen), Cea And Laboratory Of Neurodegenerative Diseases, Fontenay-Aux-Roses cedex, France, [4]National and Kapodistrian University of Athens, School Of Medicine, athens, Greece

Aims: A30G is a novel heterozygous mutation of the SNCA gene, recently identified in five affected individuals of three non-related Greek families. This mutation is responsible for a PD phenotype, including prominent non-motor symptoms. Biochemical analysis in isolated systems revealed that the A30G SNCA mutation altered the alpha-helical structure of the protein, perturbed membrane binding and promoted fibril formation. However, the effects of this mutation in a cellular context have not been assessed. Our main aim is to unravel the biochemical properties of the A30G mutant in a cellular context, deciphering the mechanisms governing toxicity, seeding and aggregation, leading to a better understanding of PD pathogenesis.
Methods: Using WT α-synuclein recombinant fibrils (PFFs) in neuronally differentiated SH-SY5Y neuroblastoma cells with stable overexpression of mutant A30G α-synuclein, we examined the seeding and aggregation of endogenous α-synuclein by immunofluorescence and immunoblotting assays.
Results: SH-SY5Y neuroblastoma cell lines with stable overexpression of A30G α-synuclein were constructed and different clones with robust protein expression were selected. The overexpression of the A30G mutant protein resulted in the accumulation of insoluble α-synuclein species, partially phosphorylated at pS129, as well as in axonal retraction by 6 days and later neuronal death. Immunofluorescence and immunoblotting experiments showed that upon PFF addition, seeding and aggregation of endogenous A30G α-synuclein occurred within 4 days of PFF incubation.
Conclusions: The overexpression of A30G α-synuclein results in the accumulation of insoluble α-synuclein species and consequently in cell death in a neuronal cell system, while PFF-induced seeding and aggregation of endogenous A30G α-synuclein also occur at an accelerate pace compared to that previously reported for the WT protein. These results highlight the increased aggregation and toxicity propensity of the mutant A30G α-synuclein in a cellular context.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0859 / #1599

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

LYSINE-BASED CHARGE NEUTRALIZING PTMS MODULATE AGGREGATION PROPENSITY OF ALPHA-SYNUCLEIN

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Sharad Gupta[1], Joshna Gadhavi[2], Sumedha Shah[1]
[1]Indian Institute of Technology, Gandhinagar, Department Of Biological Science And Engineering, Gandhinagar, India, [2]Emory University, Department Of Biochemistry, Atlanta, United States of America

Aims: α-Synuclein (α-syn) is one of the major components of Lewy bodies and Lewy neurites, which are pathological hallmarks of Parkison's Disease (PD). α-Syn has been observed to be heavily post-translationally modified in samples derived from postmortem brain tissues of PD patients. Charge neutralizing PTMs such as Acetylation and leser known carbamylation which is an non-enzymatic age-dependent PTM could modulate amyloid formation of α-syn, tau, TDP-43 and other relevant proteins. Our aim was to understand this aggregation modulation by using short peptides from lysine rich region including KTKEGV repeats as model systems and extend our findings to the full-length α-syn.
Methods: We have monitored the aggregation propensity of KTKEGV repeats and amyloidogenic sequences (wild-type, carbamylated and acetylated) present in α-syn by various biophysical techniques including ThT fluorescence kinetic assay, SEM and Bio-AFM. Similarly, chemically modified α-syn was characterized by western blot and MALDI-TOF and it's aggregation was followed using biophysical techniques. We have further investigated the seeding propensity, a hallmark of amyloid structures.
Results: While none of the seven repeats aggregates on their own, we identified four regions that rapidly formed amyloid fibrils when carbamylated. Similarly, while 43-50 peptide WT sequence didn't aggregate even after carbamylation, disease-relevant mutated versions formed amyloid readily. At low concentrations, full length carbamylated α-syn protein aggregation indicated the formation of aggregates with many-fold higher amyloidogenic content than WT α-syn. Finally, we demonstrated that these aggregates of carbamylated α-syn can readily seed aggregation in WT monomeric α-syn preparations. This points to the strong amyloidogenic nature of carbamylated α-syn. Similar alteration in aggregation propensity were observed in acetylated α-syn repeat peptides.
Conclusions: Our studies indicate that carbamylation which is chemically similar to acetylation can significantly alter the physicochemical characteristics as well as aggregation propensity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0860 / #621

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

NEUROINFLAMMATION POTENTIATES ALPHA-SYNUCLEIN PATHOLOGY IN A MOUSE MODEL OF PARKINSON'S DISEASE.

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Hideki Hayakawa[1], Kousuke Baba[1], Hiroshi Sakiyama[1], Chi-Jing Choong[1], Yasuyoshi Kimura[1], Kensuke Ikenaka[1], Cesar Aguirre[1], Tatsusada Okuno[1], Seiichi Nagano[1], Yoshitaka Nagai[2], Hideki Mochizuki[1]
[1]Osaka University Graduate School of Medicine, Department Of Neurology, Osaka, Japan, [2]Kindai University, Department Of Neurology, Osaka, Japan

Aims: Alpha-synuclein (αsyn) is a major component of Lewy bodies, a pathognomonic feature of Parkinson's disease (PD), and its genetic mutations cause familial PD. In neurodegenerative diseases such as PD, the neuroinflammatory role of activated microglia have long been considered important, but the exact role of immune responses in disease progression is unclear. In this study, we analyzed the molecular mechanisms of αsyn propagation and aggregation mediated by neuroinflammation and microglial activation by performing osmotic minipump administration of Lipopolysaccharide (LPS) in αsyn fibril-injected mice.
Methods: αsyn fibrils were injected into the substantia nigra of wild-type and ASC (apoptosis-associated speck-like protein containing caspase recruitment domain) KO mice, and then LPS was introduced intraperitoneally using an osmotic minipump. ASC forms a complex called NLRP3 inflammasome, which induces the maturation and production of inflammatory cytokines IL-1β and IL-18 via the protease caspase-1 (Misawa T, et al. Nat Immunol. 2013). Therefore, in ASC KO mice, microglial activation and induction of inflammatory cytokine production are suppressed. αsyn fibril-injected wild-type mice and ASC KO mice were treated with LPS to induce microglial activation, which could lead to loss of nigrostriatal dopamine cells and formation of αsyn aggregates. The pathophysiology of microglial status and distribution was analyzed.
Results: Introduction of αsyn fibrils and LPS into wild-type mice showed an increase in phosphorylated αsyn aggregates and degeneration of dopamine cells. However, ASC KO mice showed no change in the aggregates of phosphorylated αsyn and degeneration of dopamine cells following LPS treatment.
Conclusions: These results suggest that neuroinflammation is involved in the formation of αsyn aggregates and the loss of dopamine cells and plays an important role in the progression of synucleinopathy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0861 / #1043

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

A NOVEL MODEL OF BRADYKINESIA AND POSTURAL INSTABILITY IN PARKINSON DISEASE BASED ON ALPHA-SYNUCLEIN AGGREGATION IN THE GIGANTOCELLULAR NUCLEI

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Vasileios Theologidis[1], Diana Gomes Moreira[1], Sara Almeida Ferreira[2], Hjalte Gram[3], Poul Jensen[3], Jens Nyengaard[4], Christian Vægter[2], Marina Romero-Ramos[2], Nathalie Van Den Berge[1], Asad Jan[2]
[1]Aarhus University, Department Of Clinical Medicine, Aarhus N, Denmark, [2]Aarhus University, Department Of Biomedicine, Aarhus C, Denmark, [3]Aarhus University, Danish Research Institute Of Translational Neuroscience, Department Of Biomedicine, Aarhus C, Denmark, [4]Aarhus University, Department Of Clinical Medicine, Core Center For Molecular Morphology, Aarhus N, Denmark

Aims: Here, we report a novel rodent model of movement disability (Bradykinesia and Postural instability) based on the induction of alpha-Syn (aSyn) aggregation within the gigantocellular nuclei (GRN) in brainstem.
Methods: As proof-of-concept (PoC), we performed stereotactic delivery of fibrillar aSyn (termed PFF) into the GRN of young (3-4 months) homozygous M83$^{+/+}$ mice (overexpressing the human mutant A53T aSyn) or wild type littermates (n=3/cohort). The mice were then subjected to a battery of motor performance tests every 2 weeks (Challenging Beam Traversal, Rotarod, Open Field, Grip Strength, Hindlimb Clasping).
Results: In the PoC M83$^{+/+}$ study, we have observed a unique phenotype of movement disability, which becomes conspicuous 3-4 weeks of PFF injection (in GRN): *i) challenging beam*: difficulty in movement initiation, slow movement, hindlimb slips and impaired posture maintenance (visible around 4 weeks post-PFF injection, more pronounced on the narrow 8mm beam) *ii) Rotarod*: abnormal motor coordination, such that the mice continue passive movement on the rotating rod and paradoxically 'outperform' the control mice *iii) Open field*: reduced spontaneous activity, increasing freezing episodes, difficulty in turning, overall slow movement As follow-up, we have initiated a larger study in cohorts of heterozygous M83$^{+/-}$ mice (n=8/cohort) with additional controls (PBS vehicle injection, Monomeric aSyn injection), and we expect to present relevant findings at the conference.
Conclusions: This novel rodent model of progressive movement disability based on aSyn aggregation in GRN (a region affected in PD brain)- especially capturing clinically relevant phenotypes of bradykinesia and postural instability- will be a highly valuable tool for: i) dissecting the neural substrate of movement disability in PD and ii) potentially testing the therapeutic relevance of novel disease modifying interventions in PD. FUNDING ACKNOWLEDGEMENT: The Michael J. Fox Foundation for Parkinson's Research

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0862 / #2886

Poster Topic: *Theme B: Taupathies / B07.b. Animal Models: Primates, naturally occuring models and brain organoids*

TAUOPATHY PROMOTES SPINAL CORD-DEPENDENT PRODUCTION OF TOXIC AMYLOID-BETA IN TRANSGENIC MONKEYS

POSTERS: B07.B. ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS

Zhuchi Tu, Sen Yan, Bofeng Han, Shihua Li, Xiao-Jiang Li
Jinan University, Guangdong-hongkong-macau Institute Of Cns Regeneration, Guangzhou, China

Aims: Tauopathy, characterized by the hyperphosphorylation and accumulation of the microtubule-associated protein tau, and the accumulation of Aβ oligomers, constitute the major pathological hallmarks of Alzheimer's disease. However, the relationship and causal roles of these two pathological changes in neurodegeneration remain to be defined, even though they occur together or independently in several neurodegenerative diseases associated with cognitive and movement impairment. While it is widely accepted that Aβ accumulation leads to tauopathy in the late stages of the disease, it is still unknown whether tauopathy influences the formation of toxic Aβ oligomers.
Methods: To address this, we generated transgenic cynomolgus monkey models expressing Tau (P301L) through lentiviral infection of monkey embryos. These monkeys developed age-dependent neurodegeneration and motor dysfunction. Additionally, we performed a stereotaxic injection of adult monkey and mouse brains to express Tau (P301L) via AAV9 infection.
Results: We found that tauopathy resulting from embryonic transgenic Tau expression or stereotaxic brain injection of AAV-Tau selectively promoted the generation of Aβ oligomers in the monkey spinal cord. These Aβ oligomers were recognized by several antibodies to Aβ1–42 and contributed to neurodegeneration. However, the generation of Aβ oligomers was not observed in other brain regions of Tau transgenic monkeys or in the brains of mice injected with AAV9-Tau (P301L), suggesting that the generation of Aβ oligomers is species- and brain region-dependent.
Conclusions: Our findings demonstrate for the first time that tauopathy can trigger Aβ pathology in the primate spinal cord and provide new insight into the pathogenesis and treatment of tauopathy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0863 / #1296

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

MOLECULAR DIVERSITY OF ALPHA-SYNUCLEIN IN PARKINSON'S DISEASE

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Zeynep Kaya, Melina Lim, Danilyn Amerna, Michael Deture, Alexandra Soto-Beasley, Owen Ross, Dennis Dickson, Pam Mclean
Mayo Clinic, Department Of Neuroscience, Jacksonville, United States of America

Aims: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized neuropathologically by the accumulation and aggregation of alpha-synuclein in the form of Lewy bodies. The disease can manifest with different clinical symptoms among subgroups, depending on the age of onset or the pace of symptom progression. However, the reasons for this clinical heterogeneity are not entirely clear. We hypothesize that the molecular diversity of alpha-synuclein impacts its seeding potential and pathology spread, contributing to clinical heterogeneity. To test this hypothesis, we characterized the levels of total alpha-synuclein and phosphorylated alpha-synuclein at serine 129 (pSer129-α-syn) in post-mortem brain extracts and conducted seeding assays to detect differences among the study groups.
Methods: Study groups were designated as fast-progressing (diseased duration <5 years), and slow-progressing (disease duration >10 years). A FRET biosensor cell line was used to perform FRET flow cytometry assay to characterize alpha-synuclein seeding activity. RT-QuIC was performed as an additional measure of seeding bioactivity. High-content imaging was performed to assess the brain homogenates' ability to support seeding and promote macroscopic aggregation. Total alpha-synuclein and pSer129-α-syn levels were measured by AlphaLISA assay and correlated to imaging and FRET assay outcomes.
Results: No significant difference was detected in total alpha-syn levels between groups. However, significantly higher phosphorylated synuclein levels were observed in the slow-progressing group when compared to the fast-progressing group. Interestingly, increased levels of pSer129-α-syn appear to correlate with increased aggregation as observed by imaging, and increased seeding activity as measured by Flow-FRET.
Conclusions: Our results demonstrate a putative connection between pSer129-a-syn levels and aggregation and seeding bioactivity. These results can enhance understanding the molecular pathophysiology of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0864 / #2277

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY AT DIAGNOSIS IN PD PATIENTS WITH PATHOLOGICALLY CONFIRMED PD

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Johannes Lange[1], Linn Oftedal[1], Irene Flønes[2], Charalampos Tzoulis[2], Ole-Bjørn Tysnes[3], Guido Alves[1], Jodi Maple-Grødem[1]
[1]Stavanger University Hospital, Stavanger, Norway., The Centre For Movement Disorders,, Stavanger, Norway, [2]University of Bergen, Department Of Clinical Medicine, Bergen, Norway, [3]Haukeland University Hospital, Bergen, Norway, Department Of Neurology, Bergen, Norway

Aims: Early and accurate Parkinson's disease (PD) diagnosis can be difficult and remains a clinical challenge. The current gold standard is post-mortem histopathological confirmation. Alpha-synuclein (a-syn) seed amplification assay (SAA) is a novel method to detect aggregatable a-syn, the pathological hallmark of PD, with the potential for early detection of PD but needs to be validated against the current gold standard. Here we used a-syn SAA to detect a-syn aggregation in CSF samples taken at the time of initial diagnosis of PD from patients with histopathologically confirmed PD diagnosis after death.
Methods: Our in-house a-syn SAA utilizes novel assay chemistry and gives a result after 48 hours. CSF samples were derived from the Norwegian ParkWest study and taken at the time of diagnosis. All patients were followed prospectively. The included samples (n=27) represent a subset of patients whose PD diagnosis was histopathologically confirmed upon death.
Results: 24 of 27 PD patients had a positive SAA result at the time of diagnosis, corresponding to a sensitivity of 88.9%. On average, SAA detected PD 10.2 years (range 5.4 – 13.2) prior to the gold standard diagnosis. All patients were Braak stage VI at autopsy. The three SAA-negative PD patients had a disease duration between 8.0 and 12.7 years.
Conclusions: Our a-syn SAA was able to detect PD pathology with high sensitivity already at the time of diagnosis with reference to the current gold standard post-mortem diagnosis. A-syn SAA has the potential to increase diagnostic accuracy at the very early clinical stages of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0865 / #579

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

SUPER-RESOLVING SOLUBLE, HUMAN BRAIN-DERIVED ALPHA-SYNUCLEIN AGGREGATES USING SINGLE-MOLECULE METHODS

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Florence Layburn[1,2], Yu Zhang[1,2], Lakmini Kahanawita[3], Caroline Williams-Gray[3], David Klenerman[1,2]
[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]University of Cambridge, Uk Dementia Research Institute, Cambridge, United Kingdom, [3]University of Cambridge, Department Of Clinical Neurosciences, Cambridge, United Kingdom

Aims: Small alpha-synuclein (αSyn) aggregates in solution are proposed to be the true drivers of neurotoxicity in Parkinson's disease (PD). However, small soluble aggregates are elusive research targets due to their variable structures and low abundance, obstructing efforts to fully understand their structures, interactions, and bioactivity in a physiologically-relevant context. The present study aims to characterise small αSyn aggregates from post-mortem human brain tissue using single-molecule techniques and super-resolution microscopy, thereby representing the heterogeneity of aggregates on the nanometer scale. This work will expand on previous limited results from our group in a larger cohort and across different brain regions.
Methods: Post-mortem human brain tissue from n= 14 PD and n=5 age-matched controls across six brain regions was acquired from the Cambridge Brain Bank and the soluble fraction was extracted for analysis. We use the single-molecule pull-down (SiMPull) assay to capture protein aggregates on a novel specialised surface using an antibody-sandwich approach. Total internal reflection fluorescence microscopy is used to visualise proteins on the surface, and super-resolution imaging enables us to characterize aggregate sizes and shapes down to 20 nm.
Results: We established a SiMPull assay for investigating αSyn aggregates from post-mortem human brain tissue, and paired with super-resolution microscopy, we found that aggregates were on average smaller and more fibrillar in PD compared to healthy controls. We extended this assay to investigate other pathological protein aggregates including tau and amyloid-beta, and compared the results with Lewy Body burden throughout the brain regions.
Conclusions: We have established a robust assay to investigate small soluble αSyn aggregates from human brain tissue at the single-molecule level and uncovered significant differences in aggregate size and morphology in PD compared to controls.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0866 / #770

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

PATHOLOGICAL A-SYNUCLEIN PROFILING IN NASAL SPECIMENS OF PATIENTS WITH PARKINSON'S DISEASE

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Mary Xylaki[1], Michael Bartl[1], Sandrina Weber[1], Luis Concha-Marabio[2], Brit Mollenhauer[1]
[1]University Medical Center Göttingen, Department Of Neurology, Göttingen, Germany, [2]Amprion, R&d, San Diego, United States of America

Aims: Parkinson's disease (PD) is a neurodegenerative disorder whose diagnosis is based on clinical criteria that can be difficult to interpret and distinguish from other parkinsonian syndromes. Biomarkers such as pathological alpha-synuclein (aSyn) detection are established in cerebrospinal fluid (CSF) which is collected by an invasive outpatient procedure. Typical PD is thought to start in the olfactory bulb which is connected to the nose, rendering easily accessible nasal samples potent for biomarker development. We sought to identify whether asyn seed amplification assay (SAA) developed to detect pathological asyn in CSF could detect pathological asyn in nasal lavage samples (NLS) and olfactory mucosa (OM). In addition we assessed the olfactory epithelium to identify the cellular subtype contributing to pathology.
Methods: In this study, OM and NLS were collected from PD patients recruited at the Paracelsus-Elena-Klinik, Kassel, Germany (DeNoPa Cohort) and from controls free of neurological disease. Samples were analysed using SAA and their seeding ability was compared to that of CSF samples. Further analyses were performed to assess the presence of aggregated forms of aSyn in the olfactory epithelium.
Results: SAA activity in OM and NLS from PD patients compared to controls indicated the specificity and sensitivity of these samples. In addition, accuracy among results of asyn SAA activity for CSF, OM and NLS from the same patient was estimated.
Conclusions: Our results suggest that asyn SAA analysis of nasal samples alone or combined with CSF testing are useful for increasing the diagnostic accuracy of PD. Finally, more research is necessary to establish the use of the assay in peripheral samples as a biomarker to detect the disease earlier and monitor progression and response to disease modifying approaches.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0867 / #599

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

SYNPHILIN-1 AS A MODULATOR OF ALPHA-SYNUCLEIN ASSEMBLY

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Diana Lázaro[1], Triana Amen[2], Ellen Gerhardt[3], Patricia Santos[3], Dragomir Milovanovic[4], Günter Höglinger[5], Tiago Outeiro[3]
[1]Perelman School of Medicine at the University of Pennsylvania, Pathology And Laboratory Medicine, Philadelphia, United States of America, [2]École Polytechnique Fédérale de Lausanne, Global Health Institute, Lausanne, Switzerland, [3]University Medical Center Gottingen, Department Of Experimental Neurodegeneration, Göttingen, Germany, [4]German Center for Neurodegenerative Diseases, Laboratory Of Molecular Neuroscience, Berlin, Germany, [5]LMU hospital, Department Of Neurology, München, Germany

Aims: In this study, we investigate the relationship between alpha-synuclein (aSyn), an intrinsically disordered protein, and synphilin-1 (Sph1).
Methods: Our new cell-based model allows real-time monitoring of aSyn-Sph1 assemblies, reflecting biologically-relevant protein-protein interactions. We identify striking morphological differences between aSyn-aSyn and Sph1-aSyn assemblies, characterized by distinct antibody recognition patterns, resistance to Proteinase K treatment, and protein mobility. We show that the Sph1-aSyn interaction can be genetically manipulated, influencing inclusion size and quantity. Additionally, protein interactions proved to be pivotal for inclusion localization and formation, with protein expression levels altering inclusion phenotypes.
Results: We show that the Sph1-aSyn interaction can be genetically manipulated, influencing inclusion size and quantity. Additionally, protein interactions proved to be pivotal for inclusion localization and formation, with protein expression levels altering inclusion phenotypes. Our study highlights the potential significance of membrane binding in inclusion formation, further emphasized by the presence of lysosomes and AP-1 vesicles within these inclusions. Our findings suggest that Sph1 expression, or lack thereof, is a critical factor in aSyn aggregation as the coiled-coil domain of Sph1 plays an essential role in its interaction/aggregation with aSyn. Furthermore, our study hints at the broader implications of Sph1 in proteostasis and neurodegenerative diseases, suggesting it may act as a sentinel protein, promoting protein clearance or compartmentalizing harmful proteins.
Conclusions: In conclusion, this study offers novel insights into the interplay between Sph1-aSyn, shedding light on potential therapeutic strategies that extend beyond conventional targets. Sph1 emerges as a key player in the modulation of protein aggregation and homeostasis, paving the way for innovative approaches to tackle synucleinopathies and related neurodegenerative disorders. Further investigations are necessary to explore the clinical relevance of Sph1 expression levels in disease contexts.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0868 / #2766

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

UNCOVERING FACTORS IN BACTERIA THAT INHIBIT PROTEIN AGGREGATION OF A-SYNUCLEIN

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Changhan Lee
Ajou University, Department Of Biological Sciences, Suwon, Korea, Republic of

Aims: Protein have their own structure and it is associated with its function and mechanism. Proteins can be denatured by various stresses such as heat, but certain proteins are naturally prone to be aggregated. Of note, the aggregation of proteins is related to the diseases in human, for example the aggregation of a-synuclein is associated with Parkinson's disease. In this study, we tried to discover known anti-protein aggregation factors in Escherichia coli.
Methods: In this study, tripartite protein folding sensors fused with a-synuclein were utilized, and transposon sequencing (Tn-seq) methodology was employed.
Results: Through the screening process. we were able to discover that the OPE1 protein exhibits potent anti-aggregation activity towards a-synuclein. In addition, we confirmed that OPE1 protein significantly contributes to the inhibition of a-synuclein aggregation. This discovery highlights OPE1 as one of the known protein aggregation inhibitors for a-synuclein.
Conclusions: This study provides important insights into the relationship between protein aggregation and diseases, with OPE1 protein being identified as an effective inhibitor of a-synuclein aggregation. These research results are expected to offer valuable information for disease-related protein aggregation studies and the potential development of therapeutic approaches.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0869 / #2271

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

EFFECTS OF ALPHA-SYNUCLEIN IN THE EXPRESSION OF PEROXISOMAL GENES AND THE DISLOCATION OF CATALASE

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

He-Jin Lee[1], Ye-Seul Yoon[1], Soojin Shin[2], Woo Jung Ahn[3], Seung-Jae Lee[2,4]
[1]Konkuk University, Anatomy, Seoul, Korea, Republic of, [2]Seoul National University, Biomedical Sciences, Seoul, Korea, Republic of, [3]Konkuk University, Ibst, Seoul, Korea, Republic of, [4]Neuramedy, Research And Development, Seoul, Korea, Republic of

Aims: Peroxisomes are small, membrane-bound organelles that contain enzymes involved in various metabolic reactions, such as lipid metabolism and the processing of reactive oxygen species. Peroxisomes in the brain also maintain cellular membrane and myelin sheath in neuron and glial cells. Peroxisomal defects result in severe neurological dysfunctions in myelination, oxidative stress, inflammation, neuronal migration, etc., but little is known about the roles of peroxisomes in neurodegenerative diseases.
Methods: This study shows that a-synuclein overexpression decreased mRNA and protein expression of some peroxisome biogenesis factor proteins.
Results: We identified that these reductions result in abnormality of catalase import into the peroxisome lumen, causing dislocation of catalase outside the peroxisomes. Interestingly, these dislocated catalase proteins co-localized with a-synuclein aggregates in the cell cytoplasm.
Conclusions: These results suggest that a-synuclein overexpression may cause peroxisome dysfunction by regulating the expression of peroxisomal proteins that are important for the transport of catalase into the peroxisomes. The resulting accumulation of ROS species and increased oxidative stress may be critically unfavorable for the progression of neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0870 / #1585

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

ANGIOTENSIN TYPE 1 RECEPTOR ACTIVATION PROMOTES NEURONAL AND GLIAL ALPHA-SYNUCLEIN AGGREGATION AND TRANSMISSION

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Lucia Lage[1,2,3], Ana Isabel Rodríguez Pérez[1,2,3], José Luis Labandeira-Garcia[1,2,3], Antonio Domínguez-Meijide[1,2,3]
[1]University of Santiago de Compostela, Morphological Sciences_ Faculty Of Medicine, Santiago de Compostela, Spain, [2]IDIS, Cellular And Molecular Neurobiology Of Parkinson´s Disease, Research Center For Molecular Medicine And Chronic Diseases (cimus), Santiago de Compostela, Spain, [3]CIBERNED, Networking Research Center On Neurodegenerative Diseases, Madrid, Spain

Aims: The brain renin-angiotensin system (RAS) has been related to dopaminergic degeneration, and high expression of the angiotensin II (AngII) type-1 receptor (AT1) gene is a marker of the most vulnerable neurons in humans. However, it is unknown whether AngII/AT1 overactivation affects α-synuclein aggregation and transmission. As such, our main AIM is to determine the effects of AngII/AT1 overactivation on α-synuclein aggregation and transmission
Methods: To answer this question, we used in vitro (α-synuclein-T/V5-synphilin-1 and a modified version of bimolecular fluorescence complementation in HMC3 and BV2 microglial, C6 astroglial and N27 neuron cell lines) and in vivo (subacute MPTP PD mouse) models to study possible effects of AngII on α-synuclein aggregation and transmission in dopaminergic neurons, and astroglial and microglial cells.
Results: In vitro, AngII/AT1 activation increased α-synuclein aggregation in dopaminergic neurons and microglial cells, which was related to AngII-induced NADPH-oxidase activation and intracellular calcium raising. In mice, AngII/AT1 activation was involved in MPTP-induced increase in α-synuclein expression and aggregation, as they significantly decreased in mice treated with the AT1 blocker telmisartan and AT1 knockout mice. Cell co-cultures (transwells) revealed strong transmission of α-synuclein from dopaminergic neurons to astrocytes and microglia. AngII induced a higher α-synuclein uptake by microglial cells, and an increase in transfer α-synuclein among astroglial cells. However, AngII did not increase the release of α-synuclein by neurons. The results further support brain RAS dysregulation as a major mechanism for progression of Parkinson's disease, and AT1 inhibition and RAS modulation as a therapeutic target.
Conclusions: AngII/AT1 overactivity and brain RAS dysregulation appears involved in major processes related to PD progression such as oxidative stress, neuroinflammation, and α-synuclein expression, aggregation, and cell-to-cell transmission, as revealed for the first time in the present study.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0871 / #222

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

HERPES SIMPLEX VIRUS TYPE 1 TRIGGERS THE PRODUCTION OF A-SYNUCLEIN IN BOTH HUMAN AND MOUSE CNS NEURONS IN VITRO.

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Ahmad Mahmoudikouhi, Ya Gao, Febe Lippens, Kathlyn Laval
Ghent university, Department Of Translational Physiology, Infectiology And Public Health, Merelbeke, Belgium

Aims: Alzheimer's disease (AD) and Parkinson's disease (PD) are progressive neurodegenerative disorders affecting millions of people worldwide. Although these two diseases have different clinical features, they share common mechanisms such as the accumulation of α-synuclein (a-syn) protein in CNS neurons, leading to neuroinflammation and neuronal death. There are currently no cures for AD and PD. The lack of etiology is the most important barrier to finding a cure. Accumulating evidence suggests that viruses, such as Herpes simplex virus type 1 (HSV1), may play a role in the pathogenesis of these diseases. Here we hypothesize that HSV1 infection directly contributes to the initiation of AD and PD by inducing the production and subsequent accumulation of a-syn in neurons.
Methods: We characterized and compared the replication kinetics of HSV1 in both mouse (N2A) and human (SH-SY5Y) CNS neuronal cells. We correlated these data with the kinetics of a-syn protein production by means of immunofluorescence staining techniques.
Results: We demonstrated that HSV1 induces the production of a-syn protein in both cell types starting from 6 hours post-inoculation (hpi). No a-syn protein was expressed in mock-infected cells. The production of a-syn significantly increased over time, as the infection progressed. This production was also found to be viral strain-dependent. Inoculation with HSV-1 virulent F strain resulted in a higher percentage of α-syn positive cells compared to inoculation with clinical isolate.
Conclusions: Overall, our data demonstrate that HSV1 specifically triggers a-syn protein expression in both mouse and human CNS cells. These results provide new direct evidence on the potential role of HSV1 in the pathogenesis of AD and PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0872 / #2412

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

METAL ION INDUCED ALPHA-SYNUCLEIN OLIGOMERS DISRUPT MEMBRANE INTEGRITY OF NEUTRALLY CHARGED LARGE UNILAMELLAR VESICLES

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Georg Nuebling[1], Frits Kamp[2], Felix Schmidt[3], Armin Giese[3], Johannes Levin[4,5,6]
[1]Ludwig-Maximilians University Munich, Department Of Neurology, Munich, Germany, [2]Ludwig-Maximilians University Munich, Division Of Metabolic Biochemistry, Faculty Of Medicine, Biomedical Center (bmc), Munich, Germany, [3]MODAG GmbH, N/a, Wendelsheim, Germany, [4]German Center for Neurodegenerative Diseases (DZNE), Site Munich, Munich, Germany, [5]Munich Cluster for Systems Neurology (SyNergy), N/a, Munich, Germany, [6]Ludwig-Maxmilians-University, Department Of Neurology, Munich, Germany

Aims: It was shown that trivalent metal ions promote the formation of alpha-synuclein (asyn) oligomers even at low nanomolar protein concentrations, and that these oligomers exhibit a pathological gain of function in binding to neutral lipid surfaces. The aim of the current study was to determine whether asyn oligomers formed in presence of ferric iron interfere with the integrity of lipid membranes upon membrane binding.
Methods: Human recombinant alpha-synuclein monomers and Fe^{3+}-induced oligomers were coincubated with large unilamellar vesicles (LUV) derived from 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) at final protein concentrations of 10-20 nM. POPC-LUV contained the Ca^{2+} sensitive dye Fluo4. After baseline measurements, Ca^{2+} was added to the solution (final concentration 0.2mM). Applying single-particle fluorescence techniques (fluorescence correlation spectroscopy, FCS, and Scanning for Intensely Fluorescent Targets, SIFT) and fluorescence spectrometry, protein-membrane interactions were observed at nanomolar and micromolar protein concentrations at the single particle level. For FCS/SIFT experiments, asyn was labeled with the fluorescent dye Alexa-647-O-succiminidylester.
Results: As demonstrated previously, Fe^{3+} induced asyn oligomers, but not monomers, exhibited binding to POPC-LUV. Upon addition of Ca^{2+}, POPC-LUV with bound asyn oligomers showed a fluorescence intensity shift indicating the intrusion of Ca^{2+} ions into the vesicles and activation of the Ca^{2+} sensitive dye. This effect could be reversed upon addition of the Ca^{2+}-binding agent EDTA. Similarly, an increase in fluorescence was observed in fluorescence spectroscopy experiments upon coincubating POPC-LUV and asyn oligomers, but not monomers.
Conclusions: In conclusion, the results presented here demonstrate a pathological gain of function of metal ion induced asyn oligomers in disrupting lipid membranes. These findings have implications for the pathological role of asyn oligomers both concerning the disruption of intracellular organelles and intercellular spreading of pathological asyn oligomer species.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0873 / #1277

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

EFFECTS OF SPLICE VARIANTS ON THE PATHOGENIC AGGREGATION OF ALPHA-SYNUCLEIN

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Alexander Röntgen, Zenon Toprakcioglu, Samuel Dada, Owen Morris, Michele Vendruscolo
University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom

Aims: The aberrant aggregation of alpha-synuclein has long been associated with Parkinson's disease (PD) and related synucleinopathies. The predominant isoform of alpha-synuclein is expressed as a 140-amino acid protein (aSyn-140). However, alpha-synuclein does not exist as a single molecular species in cellular environments but as a variety of proteoforms, generated by variations in splicing, with increasing evidence suggesting that such variants are involved in the overall aggregation process and in the progression of the disease. We therefore investigate the role of splice variants in aggregation and cytotoxicity, as well as their aggregation in mixtures.
Methods: We employed computational solubility predictors, fluorescence-based aggregation assays, kinetic analysis and modelling, as well as electron microscopy to elucidate the mechanism of alpha-synuclein aggregation. In parallel, we used cell viability assays to determine the cytotoxicity of the formed aggregates on SH-SY5Y neuroblastoma cells.
Results: Variations in splicing led to marked differences in the aggregation kinetics and mechanisms, as well as morphological and cytotoxic properties of the proteoform aggregates. Moreover, we determined that the aggregation of aSyn-140 was influenced and modulated by the presence of splice variants.
Conclusions: Our findings imply that the mechanisms leading to the production of diverse proteoforms of alpha-synuclein may be involved in the pathogenesis of synucleinopathies. These results may open the possibility to further understand the role of alpha-synuclein splice variants in the pathological aggregation of this protein and therefore the development of synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0874 / #1467

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

KAJO NEUROTECHNOLOGIES: HUMAN ALPHA-SYNUCLEIN AGGREGATION MODELS FOR DRUG DISCOVERY

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Vassilis Stratoulias[1,2], Amanda Sandelin[1,2], Irena Hlushchuk[1], Safak Er[1], Simas Janutenas[1,2], Jenni Montonen[1,2], Joel Noutere[1,2], Mikko Airavaara[1,2]
[1]University of Helsinki, Faculty Of Pharmacy, Helsinki, Finland, [2]University of Helsinki, Neuroscience Center, Helsinki, Finland

Aims: Developing drugs is a highly risky venture, with only a 0.1% success rate for preclinical candidates gaining approval. The current models employed in drug discovery and development, including in vivo and in vitro rodent models and human cell lines, do not completely replicate human neurodegenerative disorders. Our objective is to create a high-throughput in vitro human model using human cells that mimics pathological features of Parkinson's disease.
Methods: We produce dopaminergic neurons from human stem cells and validate their functionality through assessments of dopamine expression, electrophysiology, biochemical analysis, and transcriptomic profiling. Additionally, we have implemented innovative techniques to induce the formation of Lewy body-like alpha-synuclein aggregates within these dopaminergic neurons derived from human stem cells.
Results: We can induce the formation of alpha-synuclein aggregates within dopaminergic neurons derived from human stem cells. These aggregates can be analyzed using an unbiased high-throughput manner.
Conclusions: Our model, which utilizes alpha-synuclein aggregation in human stem cell-derived dopaminergic neurons, holds promise for drug screening purposes in the context of Parkinson's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0875 / #2288

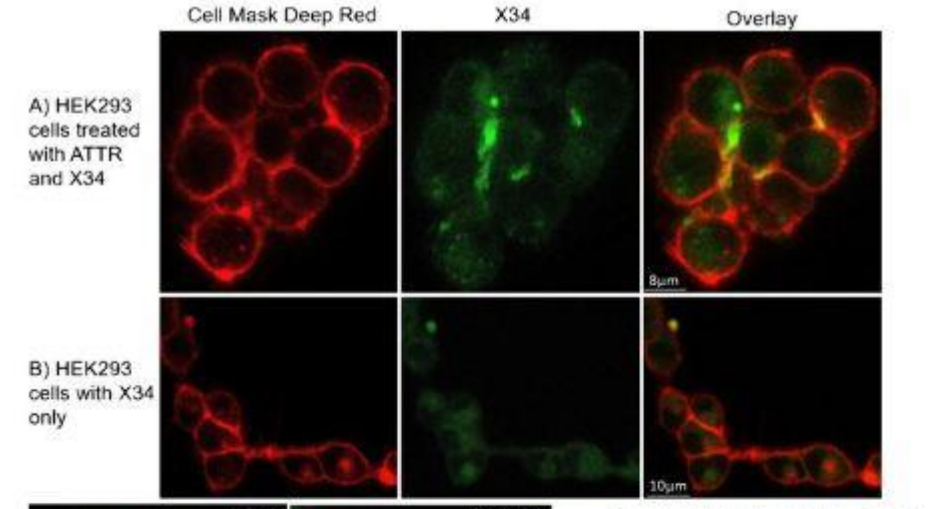
Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

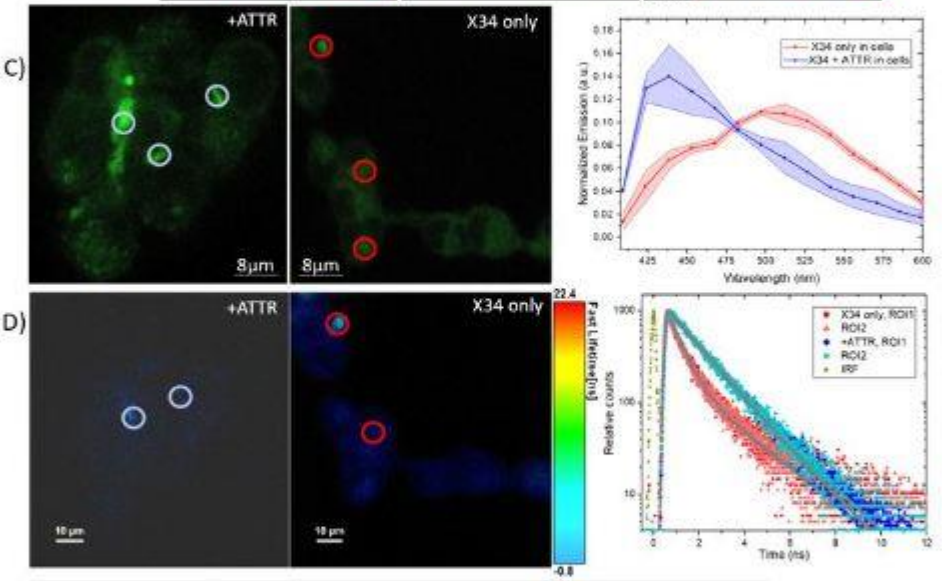
HYPERSPECTRAL IMAGING OF AMYLOID TRANSTHYRETIN (ATTR) AND ASYNUCLEIN IN CELL-MODELS USING NOVEL AMYLOID SPECIFIC FLUORESCENT LIGANDS

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Priyanka Swaminathan[1], Marikken Sundnes[1], Mikael Lindgren[1], Odrun Gederaas[2], Ebba Hellstrand[3], Per Hammarström[3], Sofie Nyström[3], Therése Klingstedt[3], Peter Nilsson[4], Nathalie Van Den Berge[5]
[1]Norwegian University of Science and Technology, Department Of Physics, Trondheim, Norway, [2]University of Agder, Department Of Natural Sciences, Kristiansand, Norway, [3]Linköping University, Department Of Physics, Chemistry And Biology, Linköping, Sweden, [4]Linköping University, Dpt. Of Physics, Chemistry & Biology, Linköping, Sweden, [5]Aarhus University, Department Of Clinical Medicine, Aarhus N, Denmark

Aims: Pathological accumulation and misfolding of certain proteins into insoluble protein aggregates, known as amyloids, is typical to many neurodegenerative disorders. Furthermore, adding to the structural complexity, the cellular environment in which the amyloid protein tends to form aggregates, is also known to influence its molecular conformation. Therefore, we aim to use *in-vitro* cell-models to understand the conformation-specific amyloid pathology in cellular milieu. Here, we present the preliminary results of the hyperspectral imaging of amyloid Transthyretin (ATTR) filaments in Human Embryonic Kidney (HEK)293 cells in order to understand whether the cellular environment influences the spectral features of ATTR in these cells. This study also lays groundwork for detecting and study various polymorphic amyloid protein aggregates including, asynuclein and tau in future.
Methods: HEK293 cells were exposed to ATTR filaments in a serum-free growth medium. 48 hours post protein exposition, the cells were stained with a novel amyloid-specific fluorescent ligand, X34 and subsequently, they were incubated for 2 hours before imaging. The cells were then washed with PBS, followed by staining with a marker for cell membrane, Cell Mask Deep Red. They were then imaged using Confocal Laser Scanning Microscope (CLSM). Fluorescence lifetime imaging microscopy (FLIM) was measured using the PicoQuant's single photon counting feature of the CLSM.





E)

Samples	τ_1 ns (a_1)	τ_2 ns (a_2)	τ_{avg} (ns)
+ATTR	2.3 ± 0.2 (0.24)	1.2 ± 0.1 (0.76)	1.62 ± 0.02
X34 only	2.7 ± 0.07 (0.15)	0.6 ± 0.01 (0.85)	1.56 ± 0.03

Figure 1: Hyperspectral imaging to decipher the spectral characteristics of ATTR in HEK293 cells. **A)** HEK293 cells exposed to 7µM ATTR along with 1µM X34 (bright green) which is excited using 405 nm laser. Fluorescence intensity of X34 increased when it bound to ATTR within cells. **B)** HEK 293 cells exclusively exposed to 1µM X34.**C)** Emission spectrum of X34 is constructed using different Regions of interest (ROIs) within cells. The emission spectrum of X34 when it is bound to ATTR is considerably blue shifted in relation to emission spectrum of X34 when it is alone in cells. **D)** Color-coded images of X34 excited using 405 nm laser, acquired when it is exclusively exposed to HEK 293 cells or when it is bound to ATTR in cells. The color bars represent lifetimes ranging from -0.8 ns to 22.4 ns. The lifetime plots of X34 (red, orange) and when it is bound to ATTR (turquoise blue, dark blue), are constructed by selecting different ROIs within the cells and fitting the FLIM data to a double exponential function. **E)** The average lifetime of X34 when it is bound to ATTR in cells is significantly longer in comparison to the average lifetime of X34, when it is alone in cells.

Results: The spectral features of ATTR when it binds X34 in HEK293 cells is considerably blue shifted in relation to X34 when they are alone in cells .The ensuing fluorescence decay upon ATTR- X34 interaction exhibits longer lifetime.

Conclusions: The spectral feature of ATTR when it is bound to X34 in cells is significantly blue-shifted and exhibits longer lifetime which suggests that the structural morphology of ATTR might by influenced by hydrophobic interactions within the cellular environment .

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0876 / #2934

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

INVESTIGATION OF THE RELATIONSHIP BETWEEN LRRK2 AND ALPHA-SYNUCLEIN IN PARKINSON'S DISEASE

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Giuseppe Madaro[1], Laura Volpicelli-Daley[2], Kurt De Vos[1]
[1]University of Sheffield, Neuroscience, Sheffield, United Kingdom, [2]University of Alabama at Birmingham, Neurology, Birmingham, United States of America

Aims: LRRK2 mutations are the most common monogenic cause of Parkinson's disease (LRRK2-PD). LRRK2-PD is characterized by intraneuronal inclusions, prion-like spreading of aggregated alpha-synuclein, and dopaminergic neuron degeneration. LRRK2 is a protein with GTPase and kinase activity that regulates several biological functions, including autophagy and subcellular trafficking. We have previously shown that LRRK2 interacts with histone deacetylase 6 (HDAC6), a cytoplasmic deacetylase that regulates inflammation, axonal trafficking, and clearance of ubiquitinated protein aggregates via aggrephagy. Preliminary data indicate that LRRK2 may regulate HDAC6 by phosphorylation and that the kinase hyperactive LRRK2 mutant G2019S disrupts ubiquitin-dependent aggresome formation in PD. HDAC6 and LRRK2 have been independently linked to clearance and propagation of aggregated alpha-synuclein. However, how LRRK2 mutations cause alpha-synuclein pathology remains elusive.
Methods: Using *in cellulo* assays, we characterized the interaction between LRRK2 and HDAC6 and investigated the role of LRRK2 and HDAC6 in alpha-synuclein metabolism.
Results: We observed that LRRK2 kinase activity influences its binding to HDAC6, but does not regulate ubiquitin-dependent aggresome formation, NLRP3 inflammasome activation, or microtubule acetylation. We did not find evidence that PFF-induced alpha-synuclein aggregates are targeted to the aggresome via HDAC6. However, HDAC6 inhibition led to accumulation of both soluble and PFF-induced alpha-synuclein aggregates, indicating a role of HDAC6 in alpha-synuclein homeostasis under physiological and pathological conditions. Additionally, LRRK2 kinase inhibitors increased α-synuclein expression levels but had no impact on seeded alpha-synuclein aggregation. No changes were detected in basal alpha-synuclein secretion and subcellular localization upon either LRRK2 or HDAC6 inhibition.
Conclusions: Our data indicate that both LRRK2 and HDAC6 may be involved in alpha-synuclein homeostasis by influencing its clearance and aggregation. Future research will elucidate how LRRK2 regulates HDAC6 functions and how these intersect with alpha-synuclein dyshomeostasis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0877 / #871

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

DISCOVERY OF PINK1/PARKIN SMALL MOLECULE MODULATORS AS TREATMENTS FOR PARKINSON'S DISEASE

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Arwa Alghamdi, Azeza Fdel, Youcef Mehellou
Cardiff University, School Of Pharmacy And Pharmaceutical Sciences, Cardiff, United Kingdom

Aims: Loss of function mutations in the serine/threonine protein kinase PINK1 have been associated with the development of Parkinson's disease (PD) in humans. These mutations lead to impairment in mitophagy, a cellular process that removes damaged or depolarized mitochondria, consequently protecting cells from oxidative stress and eventually neuronal cell death. Upon mitochondrial depolarization, PINK1 gets stabilized on the outer mitochondrial membrane (OMM) and phosphorylates ubiquitin and the E3 Ubiquitin ligase, parkin, ultimately triggering mitophagy. Hence, PINK1 activation has been highlighted as a potential therapeutic approach for PD by promoting neuroprotection through the activation of mitophagy. Our aim of this work is to design and synthesize a series of small molecule PINK1 activators as potential treatments for PD.
Methods: We used chemical synthesis to generate a series of small molecules, and Western blotting/ELISA to probe their ability for activating PINK1 in cells and neurons. Also, we used *mito*-QC assay to assess the ability of these molecules to induce PINK1-dependent mitophagy in mouse embryonic fibroblasts (MEFs).
Results: Our compounds were able to activate PINK1 in cells as judged by the phosphorylation of parkin, a PINK1 physiological substrate. Intriguingly, such compounds were able to protect the cells from the formation of elevated phosphoubiquitin levels caused by mitochondrial damaging agents such as CCCP and niclosamide in cells and in neurons, a hallmark of PD. Subsequently, the compounds were found to trigger mitophagy in a PINK1-dependent manner in MEFs.
Conclusions: We have discovered a series of PINK1 activators that can trigger physiologically relevant PINK1-dependent mitophagy that is capable of suppressing the accumulation of phosphoubiquitin. Given the promise of such compounds, they warrant further development and investigation as potential PD treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0878 / #1041

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

EXPLORING LRRK2-CLUSTERIN PATHWAY IN ASTROCYTES: IMPLICATIONS FOR ALPHA-SYNUCLEIN CLEARANCE AND SPREADING

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Alice Filippini[1], Giulia Carini[1], Veronica Mutti[2], Massimo Gennarelli[1,2], Isabella Russo[1,2]
[1]University of Brescia, Molecular And Translational Medicine, Brescia, Italy, [2]IRCCS-Istituto Centro San Giovanni di Dio Fatebenefratelli, Unit Of Genetics, Brescia, Italy

Aims: Accumulating evidence highlights that dysfunction of astrocytes biology might contribute to Parkinson's disease (PD) onset and progression. To this regard, we recently showed that extracellular clusterin binds to and limits the uptake of alpha-synuclein fibrils by astrocytes, suggesting that its modulation might control alpha-synuclein spreading. Of relevance, we observed that Leucine-rich repeat kinase 2 (*LRRK2*), a gene linked to genetic and familial PD, regulates clusterin levels. Thus, in this study we explore LRRK2-Clusterin pathway in astrocytes to understand whether dysfunctions of this process might contribute to the spreading of alpha-synuclein species between neurons.
Methods: To this aim, we used primary astrocytes cultures and ex-vivo brain tissues from wild type (WT), LRRK2 knock-out (KO) and G2019S knock-in (KI) mice.
Results: Our results show that brain lysates and primary astrocytes from LRRK2 G2019S KI mice exhibit increased clusterin levels compared to their respective WT. Accordingly, we found an opposite effect in brain lysates and in primary astrocytes from LRRK2 KO mice in comparison to their WT. To gain insights in the molecular mechanism underlying LRRK2-dependent clusterin modulation, we found that LRRK2 controls clusterin at the translation level through the regulation of miR-22-5p. We are now validating miR-22-5p as a miRNA clusterin target. Moreover, in relation to PD pathology, we found that astrocytic LRRK2-clusterin pathway affects the spreading of alpha-synuclein aggregates between neurons.
Conclusions: Future studies will allow us to understand whether the modulation of this process through LRRK2 kinase inhibition might improve the ability of astrocytes to clear alpha-synuclein and thus to attenuate neuronal spreading of alpha-synuclein pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0879 / #793

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

REBALANCE OF MITOPHAGY BY INHIBITING LRRK2 IMPROVES PARKINSON'S DISEASE-RELATED COLON DYSFUNCTIONS

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Alerssia Filippone, Deborah Mannino, Giovanna Casili, Marika Lanza, Laura Cucinotta, Irene Paterniti, Emanuela Esposito
University of Messina, Chemical, Biological, Pharmaceutical And Environmental Sciences, Messina, Italy

Aims: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common genetic causes of Parkinson's disease (PD). Mutations of LRRK2 cause dopaminergic neuron death, impaired neurotransmission, and inflammatory response. Also, approximately 80% of PD patients suffer from gastrointestinal dysfunction so the treatment of gut symptoms has been recognized as an important part of the management of PD. Recent studies have demonstrated that mutations of LRRK2 contribute to an increase of intestinal disorders, revealing that variants in LRRK2 genetically link dysfunctions to PD. We aimed to evaluate whether the selective inhibitor of LRRK2, PF-06447475 (PF-475), attenuates the PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in CNS and in the gastrointestinal system.
Methods: Animals received 4 injections of MPTP (20 mg/kg) at two hours intervals in one day. After 24 hours PF-475 was administered (2.5, 5 and 10 mg/kg) for seven days.
Results: LRRK2 targeting reduced brain α-Synuclein accumulation and modulated mitochondrial autophagic processes. Furthermore, PF-475 administration reduced pro-inflammatory markers like iNOS and COX-2 and α-Synuclein aggregates in colonic tissues PD-mice through the modulation of mitoautophagy proteins like p62, optineurin and LAMP2. LRRK2 inhibition suppressed MPTP-induced enteric dopaminergic neuronal injury through modulation of product 9·5 (PGP9.5) and neuron-specific enolase (NSE) and protected tight junction like ZO-1 and occludin disrupted by MPTP in the colon tissue.
Conclusions: We indicated that selective inhibition of LRRK2 restores disruption of colonic integrity and enteric dopaminergic neurons in an MPTP-injected mouse PD model via the mitoautophagy pathway, suggesting that PF-475 may attenuate gastrointestinal dysfunction associated with PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0880 / #2427

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

SYNAPTOJANIN 2-MEDIATED TRANSPORT OF MRNA MAINTAINS MITOPHAGY AND MITOCHONDRIAL FUNCTION IN AXONS AND SYNAPSES

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Whitney Gibbs, Thomas Schwarz
Boston Children's Hospital, Neurobiology, Boston, United States of America

Aims: A unique problem for neurons is providing sufficient energy and protein synthesis to support distant axons and dendrites. Proteins that have short half-lives will not make it to the distal neuron, as it can take weeks for proteins to travel from the soma. Our work uncovered that the RNA recognition motif (RRM) of Synaptojanin 2(SYNJ2) tethers transcripts of PINK1, a short-lived protein mutated in a hereditary form of Parkinson's disease, to motile mitochondria for local protein synthesis. This novel work is the first to explore the unappreciated SYNJ2 RRM with respect to its RNA binding function as a mediator of mitochondrial and neuronal health.
Methods: Three alanine point mutations in SYNJ2 RRM ($SYNJ2^{AAA}$) prevented its RNA binding capacity. These mutations were endogenously expressed in SYNJ2 of mice and human iPSCs using CRISPR/Cas9 technology. iPSCs were differentiated into iNeurons.In situ hybridization allowed for the visualization of PINK1 mRNA in axons. To determine if mitophagy was impacted, we monitored phospho-ubiquitin staining under stress conditions. Mitochondrial respiratory capacity and metabolomic profile were determined using isolated synaptosomes. Electron microscopy was utilized to assess mitochondrial morphological changes.
Results: Axonal PINK1 mRNA and protein stabilization are absent in $SYNJ2^{AAA}$ axons. Antimycin-A increased levels of PINK1 protein and pUb in control, but was attenuated in $SYNJ2^{AAA}$ neurons, indicating decreased mitophagy. $SYNJ2^{AAA}$ synaptosomes exhibited decreased maximal respiration and spare capacity. Key mediators of the glycolytic pathway are upregulated in $SYNJ2^{AAA}$ synaptosomes, potential compensation for impaired mitochondrial respiration. Sciatic nerve mitochondria from aged $SYNJ2^{AAA}$ mice have irregular cristae area and regions with no discernible cristae.
Conclusions: Our work provides fresh insights into a newly discovered mechanism of how mRNA transport and local translation are required to keep the distal axon functioning properly.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0881 / #1765

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

ELUCIDATING THE DEFECTS IN MITOCHONDRIAL DYSFUNCTION AND NUCLEOTIDE METABOLISM IN LRRK2 MODELS OF PARKINSON´S DISEASE

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Haizea Hernández Eguiazu, Saioa Moragón Rodríguez, Andrés Jiménez Zúñiga, Adolfo López De Munain, Javier Ruiz Martínez, Ian Holt, Gorka Gereñu Lopetegi
HRI Biogipuzkoa, Neuroscience, San Sebastian, Spain

Aims: Parkinson's disease (PD) represents a significant neurodegenerative disorder, and its occurrence is on the rise within our aging population. The loss of dopamine-producing neurons, which is at the core of PD, has long been associated with compromised energy production within the mitochondria. Meanwhile, ongoing research suggests that irregularities in DNA metabolism and the recycling of cellular components (autophagy) also play crucial roles in the development of this disease. Recent investigations have revealed deviations in mitochondrial function and nucleotide metabolism linked to PD in human neurons. Mitochondria, housing DNA (mtDNA) vital for energy production and overseeing autophagy, form a functional loop that we propose includes defects in mitochondrial DNA maintenance. Any alterations in these pathways, particularly in highly susceptible cell types, can potentially lead to neuronal cell death and the onset of PD. Our project aims to explore the relevance of Parkinson's disease-causing mutations, specifically LRRK2 mutations, in relation to mitochondrial function, autophagy, and DNA metabolism.
Methods: We use fibroblasts extracted from skin biopsies of PD patients carrying LRRK2 mutations, as well as idiopathic PD patients and *Drosophila melanogaster* models to develop different molecular and functional assays.
Results: In our study, we demonstrate that hyperactivation of LRRK2 within our Parkinson's disease (PD) models not only results in impaired lysosomal function but also disrupts mitochondrial function and compromises the maintenance of mitochondrial DNA (mtDNA).
Conclusions: Through the analysis of functional and molecular outcomes derived from our models, we demonstrate that hyperactivation of LRRK2, causing alterations in autophagy, results in mitochondrial dyfunction and mtDNA metabolism defects, ultimately affecting neuronal survival and locomotor function.These findings could shed light on their potential contribution to the pathogenesis of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0882 / #2768

Poster Topic: *Theme C: α-Synucleinopathies / C01.a. Disease Mechanisms, Pathophysiology: a-synuclein aggregation*

ALPHA-SYNUCLEIN AGGREGATE FORMATION IN THE OLFACTORY EPITHELIUM OF SUBJECTS WITH NEURODEGENERATION AND COVID-19

POSTERS: C01.A. DISEASE MECHANISMS, PATHOPHYSIOLOGY: A-SYNUCLEIN AGGREGATION

Nathalie Lengacher[1], Ann-Kristen Jochum[2], Jonas Franz[3], Alp Ozgun[1], Karim Zahr Eddin[1], Omar Hasan Ali[4], Lukas Flatz[2], Jay Maxwell[5], Josef Penninger[4], Omar El-Agnaf[6], Christine Stadelmann[3], John Woulfe[1,7], Julianna Tomlinson[1,8], Michael Schlossmacher[1,8]
[1]Ottawa Hospital Research Institute, Program In Neuroscience, Ottawa, Canada, [2]Kantonspital St. Gallen, Department Of Pathology, St. Gallen, Switzerland, [3]University of Goettingen Medical Centre, Neuropathology Institute, Goettingen, Germany, [4]University of British Columbia, Research, Vancouver, Canada, [5]The Ottawa Hospital, Department Of Pathology, Ottawa, Canada, [6]Hamad Bin Khalifa University, Brain Research Institute, Doha, Qatar, [7]The Ottawa Hospital, Pathology, Ottawa, Canada, [8]University of Ottawa, Brain And Mind Research Institute, Ottawa, Canada

Aims: Hyposmia and accumulation of insoluble αSynuclein aggregates in the olfactory bulbs are associated with early, pre-motor stages of typical Parkinson disease (PD). In this study we investigated αSynuclein pathology in the human olfactory epithelium and whether it reflects pathology inside the nervous system and responds to environmental triggers such as viral infections.
Methods: We resected the nasal cavity at autopsy from >45 adults with PD, dementia with Lewy bodies, other neurodegenerative diseases, COVID-19 and controls. Nasal bone structures were decalcified and processed for immunohistological and immunofluorescence-based microscopy to screen for and localize aggregated αSynuclein within olfactory and respiratory epithelia.
Results: Select regions of nasal epithelia contained αSynuclein aggregates with four typical staining patterns observed. These were present most often in olfactory neurons, including in their apical dendrites, and in cells of the Bowmann glands in the form of small punctae. Large aggregates were seen in synucleinopathy cases at a rate of 50% and in subjects that died of COVID-19 at ~65%. αSynuclein aggregates were also detected to a lesser extent in control cases (at ~20%). In general, we found poor correlation between these aggregates in nasal epithelia and Lewy-type inclusions in the olfactory bulb and tract from the same subjects.
Conclusions: Our findings indicate that αSynuclein can physiologically form aggregates in the nasal cavity. These may represent the earliest Parkinson's-linked misfolding events described to date. Our results also suggest that environmental triggers, such as a nasal RNA virus infection, could play a role in the formation of such aggregates. The correlation of αSynuclein aggregate formation in relation to inflammation and epithelial turnover remains under investigation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0883 / #125

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

INVESTIGATING THE INTERACTIONS BETWEEN LRRK2 AND GBA1 IN MOUSE AND HUMAN IPSC-DERIVED ASTROCYTES IN PARKINSON DISEASE

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Chiao-Yin Lee[1,2], Matthew Gegg[1,2], Anthony Schapira[1,2]
[1]University College London, Department Of Clinical And Movement Neurosciences, London, United Kingdom, [2]Collaborative Research Network, Aligning Science Across Parkinson's (asap), Chevy Chase, United States of America

Aims: Variants in the genes for leucine rich repeat kinase 2 (LRRK2) and glucocerebrosidase 1 (GBA1) are risk factors for Parkinson disease. An observational study reported that the gain-of-function G2019S-LRRK2 mutation has a protective effect in patients carrying a loss-of-function GBA1 mutation, but the biochemical basis of this interaction remains unclear. This project aims to identify the mechanisms by which LRRK2 influences GBA1 protein expression and activity via the lysosomal pathway, Rab8A and Rab10, as well as to determine if GBA1 exerts an effect on LRRK2.
Methods: Mouse and hiPSC-derived astrocytes carrying the G2019S-LRRK2 and/or N370S-GBA1 mutations were treated with the LRRK2 kinase inhibitor MLi-2 for 24 hours or the lysomotropic drug chloroquine for 5 hours, which has been shown to enhance LRRK2-dependent phosphorylation of Rab8A/10. Immunofluorescence, Western blot, lysosomal activity assays and LysoID are used to investigate how LRRK2 kinase activity impacts alpha-synuclein, GBA1 protein expression and activity and the lysosome, and if reduced GBA1 activity affects LRRK2 activity.
Results: As expected, phosphorylation of Rab8A and Rab10 in mouse and human iPSC-derived astrocytes were decreased or increased by MLi2 and chloroquine, respectively. Preliminary results suggest that in human astrocytes carrying both G2019S and N370S, G2019S rescues the loss of GBA1 protein, and partially rescues reduced lysosomal GBA1 activity, possibly through increasing overall lysosomal content. N370S also appears to slightly increase LRRK2 kinase activity in both mouse and human astrocytes.
Conclusions: Understanding the mechanisms of which GBA and LRRK2 interact within the lysosomal pathway will increase our knowledge of how the two genes cause disease as well as help identify possible drug targets for GBA1- or LRRK2- associated Parkinson disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0884 / #1026

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

EXPLORING OLIGODENDROCYTES AS A NEW PLAYER IN THE PATHOGENESIS OF PARKINSON'S DISEASE

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Isabella Russo[1,2], Valentina Mazziotti[2], Elena Cannone[1], Alice Filippini[3], Giulia Carini[1], Veronica Mutti[2], Massimo Gennarelli[2,3], Marco Schiavone[1]
[1]University of Brescia, Department Of Molecular And Translational Medicine, Brescia, Italy, [2]IRCCS-Istituto Centro San Giovanni di Dio Fatebenefratelli, Unit Of Genetics, Brescia, Italy, [3]University of Brescia, Molecular And Translational Medicine, Brescia, Italy

Aims: Parkinson's disease (PD) is a neurodegenerative disorder pathologically characterized by progressive neuron loss in many brain regions, with a predominant effect in the *substantia nigra*. The mechanism on onset and progression of PD is currently unknown. Emerging evidence highlights that oligodendrocytes (OLGs) could play a causal role in the pathology, providing a new clue into PD etiology. *Via* their densely packed myelin sheaths, OLG intimately communicate with axons providing neurotrophic/metabolic support and maintaining their integrity/functionality. Intriguingly, recent literature reports OLGs pathophysiology in PD and a striking association of OLGs with PD-related *Leucine-rich repeat kinase 2* (*LRRK2*) gene, thus proposing OLGs as a new player in the PD pathogenesis. In this this study, we explore the role of LRRK2 in OLGs, to understand whether OLGs defects might lead to axonal and neuron degeneration observed in PD.
Methods: To this aim, we used murine primary OLGs, *ex-vivo* brain tissues from LRRK2 wild-type (WT) and knock-out (KO) mice and zebrafish model with LRRK2 morpholine.
Results: We observed that LRRK2 KO OLGs display 1) less branched cellular processes, 2) an increased number of OLG precursor cells (OPCs) and 3) a strong reduction of mature OLGs compared to LRRK2 WT cells, indicating defects in the transition of OPCs into OLGs. Consistently, we found a reduction of myelin basic protein (MBP) signal (a marker of mature OLGs) in the striasomes of LRRK2 KO mice and in the MBP:RFP transgenic zebrafishes injected with LRRK2 morpholine compared to control animals.
Conclusions: Overall, these findings indicate a crucial role of LRRK2 in OLGs maturation. Future investigations will allow us to understand if LRRK2 KO OLGs display defects in the functionality and if OLGs dysfunctions might lead to axonal and neuron degeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0885 / #800

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

LRRK2 ACTIVATION AND RECRUITMENT TO LYSOSOMES PARTIALLY PROTECTS AGAINST LYSOSOMAL STRESS IN PRIMARY ASTROCYTE CULTURE WITH PARKINSON'S-LINKED D620N VPS35 MUTATION

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Dorian Sargent[1], P. Otero[2], Vanessa Howland[1], Darren Moore[1]
[1]Van Andel Institute, Department Of Neurodegenerative Science, Grand Rapids, United States of America, [2]Ohio State University, Department Of Neurological Surgery, Columbus, United States of America

Aims: Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) and *vacuolar protein sorting ortholog 35* (*VPS35*) genes cause late-onset, autosomal dominant familial Parkinson's disease (PD). It is widely accepted that LRRK2 mutations enhance LRRK2 kinase activity, which induces multiple cellular defects including an impairment of the endolysosomal pathway. Interestingly, the PD-linked *D620N VPS35* mutation has been reported to increase LRRK2 substrate phosphorylation in both a *D620N VPS35* knockin (KI) mouse model and in PD subjects bearing a *D620N* mutation. Our aim is to identify which cell type exhibit LRRK2 hyperactivation in the brain of *D620N VPS35* KI mouse and evaluate the potential impact on the endolysosomal pathway.
Methods: We detected LRRK2 substrates phosphorylation in the brain and in primary culture from *D620N VPS35* KI mice and evaluated the impact of LRRK2 hyperactivation on endolysosomal function using a LRRK2 kinase inhibitor.
Results: In the brain of D620N VPS35 KI mice, we find that Rab12 phosphorylation is robustly increased relative to Rab10. In primary culture, our data suggests that LRRK2 kinase hyperactivation is prominent in cortical astrocytes but not cortical neurons and that LRRK2 is partially recruited to lysosomes in D620N VPS35 KI astrocytes. The basal levels of endolysosomal pathway components, autophagic flux or lysosomal protease activity are not significantly altered in D620N VPS35 KI astrocytes, suggesting that the impact of LRRK2 hyperactivation on lysosomal function is limited. Interestingly, upon lysosomal stress using lysosomotropic agents, VPS35 KI astrocytes exhibit reduced lysosomal enlargement compared to wild-type cells that is reversed by LRRK2 kinase inhibitor treatment.
Conclusions: Altogether, our study suggests that LRRK2 is recruited to lysosomes and becomes activated in astrocytes from *D620N VPS35* KI mice where it plays a role in lysosomal homeostasis upon stress.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0886 / #620

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

MECHANISM OF PARKIN UBIQUITIN LIGASE ACTIVATION BY SMALL-MOLECULE ALLOSTERIC MODULATORS

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Veronique Sauve[1,2], Thomas Goiran[3,4], Nathalie Croteau[2,5], Eric Stephan[6], Simone Sciabola[6], Laura Silvian[6], Warren Hirst[6], Addy Hadzipasic[6], Jing Fang[6], Edward Fon[3,4], Kalle Gehring[1,2], Jean-Francois Trempe[2,5]
[1]McGill University, Biochemistry, Montreal, Canada, [2]McGill University, Centre De Recherche En Biologie Structurale, Montreal, Canada, [3]McGill University, Mcgill Parkinson Program, Montreal Neurological Institute, Montreal, Canada, [4]McGill University, Montreal Neurological Institute And Hospital, Montreal, Canada, [5]McGill University, Pharmacology & Therapeutics, Montreal, Canada, [6]Biogen, Physical Biochemistry, Biotherapeutics And Medicinal Sciences, Cambridge, United States of America

Aims: Mutations in parkin and PINK1 cause early-onset Parkinson's disease (EOPD). The ubiquitin ligase parkin is recruited to damaged mitochondria and activated by PINK1, a kinase that phosphorylates ubiquitin and the ubiquitin-like (Ubl) domain of parkin. Activated phospho-parkin then ubiquitinates mitochondrial proteins to target the damaged organelle for degradation. Last year, Biogen reported a new class of small-molecule allosteric modulators that enhance parkin activity in the presence of phospho-ubiquitin (pUb) (Shlevkov, *et al*, 2022, *iScience*). We aim to elucidate the mechanism of activation of the most potent modulator (BIO-2007817, EC_{50} = 150 nM), and characterize its ability to rescue pathogenic parkin mutants.
Methods: Ubiquitination assays and isothermal titration calorimetry were performed with parkin variants to identify the pUb binding site required for activation by BIO-2007817. X-ray crystallography was used to solve the structure of parkin bound to pUb and a BIO-2007817 derivative. The binding site was confirmed by nuclear magnetic resonance. Structure-activity relationships were established using in silico docking. In-organello and cell-based mitophagy assays were performed with pathogenic parkin mutants.
Results: BIO-2007817 binds to the RING0 domain with high affinity (K_d = 10 nM) and extends to the pUb moiety bound to RING0, at the same position as the phospho-Ubl domain. This bridging enhances the affinity for pUb, forcing parkin to adopt a conformation similar to phospho-parkin. The modulators thus mimic the parkin activation element and stimulates its activity by displacing the catalytic RING2 domain. Consistent with our model, BIO-2007817 rescues the activity of the parkin EOPD mutants R42P and V56E in the Ubl, as well as R275W.
Conclusions: The structure of parkin bound to allosteric modulators will serve as a scaffold for the design of parkin activators, a potential therapeutic treatment for EOPD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0887 / #1400

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

METABOLIC ALTERATIONS IN LRRK2 G2019S MICROGLIA DERIVING FROM STEM CELLS OF PD PATIENTS

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Maria Tziortziou[1], Katja Badanjak[1], Zied Landoulsi[1], Patrick May[1], Philip Seibler[2], Sandro Cardoso Pereira[1], Anne Grünewald[1]
[1]University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Esch-sur-Alzette, Luxembourg, [2]University of Lübeck, Institute Of Neurogenetics, Lübeck, Germany

Aims: The G2019S mutation in the *leucine-rich repeat kinase 2* (*LRRK2)* gene is the most common genetic cause of PD and is inherited with reduced penetrance. Growing evidence supports an inflammatory component in PD and highlights microglia as key players in the etiology of this condition. Therefore, the aim of this study is to investigate alterations in metabolic pathways within microglia carrying the G2019S mutation in the *LRRK2* gene and assess their contribution to LRRK2-PD penetrance.
Methods: iPSC-derived microglia were generated from PD manifesting and non-manifesting G2019S mutation carriers and healthy individuals, following established protocols. Isogenic lines were also included. The expression of microglial markers was verified by immunocytochemistry and qPCR. The phagocytic ability was assessed by uptake of Zymosan particles. Cells were treated with interferon gamma (IFN-γ) and the kinase inhibitor MLi-2, and Western Blotting was performed for the evaluation of LRRK2 kinase activity. We are further exploring the metabolic profile of these cells assessing the mitochondrial function through Seahorse and microscopy methods. Intra- and extra-cellular metabolites will be examined by LC- and GC-MS analyses. Finally, these results will be combined with existing RNA-seq data.
Results: The presence of TMEM119 and P2RY12 verify the microglial identity. Furthermore, the LRRK2 G2019S mutation does not seem to interfere with the capacity of the cells to differentiate or phagocytose Zymosan particles. Additionally, the results indicate that upon IFN-γ treatment, there is a LRRK2 genotype-specific upregulation in the S1292 phosphorylation, a read-out of LRRK2 kinase activity, which was reversed after MLi-2 treatment.
Conclusions: With microglia being the immune cells of the brain, we hope that this study will provide invaluable insights into their role in PD and shed more light in the underlying mechanisms of LRRK2-PD penetrance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0888 / #2170

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

PROTEIN PURIFICATION AND CHARACTERISATION OF EIF2AK1 AND ITS MUTANTS

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Muzuki Ueda
Newcastle University, School Of Medicine, Newcastle upon Tyne, United Kingdom

Aims: Parkinson's disease is associated with impaired mitophagy, a process of selective removal and degradation of damaged mitochondria. Singh et al., screened all (n=428) known human Serine/Threonine kinases and found that Eukaryotic Translation Initiation Factor 2 Alpha Kinase 1 (EIF2AK1) acts as a negative regulator of PINK1 protein activity, thereby downregulating mitophagy. This study aims to characterise purified EIF2AK1 and its mutants.
Methods: GST-tagged plasmids, including Wild Type (WT), Serine 41 to Alanine mutation (S41A), Kinase Dead mutation (KD), and S41A+KD were transformed into BL21 E. coli cells. Cells were cultured in 1 litre growth medium and protein expression was induced with IPTG. Cells were lysed using sonication. EIF2AK1 proteins were purified using column chromatography.
Results: Western blotting and Coomassie staining were used to analyse purified EIF2AK1 proteins. EIF2AK1 antibody was detected in the western blot, suggesting that the target protein has been eluted. The most prominent band in the Coomassie staining of EIF2AK1 appeared slightly below 75 kD, aligning with the expected molecular weight of EIF2AK1, which is 71 kD. Both Coomassie stains and western blots revealed faint bands above the darkest bands for WT and S41A, while KD and KD+S41A did not exhibit such bands. This suggests that the faint band indicates phosphorylated EIF2AK1, which is absent in KD and KD+S41A due to the absence of kinase activity.
Conclusions: The results indicate that Serine 41 is not the sole kinase domain of EIF2AK1. To further investigate, a kinase assay will be conducted to explore the time and concentration-dependent kinetics of EIF2AK1 and its mutants. Furthermore, EIF2AK1 and PINK1 will be incubated together in a kinase assay to study whether EIF2AK1 directly influences PINK1 phosphorylation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0889 / #1475

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

MICRO- AND MESOSCALE ASPECTS OF NEURODEGENERATION IN MULTI-NODAL HUMAN NEURAL NETWORKS CARRYING THE LRRK2 G2019S MUTATION

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Vibeke Valderhaug[1,2], Ola Ramstad[1], Roos Van De Wijdeven[3], Kristine Heiney[4,5], Stefano Nichele[5,6], Axel Sandvig[1,7,8], Ioanna Sandvig[1]
[1]Norwegian University of Science and Technology, Department Of Neuromedicine And Movement Science, Trondheim, Norway, [2]Helse Møre og Romsdal HF, Department Of Research And Innovation, Ålesund, Norway, [3]Norwegian University of Science and Technology, Department Of Clinical And Molecular Medicine, Trondheim, Norway, [4]Norwegian University of Science and Technology, Department Of Computer Science, Trondheim, Norway, [5]Oslo Metropolitan University, Department Of Computer Science, Oslo, Norway, [6]Østfold University College, Department Of Computer Science And Communication, Halden, Norway, [7]Umeå University Hospital, Department Of Clinical Neuroscience, Umeå, Sweden, [8]Umeå University, Department Of Community Medicine And Rehabilitation, Umeå, Sweden

Aims: Advances in neural engineering now enable modelling of selected pathological aspects of neurodegenerative disease in human neural networks *in vitro*. Of particular interest is how neurodegenerative pathology may manifest and affect network behaviour at the microscale and mesoscale, i.e., before it progresses to affect the entire network. In this study, we utilized multi-nodal human neural networks carrying the Parkinson's related LRRK2 G2019S mutation and healthy isogenic control networks to study early expression of pathology.
Methods: We engineered multi-nodal neural networks from human iPSC-derived neural stem cells with and without the LRRK2 G2019S mutation on custom-designed microfluidic devices. The axon tunnels and synaptic compartments of the microfluidic devices allowed for the selective manipulation and isolated investigation of neurites and their organelles, as well as their synaptic elements, i.e. network sites particularly related to early manifestation of neurodegenerative disease pathology. Furthermore, combining the microfluidic devices with an MEA interface in parallel assays allowed for investigation of network electrophysiology.
Results: We found that the LRRK2 G2019S neurons self-organized into networks exhibiting aberrant morphology and containing neuritic mitochondria moving at heightened speeds, compared to the healthy isogenic controls ($p = 0.0038$) . Furthermore, following a transient excitatory event, the LRRK2 neural networks exhibited behaviour suggestive of an impaired response, i.e. displaying less signs of neurite remodelling, synaptic plasticity, and a smaller relative change in total network correlation, compared to the healthy control neural networks.

Conclusions: Micro- and mesoscale signs of neurodegeneration manifest early in the development of self-organizing human neural network carrying the LRRK2 G2019S mutation *in vitro.* Furthermore, the combination of neural engineering and microfluidic devices, together with MEAs, make powerful tools for modelling and for further elucidation of pathological processes in early stages of neurodegenerative disease development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0890 / #2381

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

THE IMPACT OF LRRK2 KINASE INHIBITION ON GUT-TO-BRAIN SPREADING IN NOVEL PD MOUSE MODELS

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Pauline Vessiere[1], Solène Ferreira[1], Joana Domingues[1], Giulio Deangeli[1], Zhiguang Zheng[1], Matthew Mason[1], Emma Carlson[1], Francesca Tonelli[2], Dario Alessi[3], Maria Grazia Spillantini[1]
[1]University of Cambridge, Clinical Neurosciences, Cambridge, United Kingdom, [2]University of Dundee, Medical Research Council Protein Phosphorylation And Ubiquitylation Unit, Dundee, United Kingdom, [3]University of Dundee, Mrc Protein Phosphorylation And Ubiquitylation Unit, Dundee, United Kingdom

Aims: Parkinson's disease (PD) is a neurodegenerative disease characterized by the spread of a-synuclein throughout the CNS. Most cases are sporadic but approximately 10% of cases are inherited due to genetic mutations in genes, such as the Leucine-rich repeat kinase 2 (LRRK2) gene. PD causing mutations in this gene lead to the hyperactivity of the LRRK2 protein. Therefore, inhibiting LRRK2 is thought to be of therapeutic benefit, however the effects of this inhibition on a-syn spreading remain unclear. The objective of the present study is to investigate the effects of LRRK2 inhibition on gut-to-brain a-syn spreading in novel PD mouse models.
Methods: Two new PD mouse models, Vitras and Vitras6J, have been used in this study. The former expresses human, 1-120 truncated a-syn in the gut and olfactory epithelium in an a-syn null background, while the latter expressed the same transgenic a-syn in a murine a-syn background. The LRRK2 inhibition was performed by supplementing the diet of adult mice with LRRK2 kinase inhibitor (MLi-2) for 3 months.
Results: The 3-month MLi-2 treatment did not affect animal survival but prevented animal weight gain in transgenic mice lacking endogenous a-synuclein. The increased faecal output, usually present in Vitras and Vitras6J mice, was reduced after MLi-2 treatment, showing that LRRK2 inhibition normalised bowel transport of the transgenic mice. Ongoing experiments are investigating whether LRRK2 inhibition influences a-synuclein spreading from gut to brain.
Conclusions: The MLi-2 treatment performed in the novel PD transgenic mice described above, will be valuable to assess whether the inhibition of the LRRK2 impacts periphery-to-brain transfer of a-syn. The results from this study will help shed light on whether LRRK2 inhibition could be a therapeutic target capable of slowing down PD progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0891 / #1444

Poster Topic: *Theme C: α-Synucleinopathies / C01.b. Disease Mechanisms, Pathophysiology: LRKK2, parkin, PINK1, DJ-1*

FLUORESCENT CELLULAR MODELS OF MITOPHAGY FOR DRUG SCREENING OF THE PINK1/PARKIN SIGNALLING PATHWAY

POSTERS: C01.B. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LRKK2, PARKIN, PINK1, DJ-1

Patricia Villace, Rosa M Mella, Meritxell Roura, Clarisa Salado, Miguel Peco
INNOPROT, Cellular And Molecular Lab, DERIO, Spain

Aims: It is widely accepted that the pathogenic mechanisms in a subset of people with PD is the mitochondrial stress linked to dysfunctional regulation of mitophagy. PINK1 regulates PARKIN translocation in impaired mitochondria and drives their removal by selective mitophagy maintaining cellular energy homesostasis. Image-based cellular models for monitoring PINK1/PARKIN signalling have been used to screen a chemical library of 1,280 molecules to identify compounds that modulate the cellular mitophagy. The hit compounds were chosen for further testing, based on the strength of the initial response and lack of cytotoxicity. The results indicated that this assay is a robust (Z' > 0.5) and valid strategy to test potential candidates for preclinical studies and to facilitate the drug discovery process.
Methods: Generation of stable cell line: Cell lines were obtained with a single-cell dispenser by fluorescence sorting F-Sight (Cytena GmbH). **Liquid Handling and phenotype-based screening assay:** For dispensing of the liquid media containing cells and compounds, the Hamilton's Microlab Star automated liquid handling workstation was used. Cells were treated with CCCP or FCCP (positive controls) for 3 hours and the library of compounds at 10 µM for 24 hours in Optimem medium before image acquisition. **Image acquisition and analysis:** Fluorescence images were acquired in the CellInsight™ CX7 High Content Analysis Platform with a x20 dry objective.
Results: - Screening of 1,280-compound library was performed. Eight positive compounds were identified. - Image cellular redistribution assay of Parkin_ mitochondria and PINK1 in the presence of positive compounds was performed at 10 µM. - Dose-response curves of the positive compounds were assayed.
Conclusions: Fluorescent cell-based models can be applied for the screening of compound libraries in multiple High Content Bioimaging Platforms

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0892 / #466

Poster Topic: *Theme C: α-Synucleinopathies / C01.c. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

BACTERIAL AMYLOIDS SECRETED BY S. AUREUS INDUCE ALPHA-SYNUCLEIN AGGREGATION PROMOTING KEY PATHOLOGICAL FEATURES OF PARKINSON'S DISEASE

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Maria Izco Gaviria[1], Jaione Valle[2], Lydia Alvarez-Erviti[3]
[1]Fundación Rioja Salud, Molecular Neurobiology, Logroño, Spain, [2]Instituto de Agrobiotecnología (IDAB). CSIC-Gobierno de Navarra, Molecular Biology Of Bacterial Pathogens, Pamplona, Spain, [3]Fundacion Rioja Salud, Molecular Neurobiology, Logroño, Spain

Aims: Recent studies show that persons with neurodegenerative disorders have an altered microbiome, moreover, studies in animal models pointed to a central role of microbiota in PD pathology. Initial results have shown that the gastrointestinal microbiome expresses functional amyloids as scaffold components of its biofilm and cross-seeding of amyloidogenic proteins by bacterial amyloids has been documented both in vivo and in vitro. The overall goal of this proposal is to investigate if bacterial amyloids secreted by S*. aureus* induce alpha-synuclein aggregation promoting key pathological features of Parkinson's disease.
Methods: SH-SY5Y cells expressing alpha-synuclein were treated with Bap preformed fibrils (rBap-PFF) to evaluate alpha-synuclein aggregation. Mice received unilateral intrastriatal injection of rBap-PFF or vehicle and were sacrificed 7 months later to assess alpha-synuclein pathology, dopaminergic degeneration and microglia and astrocyte activation.
Results: The treatment with rBapB-PFF amyloids resulted in an increase of phosphorylated alpha-synuclein aggregates in SH-SY5Y cells. The intrastriatal injection of rBapB-PFF amyloids in wildtype mice caused impairment in fine motor performance. These behavioural changes were associated with a unilateral loss of dopaminergic innervation in the striatum and a loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The PD pathology was associated with the presence of phosphorylated alpha-synuclein aggregates in the SNpc, cortex and thalamus. The neurodegenerative process was not associated with a neuroinflamatory response to Bap fibrils.
Conclusions: Bacterial amyloids secreted by *S. aureus* have direct impact on alpha-synuclein aggregation and pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0893 / #690

Poster Topic: *Theme C: α-Synucleinopathies / C01.c. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

THE ROLE OF SMALL EXTRACELLULAR VESICLES IN A-SYNUCLEIN TRANSMISSION

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Dimitra Sotiria Karampela[1], Marina Pantazopoulou[2], Anastasios Delis[1], Ronald Melki[3], Kostas Vekrellis[1]
[1]Biomedical Research Foundation of the Academy of Athens, Division Of Basic Neurosciences, Athens, Greece, [2]Biomedical Research Foundation, Academy of Athens, Clinical- Experimental Surgery & Translational Research, Athens, Greece, [3]Institut Francois Jacob (MIRCen), Cea And Laboratory Of Neurodegenerative Diseases, Fontenay-Aux-Roses cedex, France

Aims: Small extracellular vesicles (sEVs) have recently emerged as key players in cellular communication in both physiological and pathological processes in the brain, particularly in synucleinopathies. Our recent work indicates that brain-derived sEVs are internalized by glial cells (microglia and astrocytes) through macropinocytosis and are sorted to endolysosomes for subsequent processing. The current study aims to examine the intracellular trafficking pathway of sEVs in glial cells linked with the sEV-associated α-synuclein (α-Syn) transmission.
Methods: Glial primary cultures were incubated with DiI-stained mouse brain-derived sEVs, in the absence or presence of recombinant fibrillar human α-Syn (pre-formed fibrils, PFFs). The internalization and trafficking pathways in cells treated with pharmacological reagents that block the major endocytic pathways, were analyzed by immunofluorescence, using the Imaris analysis software.
Results: PFFs were internalized by both microglia and astrocytes at early time points of PFF incubation. In microglia, PFF uptake occurred within 15 min, whereas in astrocytes PFFs were efficiently internalized 1h post-incubation. In the presence of sEVs, a delay in the PFF uptake was observed in both glial cell types. Treatment with dynasore, that inhibits dynamin-dependent endocytosis, affected PFF uptake only in the absence of sEVs. sEV-associated PFFs seemed to utilize macropinocytosis and/or phagocytosis as the main pathway of endocytosis. Fibrillar α-Syn when associated with sEVs enter the endosomal pathway and are targeted to the lysosome for subsequent degradation. In the absence of sEVs, only a small portion of fibrillar α-Syn is sorted to the endolysosomal pathway.
Conclusions: Our data indicate that brain-derived sEVs serve as scavengers and mediate a rather slow cell-to-glia transfer of pathological α-Syn which is targeted to the endolysosomal pathway, suggesting a beneficial role in glia-mediated clearance of toxic protein aggregates, present in numerous neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0894 / #2255

Poster Topic: *Theme C: α-Synucleinopathies / C01.c. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

MUTATION-INDUCED GLUCOCEREBROSIDASE DEFICIENCY EXACERBATES ALPHA-SYNUCLEIN PATHOLOGY IN THE VAGAL SYSTEM

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Pietro La Vitola, Eva Szegoe, Rita Pinto Costa, Angela Rollar, Eugenia Harbachova, Donato Di Monte
DZNE (German Center for Neurodegenerative Diseases), Neurodegeneration And Neuroprotection In Parkinson's Disease, Bonn, Germany

Aims: The dorsal motor nucleus of the vagus nerve (DMV) represents a primary site where pathological alpha-synuclein (A-SYN) aggregates are formed and from where A-SYN pathology could spread rostrally throughout the brain in Parkinson's disease (PD). Variants in the glucocerebrosidase gene (*GBA1*) are common PD genetic risk factors and have been linked to earlier PD onset and more severe disease progression. The aim of this study was to investigate the relationship between *GBA1* mutations and A-SYN aggregation and spreading in a mouse model of overexpression-induced A-SYN pathology.
Methods: Experiments were carried out in heterozygous *Gba1* mice carrying a L444P knock-in mutation (L444P/+) and non-transgenic (NTG) littermates. Overexpression of human A-SYN targeting the DMV was induced by a unilateral injection of adeno-associated vectors (AAVs) delivering hA-SYN DNA into the vagus nerve. Mice were sacrificed 6 weeks post-injection.
Results: Frozen brain tissue was used to measure glucocerebrosidase (GCase) activity that was significantly decreased in naive L444P/+ as compared to NTG mice. After vagal AAV injections, hA-SYN aggregation was detected using proximity ligation assay and found to be markedly enhanced in mice carrying the L444P mutation. To assess spreading, tissue sections were collected throughout the brain and processed for immunohistochemistry with anti-hA-SYN. Data revealed a significant increase in number of hA-SYN-positive axons in the pons, midbrain and forebrain of transgenic as compared to control animals.
Conclusions: Our findings support an increased vulnerability to A-SYN pathology associated with L444P mutation-induced GCase deficiency. We demonstrate that, in the presence of GCase deficiency, enhanced A-SYN expression in the vagal system is accompanied by more severe aggregate pathology. As importantly, under these conditions, A-SYN spreading is promoted, resulting in its enhanced transfer toward brain regions rostral to the DMV-containing medulla oblongata.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0895 / #1823

Poster Topic: *Theme C: α-Synucleinopathies / C01.c. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

REM-SLEEP BEHAVIORAL DISTURBANCES IN MICE FOLLOWING SEEDED ALPHA-SYNUCLEINOPATHY

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Hansoo Yoo[1], Russell Luke[2], Brittany Dugan[2], Jimmy Fraigne[2], Jefferson Steltz[3], Jonah Lourie[3], Lauren Torres[3], John Peever[2], Kelvin Luk[3]
[1]Yonsei University, Neurology, Seoul, Korea, Republic of, [2]University of Toronto, Cell & Systems Biology, Toronto, Canada, [3]University of Pennsylvania, Pathology And Laboratory Medicine, Philadelphia, United States of America

Aims: To develop a mouse model of REM-sleep behavioral disorder using a synuclein fibril targeting approach
Methods: Alpha-synuclein fibrils were stereotactically targeted to the sublateraldorsal tegmental region (SLD) of wildtype (C57Bl6/C3H) mice. Animals were then assessed using electroencephalography (EEG), electromyography (EMG), behavioral testing (motor and cognitive), and histologically at 1, 3, 6, and 12 months post injection with preformed fibrils.
Results: Synucleinopathy was initiated by fibril injection into the SLD, and disseminated through the associated connectome over time. Immunohistochemical analysis revealed selectively vulnerable neuron and non-neuronal populations that were affected over time. EEG/EMG examination also showed abnormalities, specifically an increase in muscle activity during REM-sleep.
Conclusions: Targeting of alpha-synuclein PFFs drives the formation of pathology in the SLD and associated brain regions. These cumulatively result in the development of a phenotype that recapitulates a subset of prodromal synucleinopathy subjects. Additional studies are underway to understand the substrate for these alterations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0896 / #171

Poster Topic: *Theme C: α-Synucleinopathies / C01.c. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

SOLUBLE PROTEIN POST-TRANSLATION MODIFICATIONS: UNEXPECTED REGULATORS OF PATHOLOGICAL PROTEIN TRANSMISSION

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Chao Peng[1], Virginia Lee[2], Shujing Zhang[1], Hilal Lashuel[3], James Petersson[2]
[1]University of California Los Angeles, Department Of Neurology, Los Angeles, United States of America, [2]University of Pennsylvania, Pathology & Lab Medicine, Philadelphia, United States of America, [3]Swiss Federal Institute of Technology, Laboratory Of Molecular And Chemical Biology Of Neurodegeneration, Brain Mind Institute, Lausanne, Switzerland

Aims: Cell-to-cell transmission and subsequent amplification of pathological proteins promotes neurodegenerative disease progression. Most research on this has focused on pathological protein seeds, but how their normal counterparts, which are converted to pathological forms during transmission, regulate transmission is less understood.
Methods: We used various novel cell models and in vitro seeding assays to evaluate whether soluble α-synuclein modulate the transmission of pathological α-synuclein. We also performed mulitple rounds of LC-MS/MS studies to identify novel PTMs on soluble α-synuclein.
Results: We show in cultured cells that phosphorylation of soluble, non-pathological α-Syn at previously identified sites dramatically affects the amplification of pathological α-Syn, which underlies Parkinson's disease (PD) and other α-Synucleinopathies, in a conformation- and phosphorylation site-specific manner. We performed LC-MS/MS analyses on soluble α-Syn purified from PD and other α-Synucleinopathies, identifying many novel α-Syn post-translational modifications (PTMs). In addition to phosphorylation, acetylation of soluble α-Syn also modified pathological α-Syn transmission in a site- and conformation specific manner. Moreover, phosphorylation of soluble α-Syn could modulate the seeding properties of pathological α-Syn. Our study represents the first systematic analysis how of soluble α-Syn PTMs affects the spreading and amplification of pathological α-Syn, which may affect disease progression. Moreover, our recent study demontrated that the regulation of pathological protein amplification by soluble protein is not limited to α-Syn. We found that soluble tau PTMs could also dramatically modulate the transmission of pathological tau.
Conclusions: Our study demenstrated that souble protein PTMs represents a novel mechanism that modulate the transmission of pathological protein in neurodegenrative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0897 / #1688

Poster Topic: *Theme C: α-Synucleinopathies / C01.c. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

DETECTION OF ALPHA SYNUCLEIN MISFOLDED AGGREGATES BY SEED AMPLIFICATION ASSAY

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Michelle Pinho, Claudio Soto, Sandra Pritzkow
Mitchell Center for Alzheimer's Disease and Related Brain Disorders, Department of Neurology, University of Texas McGovern Medical School at Houston, Houston, TX, USA, Neurology, Houston, United States of America

Aims: Alpha-synuclein (αSyn) misfolding, aggregation, and cerebral accumulation is associated with neurodegenerative diseases like Parkinson's disease (PD), multiple system atrophy (MSA) and dementia with Lewy bodies (DLB). While research has primarily focused on the role of αSyn deposits in the central nervous system, emerging evidence suggests that αSyn may also be distributed throughout the peripheral system, including the autonomic nervous system and peripheral organs. This study aims to assess the utility of a seed amplification assay (αSyn-SAA) for the detection of αSyn aggregates in peripheral tissues.
Methods: Peripheral tissue samples, including stomach, small intestine, heart, liver, kidney, spleen, and colon, were collected from PD, MSA, DLB patients, and controls. Samples were homogenized, diluted to 10^{-3}, 10^{-4}, and placed in the αSyn-SAA reaction containing recombinant αSyn, buffer, 0.1% sarkosyl, silica beads, and thioflavin T. The signal of αSyn-SAA in the presence of different samples was analyzed by the thioflavin T fluorescence over time.
Results: Our results showed detection of αSyn aggregates in various peripheral tissues using αSyn-SAA. Seed-competent aggregated αSyn was reliably detected in the small intestine, heart, and colon in patients affected by PD and DLB and to a lower extent in MSA. Controls, including people who have died of unrelated diseases or patients affected by Alzheimer's disease, did not show any signal in αSyn-SAA.
Conclusions: Our study demonstrates that αSyn-SAA is useful for detection of αSyn aggregates in peripheral tissues. Our findings indicate that αSyn accumulation does not only occur in the brain, but also becomes deposited in various peripheral organs. Our data will contribute to understanding the biology and pathogenesis of synucleinopathies. **Funding**: Grant from Michael J. Fox Foundation to SP.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0898 / #847

Poster Topic: *Theme C: α-Synucleinopathies / C01.d. Disease Mechanisms, Pathophysiology: Autophagy, lysosomes, ubiquitin, proteasome*

DISSECTING OLIGOGENIC MECHANISMS OF LYSOSOMAL SUSCEPTIBILITY IN PARKINSON'S DISEASE

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

Jinghan Zhao[1], Mingxue Gu[2], Meigen Yu[3], Ruth Barros De Paula[4], Hugo Bellen[2], Joshua Shulman[3]
[1]Baylor College of Medicine, Neurology/neuroscience, Houston, United States of America, [2]Baylor College of Medicine, Molecular & Human Genetics, Houston, United States of America, [3]Baylor College of Medicine, Neuroscience, Houston, United States of America, [4]Baylor College of Medicine, Neurology, Houston, United States of America

Aims: Besides *GBA*, variation in other lysosomal storage disorder (LSD) genes are associated with Parkinson's disease (PD) risk, and knockdown of these genes in experimental models enhances alpha-synuclein (α-Syn) mediated neurodegeneration. Our goal is to elucidate mechanisms by which *partial loss-of-function* in *GBA* contributes to Parkinson's disease (PD) along with the determinants of *GBA* penetrance.
Methods: LSD genes, variants, and their combinations were prioritized based on analyses of PD case/control cohorts with genome sequencing, along with our published results on genetic modifiers of α-Syn in *Drosophila* models. Combinatorial genetic manipulations in fly *Gba1b* and other implicated LSD genes (e.g. double-heterozygous and other synthetic genotypes), are being examined for impact on CNS structure, function, and metabolism (e.g. histology, locomotor function, electrophysiology, lysosomal markers, and lipidomics).
Results: Among PD cases, 21% harbor damaging variants in 2 or more LSD gene variants. Multi-allelic combinations between *GBA* and other causes of sphingolipidoses are 4-fold more likely than other LSD subtypes, and a similar enrichment was not seen among controls. In preliminary cross-species studies, *Gba1b* haploinsufficiency in *Drosophila* causes mild locomotor phenotypes and perturbations in sphingolipid metabolism. Partial loss-of-function in the fly ortholog of *ATP13A2*, strongly interacts with *Gba1b* heterozygozity. Lipidomic analysis of heads from α-Syn transgenic flies additionally reveals elevated ceramide species. Follow-up studies and interaction tests with other prioritized, conserved LSD genes are ongoing, including causes of sphingolipidoses (*SMPD1, SCARB2*), mucopolysaccharidoses (*MANBA*), and cholesterol storage disorders (*NPC1/2*).
Conclusions: Our preliminary findings support a hypothetical model in which partial, haploinsufficient loss of function in *GBA* alters lysosomal function and interacts with other LSD gene variants to increase vulnerability to α-Syn mediated neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0899 / #1103

Poster Topic: *Theme C: α-Synucleinopathies / C01.c. Disease Mechanisms, Pathophysiology: Cell to cell transmission, spreading of pathology, prion-like*

NITRATED A-SYNUCLEIN: MARKER AND CULPRIT OF PARKINSON PATHOGENETIC PROCESSES

POSTERS: C01.C. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE

Rita Pinto Costa, Ayse Ulusoy, Ruth Musgrove, Michael Helwig, Angela Rollar, Donato Di Monte
DZNE, Neurodegeneration And Neuroprotection In Parkinson's Disease, Bonn, Germany

Aims: Different a-synuclein (α-syn) species, including different strains and post-translationally modified forms of the protein, are likely to possess distinct properties; through these properties, they may play different roles in pathogenetic processes such as aggregate formation and interneuronal α-syn spreading. The objective of this study was to determine the relationship between α-syn nitration, a common modification of the protein seen in Parkinson's disease (PD) brain, and α-syn assembly and spreading.
Methods: Experiments were carried out in mice. Immunohistological and biochemical techniques were used to assess neuronal integrity and pathological α-syn changes (in particular, protein aggregate formation) in brain tissue sections. A new proximity ligation assay was developed and used for detection and quantification of nitrated α-syn.
Results: revealed that, under conditions of oxidant stress (e.g., neuronal hyperactivity or exposure of mice to the herbicide paraquat), intraneuronal accumulation of nitrated α-syn paralleled the formation of protein aggregates; it was also associated with a significant enhancement of neuron-to-neuron protein transfer and consequent α-syn brain spreading. Strategies aimed at reducing oxidant burden (e.g., by increasing superoxide dismutase expression) decreased the levels of nitrated α-syn and, at the same time, counteracted protein aggregation and spreading.
Conclusions: Together, these findings indicate that detection of nitrated α-syn in human brain or PD experimental models characterizes neurons that, due to oxidant stress, become not only highly vulnerable to inclusion formation but also more active sites of α-syn transfer. *In vitro* experimental evidence suggests that nitrative modifications can generate α-syn species with a greater propensity to pass from cell to cell. It is conceivable therefore that, under pro-oxidant conditions in PD and/or PD models, nitration of pathogenic α-syn species could itself promote their interneuronal brain spreading.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0900 / #1646

Poster Topic: *Theme C: α-Synucleinopathies / C01.d. Disease Mechanisms, Pathophysiology: Autophagy, lysosomes, ubiquitin, proteasome*

CHARACTERIZATION OF THE AUTOPHAGIC-LYSOSOMAL PATHWAY IN PARKINSON'S DISEASE USING PATIENT IPSC-DERIVED DOPAMINERGIC NEURONS CONTAINING LRRK2 OR GBA MUTATIONS

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

Scott Schachtele[1], Sandra Coveney[2], Kayley Lefrancois[2], Virginia Bain[2], Maia Zoller[2], Supriya Singh[2], Ali Fathi[3], Richard Cho[2], Coby Carlson[4]
[1]FUJIFILM Cellular Dynamics, Product Management, Madison, United States of America, [2]Cell Signaling Technology, Neuroscience, Danvers, United States of America, [3]FUJIFILM Cellular Dynamics, Discovery Research, Madison, United States of America, [4]FUJIFILM Cellular Dynamics, Applications, Madison, United States of America

Aims: Mechanisms of dopaminergic neuron cell death in Parkinson's Disease (PD) is complex and combinatorial, with impairments in multiple cellular pathways impacting mitochondrial function and endosomal/lysosomal protein degradation. Mutations in leucine-rich repeat kinase 2 (LRRK2) and glucocerebrosidase (GBA), have been shown to both impact kinetics of the autophagic-lysosomal pathway (ALP) and contribute to PD-associated protein accumulation and aggregation. This study uses induced pluripotent stem cells (iPSCs)-derived dopaminergic neurons (iCell DopaNeurons) generated from apparently healthy normal donors (AHN) and clinically diagnosed PD patients harboring *LRRK2* G2019S or *GBA1* N370S mutations (derived from iPSCs provided by Parkinson's Progression Markers Initiative (PPMI), part of The Michael J. Fox Foundation (MJFF)) to investigate their utility in evaluating ALP changes associated with PD.
Methods: Endosome and lysosome protein expression was quantified in iPSC-derived dopaminergic neurons at 7, 14, and 21 days using high throughput imaging of specific antibodies from Cell Signaling Technology (CST). Exogenous modulators of autophagy (Torin 1) and mitochondrial stress (Rotenone) were applied to the LRRK2, GBA and AHN dopaminergic neurons to evaluate the effect of pathway stressors on ALP protein expression. Within all conditions, neural survival and synapse formation were also quantified.
Results: We show both AHN and patient-derived iCell DopaNeurons express dopaminergic (ie., TH, FOXA1), synaptic (ie., PSD95, Synapsin-1, GAP43, VAMP2), and ALP (ie., LAMP-1, LC3, Cathepsin, Galectin 3) specific markers via immunocytochemistry. These lines were applied to high content imaging to develop methods to evaluate pathophysiological phenotype differences in synapse development, ALP kinetics, and responses to mitochondrial and autophagy stressors between control and patient-derived PD dopaminergic neurons.
Conclusions: These data demonstrate the utility of high-throughput immunocytochemistry and patient-derived iPSC dopaminergic neurons for investigating lysosomal, mitochondrial, and neurodegenerative pathway dynamics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0901 / #2741

Poster Topic: *Theme C: α-Synucleinopathies / C01.d. Disease Mechanisms, Pathophysiology: Autophagy, lysosomes, ubiquitin, proteasome*

AUTOPHAGY AND CALCIUM DEFICITS CONTRIBUTE TO SELECTIVE VULNERABILITY TO ALPHA-SYNUCLEIN AGGREGATES IN IPSC-DERIVED CORTICAL AND DOPAMINERGIC NEURONS FROM ALZHEIMER'S AND PARKINSON'S PATIENTS

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

Ajantha Abey[1], Bryan Ng[2], Rachel Heon-Roberts[1], Becky Carlyle[1], Nora Bengoa-Vergniory[3], Richard Wade-Martins[4]
[1]University of Oxford, Department Of Physiology, Anatomy, And Genetics, Oxford, United Kingdom, [2]Agency for Science, Technology, and Research, Singapore Institute For Clinical Sciences, Singapore, Singapore, [3]UPV/EHU, Achucarro Basque Center For Neuroscience, Leioa, Spain, [4]University of Oxford, Department Of Physiology, Anatomy & Genetics, Oxford Parkinson's Disease Centre, Oxford, United Kingdom

Aims: Alzheimer's (AD) and Parkinson's disease (PD) feature progressive neurodegeneration in a remarkably regionally selective manner. *Post mortem* studies have posited a role for cell autonomous mechanisms driving this, so we aimed to examine a live human induced pluripotent stem cell (iPSC) model to see whether it can replicate the phenomenon of selective neuronal vulnerability, so to better determine disease mechanisms and therapeutic targets.
Methods: iPSC-derived neurons offer a rare opportunity to examine cell autonomous vulnerability in live human cells. iPSCs from patients with AD-related presenilin-1 mutations (n=6), PD-related leucine rich repeat kinase 2 mutations (n=6), and isogenic corrected (n=4) and healthy controls (n=4) have been differentiated into both cortical and midbrain dopaminergic neurons to enable comparison of pre-formed fibril induced pathology in different neuronal subtypes from the same patient. We then examined lysosomal number, morphology, degradation, pH, and calcium using live imaging assays, alongside mitochondrial biology, and electrophysiology to understand underlying drivers of vulnerability in the cell types.
Results: Upon insult with alpha-synuclein PFFs, AD and PD dopaminergic neurons produce substantial Lewy-like pathology, whereas cortical neurons remain relatively resilient to alpha-synuclein aggregation, suggesting cell-type vulnerability. PSEN1-Intron-4-Deletion cortical neurons, however, had significantly elevated pathology. These lines displayed hyperactivity on microelectrode arrays and abnormal lysosomal biology, including increased LAMP1 and dysregulated calcium. PFF-insulted AD cortical neurons also have impaired neurite outgrowth, while PD cortical neurons are resilient.
Conclusions: These preliminary results show relative vulnerability of AD against PD cortical neurons, and dopaminergic against cortical neurons to alpha-synuclein aggregates for the first time. These suggest the selective vulnerability to proteinopathy in these diseases is reflected by the iPSC neuronal model and support the notion that cell intrinsic factors like autophagy drive vulnerability.

P0902 / #884

Poster Topic: *Theme C: α-Synucleinopathies / C01.d. Disease Mechanisms, Pathophysiology: Autophagy, lysosomes, ubiquitin, proteasome*

NOX1 TRIGGERS FERROPTOSIS AND FERRITINOPHAGY, CONTRIBUTES TO NEURODEGENERATION

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

Huiqing Wang, Wenwei Mao, Yuhan Zhang, Baohua Cheng, Fuling Yan
Southeast University, Medical College, Nanjing, China

Aims: Parkinson's disease (PD) is a neurodegenerative disorder. Ferroptosis-specific genes related to PD remain uncertain. Exploring the effects of NADPH oxidase enzyme-1 (NOX1) with the ferroptosis pathway.
Methods: We have developed an *in vitro* and *in vivo* model of PD to investigate the potential underlying mechanism of NOX1. We have manipulated the expression of NOX1 through overexpression or knockdown techniques to assess its impact on dopaminergic neurons, as well as ferroptosis and ferritinophagy. Additionally, we have utilized transcriptome sequencing to identify the involvement of the RUNX2/STK32A pathway. Furthermore, we have employed online site prediction and CO-IP experiments to identify the upstream ubiquitinating molecules associated with NOX1.
Results: Three potential ferroptosis-related genes (INOS, BECN1, NOX1) were identified, displaying favorable diagnostic properties. The present study reveals that NOX1-associated ferroptosis genes are significantly upregulated in both in vitro and in vivo models of Parkinson's disease (PD). This upregulation is influenced by the ubiquitination process of the upstream transcription factor FBXW7, which is notably reduced in PD, consequently leading to heightened NOX1 expression. Besides, the activation of the RUNX2/STK32A pathway by NOX1 facilitates ferritinophagy, thereby intensifying mitochondrial dysfunction and promoting ferroptosis, ultimately resulting in additional impairment of dopaminergic neurons.
Conclusions: In summary, our research reveals the significant role played by the upregulation of neuronal NOX1 and the activation of ferroptosis in neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0903 / #2914

Poster Topic: *Theme C: α-Synucleinopathies / C01.d. Disease Mechanisms, Pathophysiology: Autophagy, lysosomes, ubiquitin, proteasome*

MECHANISMS OF INTERACTION OF ALPHA-SYNUCLEIN AND AMYLOID-BETA CO-PATHOLOGY

POSTERS: C01.D. DISEASE MECHANISMS, PATHOPHYSIOLOGY: AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME

Samuel Wycoff, Jessica Restivo, John Cirrito
Washington University in St Louis, Neuroscience, St Louis, United States of America

Aims: There remains a large gap in knowledge about the pathological overlap of Alzheimer Disease (AD) and Parkinson's Disease (PD). Approximately half of all AD patients exhibit formation of Lewy Bodies containing α-syn, and in the roughly 30% of PD patients with dementia (PDD), amyloid plaque burden is strongly correlated to severity of dementia. The two principal proteins involved in these diseases, α-syn and Aβ, promote each other's aggregation and have synergistic toxicity in cells, while not affecting each other's protein expression. Therefore we hypothesized that common clearance mechanisms of both proteins are involved in the increased toxicity. Additionally, membrane interaction has been suggested to be key to Aβ/α-syn interaction, and key to the co-promotion of aggregation. α-syn is a naturally disordered protein, but can interact with membranes, leading to a higher rate of aggregation and interaction with Aβ. We propose that disengaging α-syn from the membrane reduces aggregation of both Aβ and α-syn and mitigates cellular toxicity.
Methods: To understand the relationship of co-pathology of Aβ and α-syn on cellular autophagy, we employed SH-SY5Y cell culture, exogenously added Aβ oligomers and α-syn fibrils, and measured autophagy with IHC and western blot. Additionally we measured levels of these proteins in a co-pathology AD/PD mouse model using reverse-microdialysis and ELISA.
Results: We show that α-syn and Aβ both inhibit ALP, with co-pathology having a multiplicative effect in vivo and in vitro. We also propose that disengaging α-syn from the membrane reduces aggregation of both Aβ and α-syn and mitigates cellular toxicity.
Conclusions: We therefore conclude that dysregulation of autophagy is an important factor in the enhanced toxicity seen in co-pathology of AD and PD. We propose that membrane interaction of asyn is another important pathway.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0904 / #1349

Poster Topic: *Theme C: α-Synucleinopathies / C01.e. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

RNA-SEQ ANALYSIS REVEALS TRANSCRIPTOME CHANGES IN DOPAMINERGIC NEURONS IN THE EARLY STAGES OF PARKINSON DISEASE MOUSE MODELS

POSTERS: C01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Kousuke Baba[1], Kit-Yeng Sheng[1], Hideki Hayakawa[1], Yasuyoshi Kimura[1], Kensuke Ikenaka[1], Cesar Aguirre[1], Goichi Beck[1], Maiko Sasano[1], Shinpei Yamaguchi[2], Hideki Mochizuki[1]
[1]Osaka University Graduate School of Medicine, Department Of Neurology, Osaka, Japan, [2]Toho University, Stem Cell Reprogramming Laboratory, Faculty Of Science Department Of Biology, -- Miyama, Funabashi-shi, Chiba, Japan

Aims: α-synuclein plays a central role in the pathogenesis of Parkinson disease. Misfolded α-synuclein accumulates in neurons and forms Lewy pathology, leading to dopaminergic neurodegeneration. These Lewy pathology and dopaminergic neurodegeneration are major pathological features of Parkinson's disease. Despite extensive efforts, the pathological molecular changes caused by misfolded α-synulein in neurons remain to be elucidated. We aimed to understand the molecular mechanism in the early phase of Parkinson disease.
Methods: To selectively obtain PFF-injected dopaminergic neurons, we adapted the α-synuclein preformed fibrils (PFF) model to a Ddc-hKO1 reporter mouse to selectively acquire α-synuclein PFF-injected dopaminergic neurons. We harvested dopamine neurons from α-synuclein PFF-injected mice in the early phase and analyzed them with RNA-sequencing.
Results: We found that lipid-related process genes, followed by protein modification and degradation-related process genes, were up-regulated in the dopaminergic neurons from α-synuclein PFF-injected mouse brain. The activation of fatty acid-binding protein 1 was particularly evident. FABP1 accumulation in dopaminergic neuron was confirmed by immunohistochemistry of Pakinson disease patients.
Conclusions: We revealed the molecular events during the early phase of α-synuclein accumulation using α-synuclein PFF-injected mouse model. Up-regulation of FABP1 in both α-synuclein PFF injection model and Parkinson disease patients' brain suggests that FABP1 plays a role in the pathogenesis of Parkinson disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0905 / #569

Poster Topic: *Theme C: α-Synucleinopathies / C01.e. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

INTRACELLULAR A-SYNUCLEIN INTERFERENCE WITH MYELINATION, ACTIN REMODELING, AND LIPID METABOLISM IN HUMAN INDUCED OLIGODENDROCYTES

POSTERS: C01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Kristina Battis[1], Jeanette Wihan[1], Denise Balta[1], Tanja Kuhlmann[2], Jürgen Winkler[1]
[1]University Hospital Erlangen, Molecular Neurology, Erlangen, Germany, [2]University Hospital Münster, Neuropathology, Münster, Germany

Aims: Functions of oligodendrocytes are severely affected in multiple system atrophy (MSA), a rare and devastating movement disorder with fast progression. MSA is classified as synucleinopathy due to the accumulation of α-synuclein (α-syn) within oligodendroglial cytoplasmic inclusions as one of the major neuropathological hallmarks of the disease. The accumulation of α-syn results in a severe myelin deficit, however, without concurrent loss of oligodendrocytes in human and murine brains. Therefore, we hypothesized that intracellular accumulation of α-syn interferes with myelination of oligodendrocytes.
Methods: A human model for MSA was established to address the underlying cellular and molecular pathogenesis. After oligodendrocyte differentiation from human induced pluripotent stem cells (hiPSCs), their cellular identity was confirmed by a thorough phenotypical characterization. Functionally, the myelinating potential of control human oligodendrocytes was demonstrated by ensheathment of nanofibers and neurites of hiPSCs-derived neurons.
Results: In a co-culture model of human, lentivirally infected α-syn-oligodendrocytes with inert nanofibers, intraoligodendroglial α-syn accumulation led to a severe reduction of myelinogenesis. These morphological changes were accompanied by an increased actin filament assembly and a dysregulation of actin binding. Additionally, several genes associate to lipid metabolism were altered, including *ABCA8*, *CAV1*, and *ANO4*. Thus, metabolomics analysis of α-syn-oligodendrocytes was exhibited and revealed disturbances predominantly in the groups of amino acids and lipids. Among the lipids the class of phospholipids as main component of myelin was mainly affected.
Conclusions: Taken together, the present findings suggest a link between α-syn overexpression, actin remodeling and lipid metabolism of oligodendrocytes associated with a profound impact on myelination. By modelling α-syn induced myelin deficits, the present human disease model represents an important tool to further delineate the mechanistic cascade underlying oligodendroglial dysfunction and may pave the way for developing promising interventional approaches.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0906 / #1145

Poster Topic: *Theme C: α-Synucleinopathies / C01.e. Disease Mechanisms, Pathophysiology: Lipids, lipoproteins and membrane trafficking*

TARGETING IRON METABOLISM AND IRON-MEDIATED LIPID PEROXIDATION IN NEURODEGENERATIVE DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

POSTERS: C01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: LIPIDS, LIPOPROTEINS AND MEMBRANE TRAFFICKING

Holly Spence, Fergal Waldron, Jenna Gregory
Institute of Medical Sciences, University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom

Aims: Patterns of regional iron increases are observed across neurodegenerative diseases including Parkinson's disease (PD) and Alzheimer's disease (AD). These increases in iron have been linked with higher disease severity and faster rate of progression. Exceedingly high iron-mediated lipid peroxidation can lead to ferroptosis and oxidative damage which are thought to underly these iron-neurodegeneration relationships.
Methods: Here we present a systematic review and meta-analysis comparing studies which assess the use of drugs targeting the iron-mediated lipid peroxidation pathway in the treatment of neurodegenerative disease. This systematic review and meta-analysis also evaluates the evidence for changes in iron-mediated lipid peroxidation pathway and downstream effects in human studies of those with neurodegenerative disease.
Results: Several drugs targeting this pathway including iron chelation drugs are entering phase 2 and 3 clinical trials for AD and PD.
Conclusions: Treatments targeting this pathway therefore show promise for use across several neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0907 / #2905

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

THE IDENTIFICATION OF DRUGGABLE NEUROINFLAMMATORY PATHWAYS INVOLVED IN LEWY BODY DEMENTIA

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Jermaine Ross, Yoonjeong Cha, Mohamedi Kagalwala
Alleo Labs, Neuroscience, San Francisco, United States of America

Aims: Inflammation plays a significant role in the development and progression of many neurodegenerative diseases, including several subtypes of dementia such as Alzheimer's disease (AD) and Lewy body dementia (LBD). The focus of this study is the discovery and characterization of neuroinflammatory pathways related to LBD and potential mechanisms for disease-modifying therapies.
Methods: We compared bulk RNA sequencing data sampled from the postmortem dorsolateral prefrontal cortex (DLPFC) of LBD and cognitively normal (CN) controls subjects that participated in the Religious Orders Study and Rush Memory and Aging Project. LBD (n=64) and control (n=169) subjects were stratified using neuropathology as well as neuropsychological assessments. We subsequently employed a standard RNA-seq analysis workflow to identify differential expressed genes using limma R package, followed by Gene Set Enrichment Analysis (GSEA).
Results: We identified 846 differentially expressed genes (DEGs) in the DLPFC of LBD subjects compared to CN controls (adjusted p-value < 0.05), made up of 419 up-regulated and 417 down-regulated genes. Among the top statistically significant DEGs, we observed up-regulation of astrocytic markers Interleukin-17 receptor B (IL17RB) and Calcium-Activated Neutral Proteinase 2 (CAPN2). Recent meta-analysis studies found that both IL17RB and CAPN2 were also up-regulated in the substantia nigra of Parkinson's patients. Consistent with these findings, GSEA pathway analysis revealed positive enrichment of multiple inflammatory-related pathways including but not limited to cytokine-cytokine receptor interaction, toll-like receptor signaling, JAK/STAT signaling cascade, NF-kB signaling, and IL-1R signaling (adjusted p-value < 0.05).
Conclusions: In this study, we found a significant relationship between neuroinflammation and LBD, including IL17RB and related inflammatory signaling cascades. Given current development of clinical candidates for IL-17 inhibitors, these results may highlight potentially druggable therapeutic mechanisms implicated in LBD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0908 / #2311

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

STUDY ON THE MECHANISM OF WUZI YANZONG PILL IN THE TREATMENT OF PD BASED ON THE INFLAMMATORY RESPONSE OF MICROGLIA MEDIATED BY AGES-RAGE PATH

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Qi Xiao[1], Hui Jie Fan[1], Li Shan Fan[1], Si Xiang Niu[1], Lei Xu[1], Bao Guo Xiao[2], Cun Gen Ma[3], Zhi Chai[3]
[1]Shanxi University of Traditional Chinese Medicine, Shanxi University Of Traditional Chinese Medicine Multiple Sclerosis Key Research Laboratory, jin, China, [2]Fudan University, Huashan Hospital, shanghai, China, [3]Shanxi University of Chinese Medicine, Shanxi University Of Traditional Chinese Medicine Multiple Sclerosis Key Research Laboratory, Jinzhong City, Shanxi Province, China

Aims: Parkinson's disease (PD) is a degenerative disease of the nervous system. Our previous study found that Wuzi Yanzong Pill (WYP) has a good therapeutic effect on PD mouse model, and is related to the regulation of inflammatory factors. The activation of NF-κB by MAPK signaling pathway promotes the formation of inflammatory factors in RAGE signaling. Combined with the results of network pharmacology and molecular docking technology, based on the PD mouse model induced by MPTP activation levels of key molecules in AGEs-RAGE signaling pathway, and to provide a new idea and experimental basis for the treatment of PD with WYP.
Methods: Male C57BL/6 mice were divided into Normal group, MPTP group, WYP Low+MPTP group, WYP Medium+MPTP group, WYP High+MPTP group, TTP488+MPTP group, The best dose WYP group. MPTP group, WYP Low+MPTP group, WYP Medium+MPTP group, WYP High+MPTP group, TTP488+MPTP group to prepare PD model. The injection dosage was D1:15mg/kg. D2:20 mg/kg; D3: d7:30 mg/kg. Meanwhile, Normal group, MPTP group and TTP488+MPTP group were given normal saline (50mL/kg/d) by gavage. WYP solution (4g/kg/d, 8g/kg/d, 16g/kg/d) was administered by gavage in low, medium and high dose groups.Immunofluorescence staining, Western blot, ELISA and other methods were used to study the molecular mechanism of WYP treatment in PD mice.
Results: Compared with the MPTP group, the secretion of AGEs, RAGE, PP38, P-NF-κB, TNF-α, IL-1β, IL-6 and increased IL-10 protein levels in the MPTP+WYP group were reduced by WYP treatment.
Conclusions: WYP may improve the expression of inflammatory factors by inhibiting AGEs-RAGE signaling pathway.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0909 / #689

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

S100A9 PROTEIN: A NEW PLAYER IN INFLAMMATION-MEDIATED NEURONAL LOSS

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Katryna Pampuscenko[1], Ramune Morkuniene[1], Vytautas Smirnovas[2], Vilmante Borutaite[1]
[1]Lithuanian University of Health Sciences, Neuroscience Institute, Kaunas, Lithuania, [2]Vilnius University, Life Sciences Center, Institute Of Biotechnology, Vilnius, Lithuania

Aims: Parkinson's disease (PD) is a neurodegenerative disease pathobiologically characterized by the progressive loss of dopaminergic neurons in *substantia nigra* and intraneuronal alpha-synuclein aggregates, so-called Lewy bodies[1]. Recently it was found that another pro-inflammatory and highly amyloidogenic protein S100A9 also participates in PD pathogenesis potentially through stimulation of alpha-synuclein aggregation[2]. However, it remains unknown whether S100A9 is toxic to neurons by itself.
Methods: In this study, neuronal-glial co-cultures from rat cerebellum were incubated with pre-aggregated recombinant S100A9 protein for 48-72h and then cell viability, number and microglial phagocytic activity were evaluated by fluorescence microscopy.
Results: Our results show that pre-aggregated recombinant S100A9 cause loss of viable neurons in rat neuronal-glial co-cultures without any sign of apoptosis and necrosis. Neuronal loss in S100A9-treated cultures was accompanied by microglial proliferation, altered morphology, as well as increased phagocytic activity. Depletion of microglial cells attenuated S100A9-induced neuronal loss suggesting that S100A9 acts through microglial activation. Treatment of neuronal-glial co-cultures with S100A9 also was found to induce exposure of phosphatidylserine on the outer leaflet of the neuronal plasma membrane acting as “eat-me” signal for microglial cells.
Conclusions: These data suggest that pre-aggregated S100A9 can be neurotoxic by itself and can induce loss of viable neurons through phagocytic uptake which is also known as death by primary phagocytosis or phagoptosis[3]. References: [1] Bloem et al. Parkinson's disease. Lancet. 2021; 397(10291):2284-2303. [2] Horvath et al. Co-aggregation of pro-inflammatory S100A9 with α-synuclein in Parkinson’s disease: ex vivo and in vitro studies. J Neuroinflammation. 2018; 15(1):172. [3] Brown GC. Cell death by phagocytosis. Nat Rev Immunol. 2023. Online ahead of print. Acknowledgements: This study has received funding from the Research Council of Lithuania (LMTLT), agreement No S-MIP-23-98.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0910 / #2671

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

CEREBROSPINAL FLUID BIOMARKERS OF NLRP3 PATHWAY ACTIVATION, NEUROINFLAMMATION AND NEURODEGENERATION IN PARKINSON'S DISEASE: A META-ANALYSIS

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Venissa Machado[1], Gennaro Pagano[2], Alina-Măriuca Marinescu[1], Thomas Kustermann[1], Kathrin Brockmann[3,4], Judith Anzures-Cabrera[5], Bastian Zinnhardt[1]
[1]F. Hoffmann-La Roche, Biomarkers And Translational Technologies, Basel, Switzerland, [2]F. Hoffmann La Roche, Early Development, Pharma Research And Early Development, Basel, Switzerland, [3]Hertie Institute for Clinical Brain Research, Department Of Neurodegenerative Diseases, Tübingen, Germany, [4]University of Tübingen, German Center For Neurodegenerative Diseases (dzne), Tübingen, Germany, [5]F. Hoffmann-La Roche Ltd., Roche Products Ltd., Welwyn, United Kingdom

Aims: Activation of the immune sensor NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and associated immune dysfunction has been suggested as a key pathogenic mechanism in Parkinson's disease (PD), preceding and accompanying neuronal damage and cell death in PD. Inflammatory mediators released into the cerebrospinal fluid (CSF) may potentially serve as biomarkers of NLRP3 pathway activation and immune dysfunction. Currently, only a few studies have investigated the levels of NLRP3 and related neuroinflammation markers in the CSF of people living with Parkinson's (PwP) compared to controls. Multiple clinical trials aiming to modulate the neuroinflammatory response in PwP are currently underway exemplifying the need for a better understanding of the levels and relevance of these biomarkers in the diagnosis and monitoring of disease progression in PD.
Methods: We performed a meta-analysis on sixteen biomarkers related to specific components of the neuroinflammatory response, including those of the NLRP3 pathway in the CSF of PwP and controls.
Results: Random-effects meta-analyses show that the levels of selected cytokines downstream of the NLRP3 pathway (e.g. IL-1ß) as well as markers for glial cells (e.g. sTREM-2, S100) and neuroaxonal damage (NfL) are elevated in the CSF of PwP compared to controls.
Conclusions: These results support the relevance of the NLRP3 pathway and immune dysfunction in PwP, and provide increased confidence in modulating neuroinflammation as a promising therapeutic avenue in the treatment of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0911 / #259

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

THE INTERACTION OF PARKINSON'S DISEASE, STRESS AND INFLAMMATION

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Daniel Rombach[1], Verena Bopp[2], Dominik Langgartner[3], Albert Ludolph[2], Stefan Reber[3], Karin Danzer[1]
[1]Deutsches Zentrum für Neurodegenerative Erkrankungen e. V. (DZNE), Mechanisms Of Propagation, Ulm, Germany, [2]University Hospital Ulm, Neurology, Ulm, Germany, [3]University of Ulm, Psychosomatic Medicine And Psychotherapy, Ulm, Germany

Aims: Previous investigations have provided numerous indications of a disrupted hypothalamic-pituitary-adrenal axis in the context of neurodegenerative diseases. For that reason, this study aims to investigate a potential dysregulation of the hypothalamic-pituitary-adrenal axis and its downstream effects in Parkinson's disease (PD). Therefore, we investigate glucocorticoid sensitivity of splenocytes in a wild-type human α-synuclein overexpressing mouse model for Parkinson's disease (V1S/SV2).
Methods: To assess chronic stress in V1S/SV2 transgenic murine splenocytes, a glucocorticoid sensitivity assay was employed. In addition, a panel of ten inflammatory cytokines as well as corticosterone levels in V1S/SV2 plasma samples were measured by ELISA. To gain insight into potential mediating effects flow cytometry, Western and qPCR analyses were used.
Results: At 16 months of age, V1S/SV2 splenocytes showed a weaker response to corticosterone, indicating a glucocorticoid resistance in our V1S/SV2 mouse model. In contrast, at the age of 20 months glucocorticoid resistance in V1S/SV2 mice was not visible anymore. For physiological stress parameters like spleen and adrenal gland weight no alteration could be observed at 16 and 20 months. Furthermore, a significant increase of TNF-α and IFN-γ in plasma of 20 months old V1S/SV2 mice suggesting a preceding inflammatory status of PD mice. Measurement of plasma corticosterone levels detected an increase in V1S/SV2 mice with proceeding age, potentially correlating with the preceding PD phenotype.
Conclusions: Our preliminary findings suggest the presence of glucocorticoid resistance in our PD V1S/SV2 mouse model at 16 months of age. This observation hints at a potential dysregulation within the hypothalamic-pituitary-adrenal axis. The potential mediating effects underlying glucocorticoid resistance and a dysregulated hypothalamic-pituitary-adrenal axis remain unexplored, providing several approaches for further research.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0912 / #292

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

THE INTERPLAY OF INFLAMMATORY CYTOKINES AND ALPHA-SYNUCLEIN IN NEURONAL CYTOSKELETON PATHOLOGY

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Veronika Sigutova[1], Elizaveta Gerasimova[1], Wei Xiang[2], Jürgen Winkler[2], Beate Winner[1], Iryna Prots[3]
[1]University Hospital Erlangen, Stem Cell Biology, Erlangen, Germany, [2]University Hospital Erlangen, Molecular Neurology, Erlangen, Germany, [3]University Hospital Erlangen, Dental Clinic 1 - Restorative Dentistry And Periodontology, Erlangen, Germany

Aims: In Parkinson's disease (PD), neuroinflammation impairs neuronal structure and function, yet the specific mechanisms remain elusive. Emerging evidence implicates pro-inflammatory cytokines as crucial mediators of neuronal degeneration. While initial data indicate that the cytokine TNF-α can interfere with neuronal microtubules and axonal transport, critical questions persist regarding the role of other cytokines in cytoskeleton pathology, their combined effects, and their contribution to PD pathology. We therefore investigated the direct impact of pro-inflammatory cytokines on the neuronal cytoskeleton and hypothesized that an increased α-synuclein dosage in PD exacerbates cytokine-induced cytoskeletal deficits.
Methods: iPSC-derived cortical neurons from healthy controls and patients with α-synuclein gene locus duplication (SNCA dupl) were treated with PD pathology-related cytokines IL-17A, TNF-α, IFN-γ, or a combination thereof. Cytokine receptor expression, axonal transport, and microtubule components and their post-translational modifications were assessed on transcriptional and protein levels.
Results: SNCA dupl neurons exhibited an increased IL-17 receptor expression and consequently displayed impaired cytokine receptor homeostasis in response to IL-17A. Mitochondrial axonal transport was differentially affected by IL-17A, TNF-α and cytokine mix depending on α-synuclein dosage, with IL-17A slowing and cytokine mix reducing mitochondrial movement specifically in PD neurons. Furthermore, cytokines exacerbated the basally elevated tubulin acetylation in SNCA dupl neurons, while displaying neurite segment-specific effects in healthy cells. Additional SNCA dupl cytoskeletal pathologies, including tubulin polyglutamylation and tau beading, were further intensified by cytokine combination.
Conclusions: Our work elucidates the detrimental effects of pro-inflammatory cytokines, particularly IL-17A, on human neuronal cytoarchitecture. We also highlight their interactions with α-synuclein pathology, suggesting that inflammation represents a second hit to the vulnerable cytoskeleton in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0913 / #1639

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

GENERATION OF HUMAN IPS-DERIVED MIDBRAIN ORGANOIDS TO STUDY NEUROINFLAMMATION BY EXTRACELLULAR VESICLE IN PARKINSON'S DISEASE.

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Ankush Yadav[1,2], Elena Vacchi[1,2], Sandra Pinton[2], Alain Kaelin Lang[1,2,3,4], Giorgia Melli[1,2,3]
[1]Università della Svizzera Italiana, Faculty Of Biomedical Sciences, Lugano, Switzerland, [2]Laboratories for Translation Research, EOC, Neurocenter Of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland, [3]Neurocenter of Southern Switzerland, Ente Ospedaliero cantonale, Neurology Department, Lugano, Switzerland, [4]Inselspital,Bern University Hospital, University of Bern, Department, Bern, Switzerland

Aims: Animal models cannot recapitulate many human neurodegenerative disease features. The ability to produce functional neuronal cells from hiPSCs and neuronal cell lines allows to study neurological disorders. But despite this progress, most protocols used hiPSCs to differentiate into neurons based on 2D methods which cannot recapitulate the function and complexity of in-vivo neuronal circuits. These limitations have led to the development of organoid models that mimic the functional characteristics of human brain tissues using hiPSCs.
Methods: We explored organoid technology to generate midbrain organoids. For this purpose, we developed a system of midbrain organoids from hiPSCs. Characterization of organoids will be done using immunohistochemistry and whole-mount immunostaining. EVs were isolated from the plasma of the PD subject and sex and aged-matched HC using size exclusion chromatography and quantified using nanoparticle tracking analysis. The functional effects of plasma-derived EVs on midbrain organoids were investigated using flow cytometry and immunohistochemistry.
Results: Whole-mount immunostaining of organoids showed that neurons are successfully differentiated at day 30 and labeled with beta-tubulin III, indicating the mature neuronal cell identity. Midbrain organoids were positively labeled with TH antibody after day 30, and astrocytes expressing GFAP after six weeks of maturation. Preliminary data on plasmatic PD-derived EVs showed increased neurotoxicity in neurons and activation of inflammatory pathways in glia cells.
Conclusions: We successfully generated midbrain organoids from hiPSCs with distinct layers of neuronal cells with functionally mature midbrain dopaminergic neurons and produced neuromelanin-like granules. Plasma-derived EVs from PD patients may exert toxic effects on neurons in midbrain organoids and influence the initiation and progression of the disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0914 / #1995

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

INVESTIGATING A-SYNUCLEIN AND INFLAMMATORY RESPONSES IN THE OLFACTORY CIRCUITRY OF MICE NASALLY INOCULATED BY A NEURONOTROPIC VIRUS

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Karim Zahr Eddin, Michaela Lunn, Nathalie Lengacher, Julianna Tomlinson, Earl Brown, Michael Schlossmacher
University of Ottawa, Cellular And Molecular Medicine, Ottawa, Canada

Aims: The importance of the olfactory system in the pathogenesis of Parkinson disease is supported by the presence of prodromal hyposmia and Lewy pathology in the olfactory bulb. We previously published that α-synuclein is expressed in dendrites, cytoplasm and axons of olfactory neurons, and that it protects mice from microbial infections. We hypothesized that viral infections of the nasal cavity could induce changes in α-synuclein metabolism and incite post-translational modifications concurrent with inflammatory responses by the host within anterior olfactory structures.
Methods: We inoculated adult C57BL wildtype mice with GFP-expressing vesicular stomatitis virus (VSV-GFP). Sagittal skull sections were analyzed microscopically at various timepoints to look at the temporal distribution of VSV-GFP and quantify the immunoreactivity of glial cells regarding phenotypical parameters. The viral burden in distinct anatomical regions was measured by peak titers, as was the presence of viral proteins. Changes in α-synuclein were monitored by monoclonal antibodies and Western blotting to assess for any changes due to the infection.
Results: Inoculation with VSV-GFP generated a progressive encephalitis, accompanied by robust microglial and astrocytic responses that peaked at 4 and 6 days post-infection (dpi), respectively. α-Synuclein was found to co-localize with VSV-GFP at points of viral entry in anterior olfactory structures. α-Synuclein formed aggregates in olfactory sensory neurons and more pSer129-α-synuclein reactivity was detected in glomeruli and mitral cells, as well as of p62 reactivity. Endogenous α-synuclein levels were also increased in infected brains when compared to mock-treated animals.
Conclusions: Infection of murine brain by a neuronotropic RNA virus can lead to changes in α-synuclein metabolism that could be of relevance to human synucleinopathies, including Parkinson disease. Future studies will explore whether such neuropathological changes are transient, chronic or progressive.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0915 / #2877

Poster Topic: *Theme C: α-Synucleinopathies / C01.f. Disease Mechanisms, Pathophysiology: Inflammation*

IMMUPARKNET: THE ROLE OF IMMUNITY IN TACKLING PARKINSON'S DISEASE THROUGH A TRANSLATIONAL NETWORK

POSTERS: C01.F. DISEASE MECHANISMS, PATHOPHYSIOLOGY: INFLAMMATION

Inês Figueira[1], Marina Romero-Ramos[2], Franca Marino[3], Laura Múñoz-Delgado[4], Neda Nikolovski[5], Yasemin Ozdemir[6], Cristoforo Comi[7]
[1]NOVA Medical School, Molecular Nutrition And Health Lab, Lisboa, Portugal, [2]Aarhus University, Department Of Biomedicine, Aarhus C, Denmark, [3]University of Insubria, Center For Research In Medical Pharmacology, School Of Medicine, Varese, Italy, [4]Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/Universidad de Sevilla/CSIC/CIBERNED, Unidad De Trastornos Del Movimiento, Servicio De Neurología Y Neurofisiología Clínica, Sevilla, Spain, [5]National Institute of Republic of Serbia, University of Belgrade, Institute For Biological Research "siniša Stanković", Belgrade, Serbia, [6]Health Sciences Institute, Koç University, Department Of Neurology, School Of Medicine, Hacettepe University, Istanbul, Turkey, [7]Neurology Unit, University Of Piemonte Orientale, Novara, Italy

Aims: Parkinson's disease (PD) affects more than one million people in the EU. It has currently no definitive cure, hence patients rely only on symptomatic treatments, which themselves are burdened by side effects. The need for advancements in both knowledge and available treatments is thus heartfelt by patients, caregivers, and health operators. This unmet need sparked the idea of orchestrating a collaborative effort via a common network – IMMUPARKNET. IMMUPARKNET COST Action focuses on PD challenges and the crosstalk with immune response. Although widely recognised, the role of immunity in the onset and development of PD is still unclear. The main goal of IMMUPARKNET is to fill this knowledge gap, establishing an innovative, multi-interdisciplinary research network, fostering expertise exchange among specialists from different countries and institutions.
Methods: Gathering scientists and clinicians studying immunity in PD and related fields, IMMUPARKNET will establish the first nucleus of a multidisciplinary ecosystem that aims at harmonising efforts and approaches, both in research and clinical practice, for boosting the development of ground-breaking treatments for PD. Through meetings, training schools, webinars, position papers and review manuscripts, IMMUPARKNET will lead fruitful exchanges of know-how among experts in the field.
Results: IMMUPARKNET Action structure relies on 5 working groups. To date, IMMUPARKNET has 119 active members from 26 different European countries. Of all these active members, 51% are young researchers, while 34% come from inclusiveness target countries.
Conclusions: IMMUPARKNET outputs will allow a better sharing and development of research resources, straightening the road to novel treatments, or pointing to drug-repurposing of existing ones, and, ultimately and hopefully, a cure for PD. **Acknowledgments:** Based upon work from COST Action CA21117 IMMUPARKNET, supported by COST (European Cooperation in Science and Technology). www.cost.eu; https://immuparknet.eu/

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0916 / #218

Poster Topic: *Theme C: α-Synucleinopathies / C01.g. Disease Mechanisms, Pathophysiology: Microglia*

TYPE-I INTERFERONS IN THE AGING BRAIN POTENTIATE THE ALPHA-SYNUCLEIN-INDUCED NEUROINFLAMMATORY RESPONSE IN A MOUSE MODEL OF PARKINSON'S DISEASE

POSTERS: C01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Shuyan Chen, Harrison Waters, Peter Crack, Juliet Taylor
The University of Melbourne, Biochemistry And Pharmacology, Melbourne, Australia

Aims: To determine the contribution of type-I interferons to the microglial response in the alpha-synuclein pre-formed fibril (alpha-syn PFF) model of Parkinson's disease.
Methods: Alpha-synuclein PFFs (8µg) or PBS were stereotaxically injected into the right dorsal striatum of wildtype (C57BL/6) or interferon-alpha receptor-1 knockout (IFNAR1$^{-/-}$) mice at 8-12 weeks (young) or 46-50 weeks of age (aged) (n=5-8). The neuroinflammatory response in the brain was determined by qPCR, western blot analysis and immunohistochemistry at 3- and 6-months, post injection (p.i). Changes in gait were assessed by DigiGait analysis.
Results: Alpha-synuclein PFF's induced a pro-inflammatory response in aged wildtype mice at 3 months (midbrain and striatum) and 6 months (striatum) p.i. Increased expression of key interferon-stimulatory genes IRF7 and STING, and the classical pro-inflammatory cytokines IL-1beta and TNF-alpha were only observed in the aged, and not young alpha-syn PFF-injected wildtype mice. Critically, age-matched alpha-syn PFF-injected IFNAR1$^{-/-}$mice displayed an attenuated neuroinflammatory profile at both timepoints. Microglial morphology analysis revealed distinct differences in branch length and cell radius in alpha-syn PFF-injected wildtype brains, compared to PBS-injected, with no difference seen in IFNAR1$^{-/-}$ mice. Significantly, alpha-syn PFFs induced significant locomotor changes in stride length and stance/swing at 3 months p.i in aged wildtype but not IFNAR1$^{-/-}$ mice.
Conclusions: This study implicates type-I interferons in mediating the age-related neuroinflammatory changes in the alpha-synuclein PFF model and supports a detrimental role for neuroinflammation in driving the progression of Parkinson's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0917 / #513

Poster Topic: *Theme C: α-Synucleinopathies / C01.g. Disease Mechanisms, Pathophysiology: Microglia*

DEVELOPMENT OF A HUMAN MIDBRAIN ORGANOID MODEL CONTAINING MICROGLIA FOR INVESTIGATING THE ROLE OF GLUCOCEREBROSIDASE IN ALPHA-SYNUCLEIN PATHOLOGY

POSTERS: C01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Charlotte Denman[1], Min-Kyoung Shin[2,3], Hoang-Dai Tran[1], Dongju Jeon[2,3,4], Haerim Kim[2,3], Runrun Han[1], Sang Myun Park[2,3,4], Bernd Kuhn[1], Gordon Arbuthnott[1], Junghyun Jo[1,2,3,4]
[1]Okinawa Institute Science and Technology, Lab 1 Level D, Okinawa, Japan, [2]Ajou University School of Medicine, Department Of Pharmacology, Suwon, Korea, Republic of, [3]Ajou University School of Medicine, Center For Convergence Research Of Neurological Disorders, Suwon, Korea, Republic of, [4]Ajou University School of Medicine, Department Of Biomedical Sciences, Suwon, Korea, Republic of

Aims: This study aimed to investigate the influence of alpha-synuclein (a-syn) levels on microglial function with reduced glucocerebrosidase (GCase) activity in the context of Parkinson's disease (PD). To achieve this, we developed a method for creating human midbrain organoids (hMOs) incorporating microglia derived from human embryonic stem cells (hESCs).
Methods: Using CRISPR/Cas9, we inserted EGFP into the *TMEM119* locus of hESCs, a specific microglia marker. Subsequently, we performed another round of gene editing to generate a *TMEM119*-EGFP::*GBA* (encodes GCase) knock-out (KO) cell line. Following these manipulations, we differentiated hESCs into haematopoietic progenitor cells (HPCs) and then into microglia. We verified successful differentiation through the assessment of CD43 and Iba1 expression, markers for HPCs and microglia, respectively. Additionally, we conducted a comprehensive transcriptomic analysis of the differentiated microglia. To assess microglial functionality, we employed a pHrodo conjugation phagocytosis assay and studied their response to a-syn pre-formed fibrils (PFFs). These microglia were co-cultured with hMOs generated from both H9-wildtype and H9-GBA KO cell lines, which was previously established in our lab.
Results: Our study revealed the impact of reduced GCase levels on microglial function. Transcriptomic analysis provided valuable insights into the molecular changes occurring in these microglia, elucidating the mechanisms involved in a-syn pathology. Functional assays demonstrated alterations in microglial phagocytic activity and their response to a-syn PFFs.
Conclusions: This study underscores the intricate balance maintained by microglia within the complex brain environment and the consequences of prolonged activation, particular in the context of PD and aberrant a-syn accumulation. By developing a method to incorporate microglia into hMOs, we can bridge the gap between animal models and human pathophysiology, providing a clinically relevant model to explore fundamental cellular mechanisms and evaluate potential therapeutic strategies for PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0918 / #993

Poster Topic: *Theme C: α-Synucleinopathies / C01.g. Disease Mechanisms, Pathophysiology: Microglia*

TRANSLOCATOR PROTEIN (18 KDA) DEFICIENCY MITIGATES EXCESSIVE SYNAPTIC ENGULFMENT INDUCED BY A-SYNUCLEIN PREFORMED FIBRILS

POSTERS: C01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Qiang Huang[1,2], Mochen Cui[1,2,3], Juan Zu[1,2,3], Yuan Shi[1,2,4], Jochen Herms[1,2,4]
[1]Ludwig-Maximilians-Universität München, Center For Neuropathology, Munich, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Department Of Translational Brain Research, Munich, Germany, [3]Ludwig-Maximilians-Universität München, Munich Medical Research School, Munich, Germany, [4]Ludwig-Maximilians-Universität München, Munich Cluster For Systems Neurology (synergy), Munich, Germany

Aims: Misfolded and aggregated α-synuclein (α-Syn) is the pathological hallmark of synucleinopathies. Preformed fibrils (PFFs), the synthetic active fibrils of α-Syn, have been demonstrated to cause synaptic loss, however, the underlying mechanisms remain elusive. Previously, we have reported that activating 18 kDa translocator protein (TSPO) causes synaptic loss via promoted microglial engulfment of synaptic materials. Here, we aim to investigate the potential mechanism of PFF-induced synaptic loss and explore the effect of PFFs on microglial functionality, in particular their phagocytic activity towards synaptic materials.
Methods: PFFs (or PBS) were stereotactically delivered to subcortical regions of 2-month-old Thy1-eGFP mice. After 5 months of inoculation, brains of both cohorts were harvested. The density and morphology of dendritic spines of GFP-labelled cortical neurons were analysed. Microglia, including their lysosomes and containing synaptic materials, were immunolablled, scanned using super-resolution microscopy and analysed using 3D reconstruction. *Tspo*$^{-/-}$ mice were employed for validation of TSPO dependency of the observed alterations.
Results: In the cortical region with confirmed spreading of aggregated α-Syn, we observed a decreased density of dendritic spines. Moreover, compared to PBS-injected mice, microglia of PFFs-injected mice showed heightened TSPO expression, coupled with increased synaptic materials (PSD95) inside lysosomes (CD68), indicating a promoted phagocytic activity towards synapses. Both effects were inhibited upon genetic depletion of TSPO, supporting the TSPO dependency of the PFFs-induced microglial synaptic engulfment.
Conclusions: Collectively, we have demonstrated that PFFs induce synaptic loss via promoted TSPO-mediated microglial engulfment of synapses. Our findings support the perspective of TSPO as a potential therapeutic target for rescuing synaptic loss induced by misfolded and aggregated α-Syn.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0919 / #188

Poster Topic: *Theme C: α-Synucleinopathies / C01.g. Disease Mechanisms, Pathophysiology: Microglia*

STAT3-MEDIATED FERROPTOSIS IS INVOLVED IN A-SYNUCLEIN PATHOLOGY

POSTERS: C01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Danyu Lin[1], Han Zhang[2], Kaixun Huang[1], Jieli Zhang[1], Enxiang Tao[1]
[1]The Eighth Affiliated Hospital, Sun Yat-sen University, Department Of Neurology, Shenzhen, China, [2]Nanfang Hospital, Southern Medical University, Department Of Neurology, Guangzhou, China

Aims: Oligomeric α-synuclein had been proved to activate microglia in Parkinson's disease (PD) pathogenesis. Our previous studies have found a decline of IL6ST and its downstream target JAK2/STAT3 pathway in α-syn-induced HMC3 cells. Accumulating investigations have illustrated that STAT3 regulates the expression of ferroptosis-related genes and finally influences the proliferation of cells. In this study, we aim to explore the exact role of STAT3 in α-synuclein pathology.
Methods: Firstly, we determined the expression of IL6ST/ STAT3/HIF-1α pathway in α-syn-induced HMC3 cells. Secondly, we performed transcriptomic analysis for α-syn-induced HMC3 cells and in α-syn-induced PD mouse models. GSEA analysis was used to screen out the STAT3-associated ferroptosis pahtway. By regulating the expression of STAT3, we detected the level of ferroptosis positive regulation (FPR) genes, lipid peroxidation and iron metabolism, as well as the change of mitochondria.
Results: We explored the exact role of STAT3 in α-synuclein pathology. α-syn could impair cell activity and the stalely by inhibiting the IL6ST/ STAT3/HIF-1α pathway in α-syn-induced HMC3 cells. Besides, we performed transcriptomic analysis for α-syn-induced PD models and GSEA indicated an association with ferroptosis pathway. The reduction in P-STAT3 resulted in the transcriptional activation of ferroptosis positive regulation (FPR) genes and significant morphological changes of mitochondria. P-STAT3 mediated ferroptotic cell death in α-syn-induced HMC3 cells by modulating lipid peroxidation and iron metabolism levels. An in vivo study revealed that the IL6ST/JAK2/STAT3/HIF-1α pathway was upregulated in PD mouse models.
Conclusions: Our research illustrated the relationship of the JAK2/STAT3/HIF-1α axis and ferroptosis in the pathological process of α-syn both in vitro and in vivo, providing new topics of interest regarding the inflammation damage hypothesis and pathogenesis in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0920 / #1203

Poster Topic: *Theme C: α-Synucleinopathies / C01.g. Disease Mechanisms, Pathophysiology: Microglia*

MICROGLIAL ACTIVATION IN AN ALPHA-SYNUCLEIN MOUSE MODEL OF PARKINSON'S DISEASE

POSTERS: C01.G. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MICROGLIA

Laurent Potvin-Trottier[1], Robin Guay-Lord[1], Lionel Breuillaud[2], Simone Zehntner[2], Elodie Brison[2], Barry Bedell[2,3]
[1]Biospective Inc, Technology, Montreal, Canada, [2]Biospective Inc., Preclinical, Montreal, Canada, [3]Research Institute of the McGill University Health Center, Department Of Neurology And Neurosurgery, Montreal, Canada

Aims: Microglia are thought to play a key role in neurological diseases, including Parkinson's disease and Alzheimer's disease [1]. In these diseases, microglial activation is often linked with pathologic progression and disease severity. The objective of this work was to quantitatively assess microglial activation in a human α-synuclein preformed fibril (hPFF) seeding and spreading mouse model of Parkinson's disease.
Methods: We have developed a novel, fully-automated method for analysis of microglial morphology in neuroanatomical regions-of-interest on immunohistochemistry (IHC) sections stained for Iba-1 leveraging advanced computer vision and machine-learning (ML) models. We have applied this methodology to tissue sections from transgenic M83+/- mice, which overexpress α-synuclein with an A53T mutation, that have undergone unilateral stereotaxic inoculation of recombinant hPFFs into the anterior olfactory nucleus.
Results: We found that cells classified as activated by our ML model had very different morphological features that were consistent with previous reports, such as a larger, less circular soma and compact, highly branched processes (Fig. 1). Measurement of the density of activated cells provided a more sensitive metric than the Iba-1 stain density, with greater fold-change that had higher statistical significance (Fig. 2 top vs bottom). In addition, using other measures, such as a continuous activation score, we show how both the distribution of morphological phenotypes and the number of microglia change in the disease model, thereby illustrating how such metrics can provide a finer quantification of the microglial
morphology.

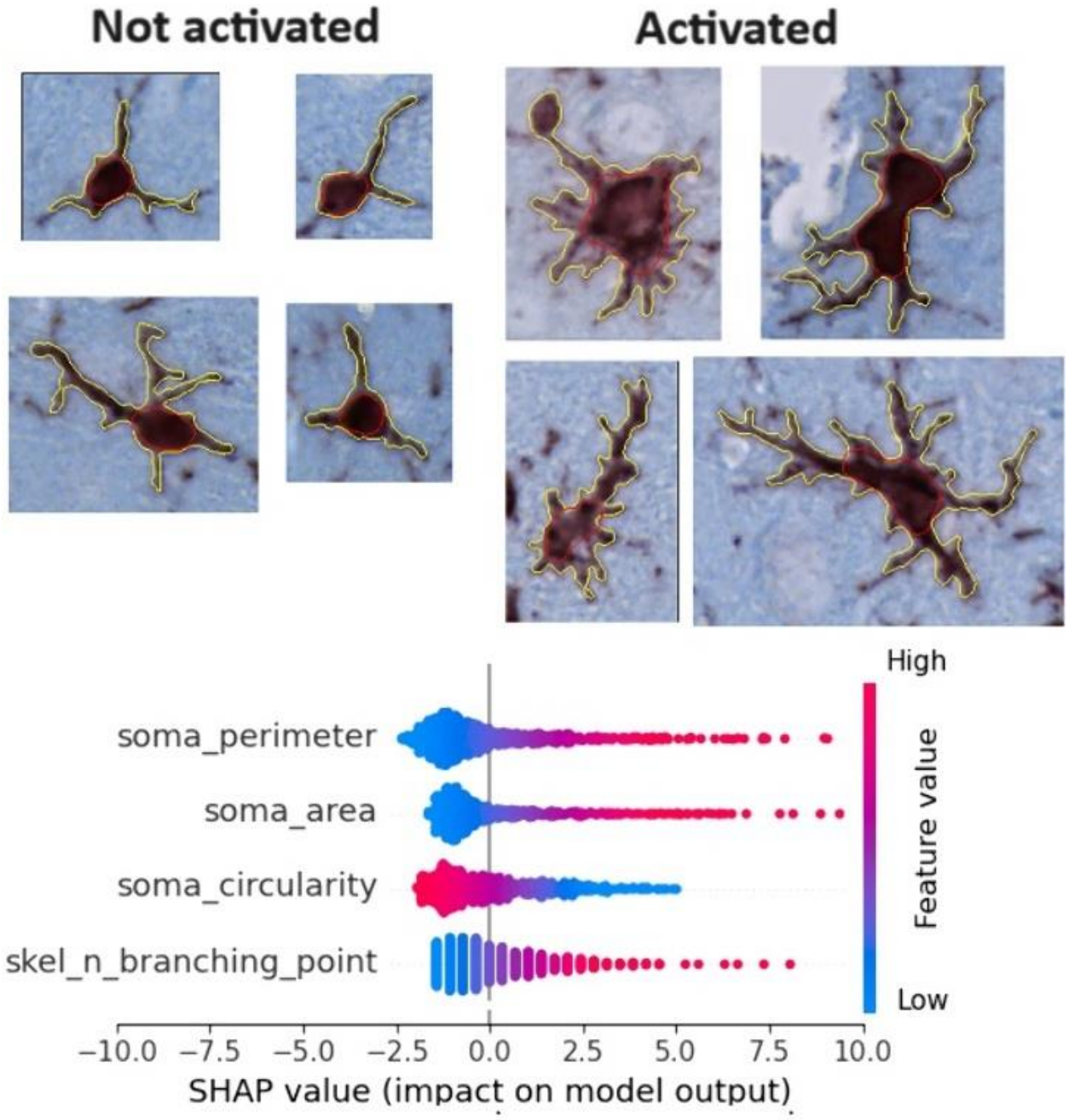

Not activated
Activated
soma_perimeter
soma_area
soma_circularity
skel_n_branching_point
High
Feature value
Low
−10.0 −7.5 −5.0 −2.5 0.0 2.5 5.0 7.5 10.0
SHAP value (impact on model output)

Fig. 1

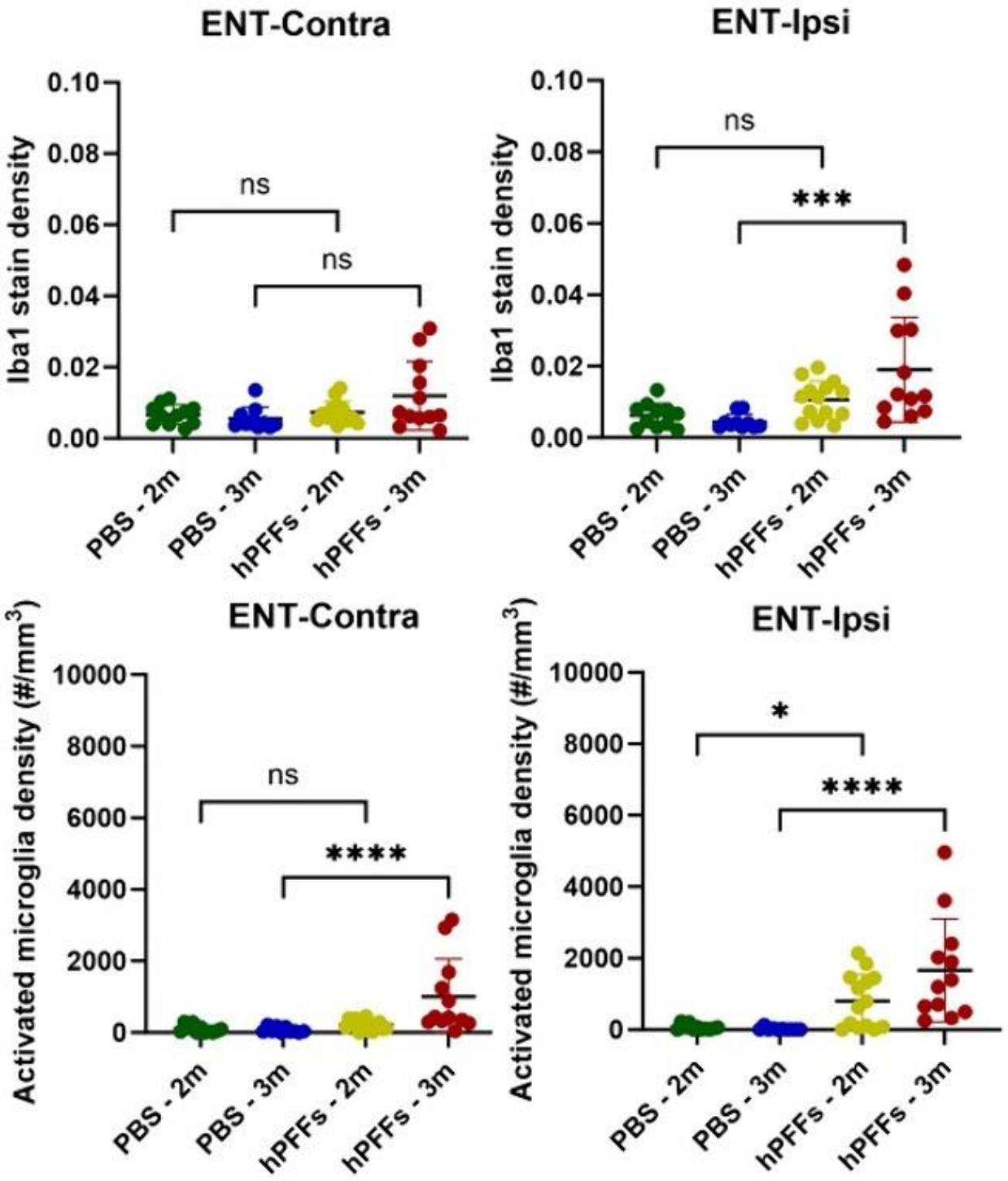


Fig. 2

Conclusions: Assessment of morphological characteristics can provide additional information about the microglial phenotype. These features may provide sensitive measures for the preclinical assessment of putative disease-modifying therapeutic agents in rodent models of neurodegenerative diseases. **References** [1] Hickman et al 2018. *Nature neuroscience*, *21*(10), 1359-1369.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0921 / #1387

Poster Topic: *Theme C: α-Synucleinopathies / C01.h. Disease Mechanisms, Pathophysiology: Astroglia*

ASSESSING THE SUITABILITY OF IPSC-DERIVED HUMAN ASTROCYTES FOR DISEASE MODELING

POSTERS: C01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Sandro Cardoso Pereira, Patrycja Mulica, Carmen Venegas, Zied Landoulsi, Katja Badanjak, Sylvie Delcambre, Maria Tziortziou, Soraya Hezzaz, Jenny Ghelfi, Semra Smajic, Jens Schwamborn, Rejko Krüger, Paul Antony, Patrick May, Enrico Glaab, Anne Grünewald
University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Belvaux, Luxembourg

Aims: Astrocytes perform pivotal roles in sustaining brain physiology and function. Accumulating evidence shows that disrupted astrocytic activity contributes to neurodegenerative disorders, including Parkinson's disease (PD). Over the past decade, various methods have been developed to generate more pertinent astrocytic models to interrogate disease mechanisms, namely using human induced pluripotent stem cells (iPSC). However, the properties of astroglia generated through different methods are inconsistent, which complicates the selection of an appropriate protocol for a given research question. Thus, we aimed to compare two approaches for the generation of iPSC-derived astrocytes that differ in their duration and serum utilization.
Methods: We obtained human iPSC-derived astrocytes employing a widely used long, serum-free ("LSF") method and an in-house established short, serum-containing ("SSC") protocol. The latter method involves the purification of expandable neural stem cells. We employed high-content confocal imaging and bulk RNA sequencing to characterize the resulting cultures.
Results: LSF and SSC protocols generate astrocytes that differ considerably in their properties. While the LSF method is more labor-intensive involving manual cutting of astrospheres and a longer cultivation time (~5 vs ~2 months), the generated cells more robustly expressed traits of mature astrocytes. This notion was strengthened by data resulting from cell-type deconvolution analysis that was applied to bulk transcriptomes from each culture to assess their similarity with human postmortem astrocytes.
Conclusions: Overall, our data highlight the need to carefully consider the advantages and disadvantages of any given differentiation method, when designing functional or drug discovery studies involving iPSC-derived astrocytes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0922 / #1398

Poster Topic: *Theme C: α-Synucleinopathies / C01.h. Disease Mechanisms, Pathophysiology: Astroglia*

GLIAL AND NEURONAL ALPHA-SYNUCLEIN PATHOLOGY OCCURS ACROSS ALPHA-SYNUCLEINOPATHIES WITH ASTROCYTIC PATHOLOGY AFFECTING PREDOMINANTLY THE LIMBIC SYSTEM OF CASES WITH DEMENTIA

POSTERS: C01.H. DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROGLIA

Maria Otero-Jimenez, Javier Alegre-Abarrategui, Marcelina Wojewska, Vincenzo De Paola
Imperial College London, Department Of Brain Sciences, London, United Kingdom

Aims: Alpha-synucleinopathies are neurodegenerative diseases including Dementia with Lewy bodies (DLB), Parkinson's disease (PD), Parkinson's Disease Dementia (PDD) and Multiple System Atrophy (MSA) characterised by the accumulation of pathological alpha-synuclein (α-syn) aggregates. Although α-syn aggregation is a key shared property, they differ in the extent of glial versus neuronal α-syn pathology and neuroanatomical regions affected in a stereotypical pattern. MSA is characterised by the presence of α-syn aggregates in oligodendrocytes, termed glial cytoplasmic inclusions (GCIs), whereas in PD, PDD and DLB α-syn aggregates are mainly present in neurons as Lewy bodies. Neuronal inclusions are present in MSA although less widespread than GCIs. Glial pathology in PD, PDD and DLB is also present but its role in pathogenesis is still unclear. We aim to investigate the hypotheses that neuropathogenesis is promoted by synergistic interaction of glial and neuronal α-syn pathology which could be detected using a machine learning (ML) based approach.
Methods: Immunohistochemistry was used to explore the cellular-specificity of α-syn pathology in a cohort including MSA, DLB, PDD (n=15) and early or late stage PD (n=20) cases using QuPath software. Analysed brain regions included those affected differentially across conditions along disease stages, including brainstem, limbic system and neocortex.
Results: ML revealed the presence of neuronal α-syn pathology in some MSA cases and widespread glial α-syn pathology in PD, PDD and DLB cases. Moreover, astrocytic α-syn pathology was predominant in the limbic system of cases with dementia in a stereotypical pattern with morphology of astrocytic α-syn pathology paralleling its severity.
Conclusions: To conclude, glial and neuronal α-syn pathology can be differentially detected using ML and is present across all alpha-synucleinopathies appearing at early disease stages while astrocytic α-syn pathology might correlate with presence of dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0923 / #2685

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

EFFECTS OF NPT520-34 ON MITOCHONDRIAL DYSFUNCTION AND INFLAMMATORY PATHWAYS RELEVANT TO NEURODEGENERATIVE DISEASES

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Adrianne Pike[1], Agata Habas[1], Ildiko Szabo[2], Diana Price[3], Douglas Bonhaus[1]
[1]Neuropore Therapies, Inc., In Vitro Pharmacology, San Diego, United States of America, [2]University of Padova, Department Of Biology, Padova, Italy, [3]Neuropore Therapies, Inc., In Vivo Pharmacology, San Diego, United States of America

Aims: The clinical stage development candidate NPT520-34 has yielded promising results in animal models of Parkinson's disease (PD) and other neurodegenerative disorders (NDs). We previously demonstrated that NPT520-34, which binds to the mitochondrial Complex 1 subunit NDUFB8, modulates inflammasome activation specifically associated with mitochondrial dysfunction. The aim of the current study was to characterize the actions of NPT520-34 on the mitochondrial production of reactive oxygen species (ROS) in comparison to secreted cytokine patterns.
Methods: Biochemical techniques including multiplex quantification of cytokine secretion, western blotting, and ROS assays were employed to gain insight into ROS production and NPT520-34-mediated inhibition of NLRP3 inflammasome activation in THP-1 cells. Established inflammasome activators and Complex I inhibitors were applied to cells after pretreatment with a concentration gradient of NPT520-34.
Results: All inflammasome activators tested led to increased ROS and cytokine production by THP-1 cells. NPT520-34 decreased NLRP3 inflammasome-mediated IL-1β and TNF-α secretion in response to Complex I inhibitors but not TLR ligands. NPT520-34 also decreased superoxide production induced by rotenone or LPS, but not by piericidin A, imiquimod, or Pam3.
Conclusions: NPT520-34 shows a selective ability to inhibit ROS production and NLRP3 inflammasome activation induced by Complex I inhibitors. These results suggest that NPT520-34 is neither a direct inflammasome inhibitor nor a simple antioxidant, but rather acts to maintain mitochondrial function by a direct action on Complex I. These beneficial actions on mitochondrial function may account for the robust actions of NPT520-34 in animal models of neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0924 / #698

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

STRATIFYING PEOPLE WITH SPORADIC PARKINSON'S DISEASE BY PATHOLOGICAL MECHANISM IN PATIENT-DERIVED FIBROBLASTS

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Toby Burgess, Thomas Payne, Stephen Bradley, Sarah Roscoe, Katy Barnes, Oliver Bandmann, Heather Mortiboys
SITRAN, Neuroscience, Sheffield, United Kingdom

Aims: The aim of this study was to stratify a new cohort of Sporadic Parkinson's disease (sPD) patients into small, homogeneous subgroups defined by specific mitochondrial and lysosomal dysfunction.
Methods: sPD is widely recognised as a heterogeneous disorder, both clinically and mechanistically. Several dysfunctional mechanisms have been identified, including mitochondrial and lysosomal dysfunction. However, clinical trials select participants without considering mechanism heterogeneity and continually fail to reach efficacy outcomes. We investigated mitochondrial and lysosomal dysfunction, two key mechanisms of sPD and promising targets for therapeutics. Imaging and biochemical assays assessed 13 mitochondrial and lysosomal health parameters in fibroblasts from a new cohort consisting of 35 sPD patients and 24 healthy individuals. The sPD population was then stratified by assessing patterns of dysfunction across these parameters. Validation of these subgroups is currently being undertaken in the patient fibroblasts and induced Dopaminergic Neurons.
Results: The sPD population was significantly more heterogeneous in 88% of mitochondrial and lysosomal parameters, but population means were only significantly different in 7.7% parameters demonstrating the diversity amongst patients. Stratification of this cohort by distinct patterns of dysfunction identified four unique subgroups, defined by mitochondrial dysfunction, lysosomal dysfunction or both. The top three patients in each subgroup were selected for validation and mechanism studies, which discovered a significant reduction in maximal respiration in the pure mitochondrial dysfunction subgroup and Cathepsin D activity deficit in the lysosomal dysfunction subgroup.
Conclusions: This study suggests that it is possible to stratify cohorts of sPD patients providing a possible model for clinical trial recruitment in order to aid the effectiveness, and therefore approval, of new therapeutics and support an approach to personalised treatment plans.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0925 / #989

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

PARKINSON'S DISEASE ASTROCYTES EXHIBIT ALTERATIONS IN MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION AND QUALITY CONTROL PROTEINS

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Chun Chen[1], David Mcdonald[2], Amy Vincent[1], Gavin Hudson[1]
[1]Newcastle University, Wellcome Centre Of Mitochondrial Research, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Flow Cytometry Core Facility,, Newcastle upon Tyne, United Kingdom

Aims: Mitochondrial dysfunction in neurons, particularly in the substantia nigra, is well-documented in Parkinson's disease (PD). However, the impact of this dysfunction on astrocytes, reliant on mitochondria, remains less clear. Impaired astrocytic support for neuronal health may play a key role in PD progression and neurodegeneration. This study aimed to investigate mitochondrial health in PD astrocytes, importantly, exploring their relationship to nearby neurons, Lewy body distribution and clinical phenotypes.
Methods: Post-mortem human brain sections from PD patients and age-matched controls underwent imaging mass cytometric analysis of key enzymes and factors of OxPhos and the mitochondrial quality control (MQC) system (PMID37553379 & 33980828). Imaging mass cytometry enables simultaneous detection of up to 47 targets at a single-cell level using lanthanide metal-conjugated antibodies. Statistical analysis included Bayesian estimation, Mann-Whitney U tests, and mixed linear regression modelling using R.
Results: We observed significant variability in astrocytic mitochondrial protein expression among individuals, with evidence of OxPhos enzyme deficiencies. These changes, particularly in mitochondrial mass, associated with PD, not solely aging. (PMID: 34779538). Additionally, lower protein abundance of key mitophagy regulator Parkin, intramitochondrial chaperone HSP60, and mitofusion2 (MFN2) was detected in PD astrocytes versus controls. This suggests impaired MQC machinery, including mitophagy and mitochondrial proteases, in PD astrocytes. Ongoing work includes examining associations between astrocytic mitochondrial proteostasis disruption, neuronal dysfunction, Lewy bodies, and clinical parameters.
Conclusions: Our data highlight mitochondrial dysfunction in PD astrocytes, impacting OxPhos and mitochondrial homeostasis. This suggests that astrocytes, similar to neurons, are susceptible to mitochondrial defects that could affect their support for neurons in PD, potentially accelerating disease progression. Future plans include utilizing a neuronal-astrocytic co-culture model to further evaluate these disease-relevant pathways, offering deeper insights into pathogenic mechanisms and potential PD therapeutic strategies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0926 / #2045

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

POLG-ASSOCIATED PARKINSONISM

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

André Fernandes, Daniel Oliveira, Rui Araújo
Centro Hospitalar e Universitário São João, Neurology, Porto, Portugal

Aims: We aim to raise awareness to a rare cause of neurogenerative parkinsonism.
Methods: We report a patient with pathogenic POLG mutation who presented with early-onset parkinsonism.
Results: A 43-year-old female presented with an 8-year history of a bilateral upper limb tremor. Additionally she complained about episodes of abnormal posturing of the left foot and pain during stressful events and resting, causing gait disturbances. She had a previous history of ocular misalignment, which led to a strabismus surgery, and important systemic reactions to viral illnesses and vaccination. Family history revealed a maternal grandfather with history of Parkinson's Disease with age of at 45-years-old. The neurological examination revealed opthalmoparesis with esotropia of the left eye and abduction restriction and a mild right eyelid ptosis. She displayed postural tremor on the upper limbs. Bilateral bradykinesia was observed in the finger tapping, hand movements and foot tapping maneuvers. Additionally, a dystonic posturing of the left foot was noted. Brain MRI was unsuspicious and the DatSCAN was compatible with right preference degeneration of dopaminergic neurons of nigostriatal pathways. The patient revealed a marked improvement after initiation of rotigotine 2mg id. A next generation sequencing panel of Parkinson's Disease and Parkinsonism detected a variant in heterozygosity in POLG, c.1402A>G (p.Asn468Asp), classified as pathogenic. The patient was treated with increasing dose of dopamine-agonist (rotigotine up to 4mg/d), with sustained dopaminergic-response.
Conclusions: Mitochondrial dysfunction has emerged as one of the possible mechanisms associated with neurodegenerative parkinsonism. The co-occurrence of other neurological and systemic symptomatology may underpin a mitochondrial disorder. POLG mutations should be suspected as a genetic cause of a neurodegenerative parkinsonism regardless of age and family history, particularly when features suggestive of a mitochondrial disorder are present.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0927 / #1512

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

SPATIAL TRANSCRIPTOMICS IDENTIFIES MOLECULAR SIGNATURES OF PRODROMAL AND ADVANCED ALPHA-SYNUCLEIN PATHOLOGY

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Lin Lin[1], Diana Gomes Moreira[2], Vasileios Theologidis[2], Yonglun Luo[1], Poul Jensen[3], Marina Romero-Ramos[1], Nathalie Van Den Berge[2], Jens Nyengaard[4], Asad Jan[1]
[1]Aarhus University, Department Of Biomedicine, Aarhus C, Denmark, [2]Aarhus University, Department Of Clinical Medicine, Aarhus N, Denmark, [3]Aarhus University, Danish Research Institute Of Translational Neuroscience, Department Of Biomedicine, Aarhus C, Denmark, [4]Aarhus University, Department Of Clinical Medicine, Core Center For Molecular Morphology, Aarhus N, Denmark

Aims: We investigated the transcriptomic profiles associated with prodromal and advanced stages of alpha-synuclein (aSyn) aggregation in mouse brain, within their histological context, using spatial transcriptomics.
Methods: We induced aSyn aggregation *in vivo* by intramuscular delivery of fibrillar (mouse) aSyn in the hindlimb of heterozygous transgenic M83 mice overexpressing the human mutant A53T aSyn. Spatial cDNA library construction was performed through 10X Genomics Visium platform, using brains section (n=4/cohort) from the following cohorts: i) Controls (vehicle), ii) Early stage (45 days post-injection, with non-significant phenotype), and iii) Terminal stage pathology (70-86 days post-injection with paralysis). See publication (PMID 34136810) for details on pathology and associated phenotypes in the model.
Results: Our differential gene expression analyses reveal remarkably distinct transcript modules in the affected brain regions at the two stages. In the prodromal (non-symptomatic) phase, we observe significant upregulation of pathways involved in the energy metabolism (ie. Oxidative phosphorylation, glucose homeostasis, fatty acid metabolism and cholesterol biogenesis), and protein translation. Intriguingly, there is a dramatic decline in these metabolic pathways at the end-stage (phenotype: paralysis), with substantial enrichment of inflammatory markers (eg, complement, interferon response). Crucially, we also identified differential expression of unique gene clusters highlighting the effects of pathological aSyn aggregation in the components of white matter, choroid plexus and brain vasculature, which otherwise remain underrepresented features in studies of Parkinson disease (PD) and related disorders. Lastly, data from validation studies involving select candidate markers in PD patient-derived microarrays datasets and immunohistochemical analyses in post-mortem brain specimen will also be presented
Conclusions: We consider that these findings will have significant implications for obtaining a refined mechanistic understanding concerning the role of aSyn aggregation in neurodegeneration and potentially hold promise for the discovery of surrogate biomarkers in PD and other synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0928 / #2362

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

FUNCTIONAL VALIDATION OF A MITOCHONDRIA-SPECIFIC POLYGENIC RISK SCORE IN PATIENT-BASED MODELS FOR STRATIFICATION OF IDIOPATHIC PARKINSON'S DISEASE

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Zied Landoulsi[1], Giuseppe Arena[1], Armelle Vitali[1], Sylvie Delcambre[1], Paul Antony[1], Ibrahim Boussaad[1], Lukas Pavelka[2], Enrico Glaab[1], Dajana Grossmann[3], Manu Sharma[4], Anne Grünewald[1], Patrick May[1], Rejko Krüger[1,5]
[1]University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Belvaux, Luxembourg, [2]Luxembourg Institute of Health, Transversal Translational Medicine, Strassen, Luxembourg, [3]University Medical Center Rostock, University of Rostock, Translational Neurodegeneration Section "albrecht-kossel", Department Of Neurology, Rostock, Germany, [4]University of Tübingen, Centre For Genetic Epidemiology, Institute For Clinical Epidemiology And Applied Biometry, Tübingen, Germany, [5]Centre Hospitalier de Luxembourg, Parkinson Research Clinic, Luxembourg, Luxembourg

Aims: Strong evidence points to mitochondrial dysfunction as a major cause of PD pathogenesis. We hypothesize that a fraction of idiopathic Parkinson's disease (iPD) cases may harbor a pathogenic combination of common variants in mitochondrial genes ultimately resulting in mitochondrial dysfunction. We aim to functionally validate mitochondrial polygenic risk profiles (mitoPRS) in patient-based cellular models to define mitochondrial pathways potentially involved in neurodegeneration in subgroups of iPD patients.
Methods: We used PD GWAS SNPs data from the Luxembourg Parkinson's study (412 iPD and 576 controls), and calculated mitoPRS to capture the cumulative effect of common variants in mitochondrial genes on PD risk. The COURAGE-PD consortium (7270 iPD and 6819 controls) was used as a replication dataset. Skin fibroblasts and iPSC-derived neuronal progenitor cells (NPCs) from iPD patients were identified based on their mitoPRS and then subjected to a comprehensive mitochondrial phenotyping.
Results: We found that distribution of mitoPRS was significantly associated with PD in both Luxembourg Parkinson's study and COURAGE-PD. Extending the PRS approach to selected mitochondrial pathways, we demonstrated that common variants in genes regulating *Oxidative Phosphorylation (OXPHOS*-PRS*)* were associated with a higher PD risk (OR=1.31[1.14-1.50], FDR-adj *p*=5.4e-04 and OR=1.23[1.18-1.27], FDR-adj *p*=1.5e-29, respectively for the Luxembourg Parkinson's Study and COURAGE-PD). Functional characterization of skin fibroblasts and corresponding iPSC-derived NPCs from iPD patients classified based on *OXPHOS*-PRSs revealed significant alteration of mitochondrial oxygen consumption rates in the high *OXPHOS*-PRS group. Finally, individuals with high *OXPHOS*-PRS tended to have earlier AAO and longer disease duration compared to low-risk patients, a phenotype particularly significant in the larger COURAGE-PD dataset.
Conclusions: We developed and functionally validated novel mitochondria specific PRSs that could be used as a genetic tool to stratify the heterogeneous group of iPD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0929 / #1131

Poster Topic: *Theme C: α-Synucleinopathies / C01.i. Disease Mechanisms, Pathophysiology: Cellular signalling, kinases, phosphatases, calcium*

ALPHA-SYNUCLEIN PHOSPHORYLATION CONSTITUTES A COMMON MOLECULAR DESTABILIZER IN HUNTINGTON'S DISEASE AND OTHER TAUOPATHIES

POSTERS: C01.I. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM

Angel White[1], Peter Gavrilyuk[1], Dahyun Yu[1], Nicole Zarate[1], Ying Zhang[2], Rocio Gomez-Pastor[1]
[1]University of Minnesota, Neuroscience, Minneapolis, United States of America, [2]University of Minnesota, Minnesota Supercomputing Institute, Minneapolis, United States of America

Aims: Alpha-synuclein (alpha-syn) is the primary component of lewy bodies, the hallmark of Parkinson's disease (PD) pathology. Accumulation and aggregation of toxic alpha-syn species in PD, such as those with enhanced phosphorylation at serine 129 (pS129), promote synaptic dysfunction and transcription and epigenetic dysregulation, ultimately leading to cell death. Interestingly, the presence of alpha-syn pS129 has also been connected to other neurodegenerative disorders (NDs) including Huntington's (HD), Alzheimer's (AD) and Frontotemporal dementia (FTD). However, the role of alpha-syn pS129 in the etiology and progression of those NDs is still unknown. We have recently shown alpha-syn-pS129 is increased in HD affected tissues correlating with enhanced expression of Protein kinase CK2 alpha prime (CK2alpha'). CK2alpha' haploinsufficiency (CK2alpha'$^{+/-}$) in an HD mouse decreased alpha-syn-pS129 levels and ameliorated HD-related phenotypes. We concluded that CK2alpha'/alpha-syn-pS129 mediated toxicity in HD occurred via specific alteration of glutamatergic-related synaptic (GRS) gene expression. Intriguingly, we found increased CK2a' in affected tissues of AD and FTD mouse and human samples implying a potential shared mechanism of neurodegeneration in HD, AD and FTD. We aim to explore the contribution of this pathway in AD and FTD.
Methods: We crossed AD (Tg576) and FTD (PS19) mice with CK2alpha'$^{+/-}$ mice. We then examined cognitive function via Barnes Maze and Y-maze, and looked at gene expression via qPCR and other pathological markers using immunoblot and brain slice immunofluorescence
Results: In the Tg2576; CK2alpha'$^{+/}$ and PS19; CK2alpha'$^{+/-}$ mice we found improved cognitive behavior along with restored expression of GRS genes and ameliorated pathology.
Conclusions: These findings confirmed the similarities by which cells undergo synaptic dysfunction and neurodegeneration between these different NDs and suggested CK2a' as a potential therapeutic target to decrease alpha-syn-pS129 for the treatment of multiple NDs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0930 / #1915

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

BIOENERGETIC AND LYSOSOMAL DEFECTS IN BLOOD-DERIVED GBA-PARKINSON'S DISEASE MACROPHAGES

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Gerardo Ongari[1], Micol Avenali[2,3], Antonio Pisani[3,4], Fabio Blandini[5], Silvia Cerri[1]
[1]IRCCS Mondino Foundation, Unit Of Cellular And Molecular Neurobiology, Pavia, Italy, [2]IRCCS Mondino Foundation, Neurorehabilitation Unit, Pavia, Italy, [3]University of Pavia, Department Of Brain And Behavioural Sciences, Pavia, Italy, [4]IRCCS Mondino Foundation, Movement Disorders, Pavia, Italy, [5]IRCCS Policlinico Maggiore Hospital, Scientific Director, Milano, Italy

Aims: Glucocerebrosidase 1 (GBA1) mutations are the most important risk factor for Parkinson's disease (PD), which primarily affect macrophages due to their intrinsic features and vulnerability for disturbances in ceramide metabolism. While it is known that GBA1-associated lysosomal dysfunctions can trigger the inflammatory response in macrophages, no studies explored the effects of GBA1 mutations on mitochondrial metabolism and oxidative stress in these cells. We then investigated mitochondrial dysfunction in macrophages of patients with GBA mutations, in association with lysosomal alterations and α-synuclein accumulation.
Methods: Thirty-four patients were recruited in the study: 10 controls (HC), 10 patients with sporadic PD (iPD), 10 PD patients with GBA mutations (PD-GBA+) and 4 healthy subjects carrying GBA mutations (HC-GBA+). Macrophages were differentiated from monocytes and stimulated to M1 and M2 phenotypes. Glucocerebrosidase and beta-hexosaminidase activities were quantified using fluorometric assays. Metabolic characterization was performed with a Seahorse Analyzer. Alpha-synuclein levels were quantified using an ELISA.
Results: Glucocerebrosidase activity was halved in PD-GBA+ and HC-GBA+ subjects compared with HC and iPD, whereas beta-hexosaminidase activity was reduced in PD-GBA+ compared to HC. Lysosomal alterations in PD-GBA+ is associated with increased α-synuclein levels, compared with iPD and HC macrophages. HC-GBA+ subjects showed α-synuclein levels similar to PD-GBA+. M2 stimulated PD-GBA+ macrophages displayed an impairment in the oxygen consumption compared to iPD, while no differences have been found between HC and iPD. Conversely, M1 macrophages of PD groups showed a decrease of respiratory parameters compared to HC, reaching the statistical significance in PD-GBA+. Preliminary results in HC-GBA+ indicated higher respiration values in M1 and M2 macrophages compared to PD-GBA+.
Conclusions: This study pointed out specific bioenergetic alterations in macrophages from PD subjects with GBA1 mutations suggesting their potential contribution in disease pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0931 / #2286

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

A-SYNUCLEIN DISRUPTS MITOCHONDRIAL METABOLISM IN NEURONS DERIVED FROM PARKINSON'S DISEASE PATIENTS

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Carmen Venegas[1], Patrycja Mulica[1], Soraya Hezzaz[1], Kristian Händler[2], Lucia Gallucci[1], Sylvie Delcambre[1], Sandro Cardoso Pereira[1], Paul Antony[1], Rejko Krüger[1], Alexander Skupin[1], Malte Spielmann[2], Anne Grünewald[1]
[1]University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Belvaux, Luxembourg, [2]University of Lübeck, Institute Of Human Genetics, Lübeck, Germany

Aims: Parkinson's disease is a complex and multifactorial neurodegenerative disorder characterized by the demise of dopaminergic neurons and the accumulation of α-synuclein (α-syn). Although many mechanisms are proposed to target the disease, α-syn accumulation and altered mitochondrial dynamics are the main features in the pathogenesis of PD. In light of these findings, the objective of the current study was to evaluate the impact of α-syn on mitochondrial function and metabolism in iPSC-derived midbrain neurons from controls and PD patients.
Methods: We differentiated iPSCs from healthy controls, sporadic and α-syn-mutant (A53T and *SNCA* triplication) PD patients into midbrain dopaminergic neurons. We performed single-cell RNA-sequencing, high-content imaging, mtDNA integrity analysis and metabolomics with stable isotope tracers at three different time points of differentiation to evaluate how the accumulation of a-syn drives mitochondrial dysfunction and metabolic alterations.
Results: RNA sequencing analysis revealed differences in the neuronal expression profile between controls and PD patients at days 14, 30 and 45 of differentiation. We could observe higher α-syn expression in all investigated PD lines compared to control cells. Interestingly, this difference further increased over time. In addition, our experiments revealed a shift from oxidative phosphorylation towards glycolysis in the PD compared to the control cultures.
Conclusions: Our data indicate that α-syn accumulation occurs in PD patient midbrain neurons and uncovered changes in the cellular metabolism of these cells. Further investigations will be performed to analyze how α-syn exerts its toxicity and to obtain insights into the functional relationship between α-syn and mitochondrial metabolism.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0932 / #323

Poster Topic: *Theme C: α-Synucleinopathies / C01.j. Disease Mechanisms, Pathophysiology: Mitochondrial dysfunction, oxidative damage*

MITOCHONDRIAL STRESS IN THE GUT EPITHELIUM OF MICE OVEREXPRESSING ALPHA SYNUCLEIN

POSTERS: C01.J. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE

Ashwaq Yehya[1], Nathan Pham[1], Linsey Stiles[1], Nuria Martinez-Lopez[1], Hoa Lam[2], Rajat Singh[1], Nigel Maidment[2], Elizabeth Videlock[1]
[1]UCLA, Medicine, Los Angeles, United States of America, [2]UCLA, Psychiatry And Biobehavioral Sciences, Los Angeles, United States of America

Aims: Mitochondrial dysfunction and inflammation (both intestinal and systemic) are strongly implicated in PD. Mitophagy (autophagic removal of damaged mitochondria) suppresses mitochondrial damage-induced inflammation and mitigates disease in both PD and colitis models. Intestinal epithelial cells (IECs) are particularly vulnerable to mitochondrial stress due to their high energetic needs. The aim of this study was to test the hypothesis that IEC mitochondria are altered in a mouse model of PD.
Methods: Intestinal crypts of mice overexpressing human wild-type α−synuclein (hα-Syn) under the neuron-specific Thy1 promoter (Thy1-hα-Syn) were used to measure the Oxygen consumption rate (OCR) in a Seahorse XF96 analyzer. Manual counts of the number of crypts per well were used for data normalization. Transmission electron microscopy was performed in the UCLA Brain Research Institute Electron Microscopy Core Facility. Analysis was performed in ImageJ with 'analyze particles' and the JACoP plugin. Intestinal epithelial organoids diameters and Western blot of Tom20 were measured and analyzed using ImageJ. Cytokines were measured by ELISA.
Results:

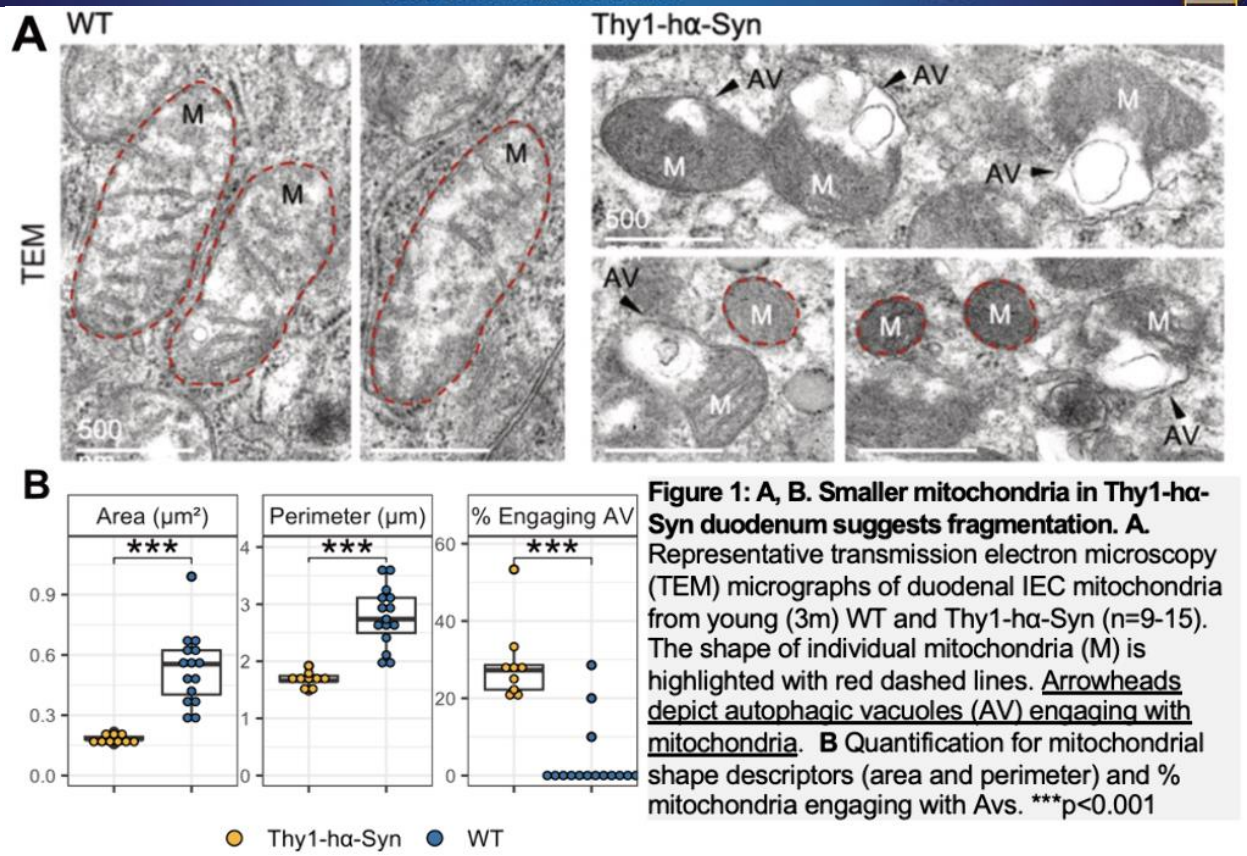


Figure 1: A, B. Smaller mitochondria in Thy1-hα-Syn duodenum suggests fragmentation. A. Representative transmission electron microscopy (TEM) micrographs of duodenal IEC mitochondria from young (3m) WT and Thy1-hα-Syn (n=9-15). The shape of individual mitochondria (M) is highlighted with red dashed lines. Arrowheads depict autophagic vacuoles (AV) engaging with mitochondria. **B** Quantification for mitochondrial shape descriptors (area and perimeter) and % mitochondria engaging with Avs. ***p<0.001

OCR was increased in Thy1-hαSyn vs WT mice ($p < 0.005$) with a greater increase in older mice. Thy1-hα-Syn mice had smaller mitochondria in duodenal tissue (Fig 1). Increased association with autophagic vesicles may suggest heightened mitophagy. IL-1β and KC (IL-8 equivalent) were higher in tissue and isolated crypts from 12-month-old Thy1-hα-Syn mice. Colonic epithelial organoids from Thy1-hα-Syn mice had smaller diameters, suggesting potential impairment in gut epithelial health compared to WT.
Conclusions: These findings provide initial support for the hypothesis that there is increased mitochondrial stress in the gut epithelium in PD. Mitochondrial stress in IECs may augment the intestinal inflammatory response to enteric neuron α-Syn, thereby producing systemic inflammation and promoting CNS α-Syn pathology in 'gut-first' PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0933 / #822

Poster Topic: *Theme C: α-Synucleinopathies / C01.k. Disease Mechanisms, Pathophysiology: Synapse pathology, neural networks, plasticity, neurogenesis*

ALPHA-SYNUCLEIN PATHOLOGY DISRUPTS CORTICOSTRIATAL SYNAPSES IN A RODENT MODEL OF PD

POSTERS: C01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS

Charlotte Brzozowski[1], Harshita Challa[1], Dominic Hall[2], Nicole Chambers[2], Ignacio Gallardo[2], Michael Millet[2], Douglas Nabert[2], Nolwazi Gcwensa[1], Laura Volpicelli-Daley[1], Mark Moehle[2]
[1]University of Alabama at Birmingham, Neurology, Birmingham, United States of America, [2]University of Florida, Department Of Pharmacology And Therapeutics And Center For Translational Research In Neurodegeneration, Gainesville, United States of America

Aims: Neuronal inclusions of α-synuclein aggregates are pathological hallmarks of Dementia with Lewy Body (DLB) and Parkinson's Disease (PD). Corticostriatal projection neurons in the supplementary motor area (SMA) in humans - secondary motor cortex (M2) in mice - are specifically vulnerable in PD, and show large burdens of α-synuclein pathology. Here, we endeavor to understand how pathological corruption of α-synuclein impairs M2, a critical brain area involved in executive functions known to be impaired in DLB and PD, to striatal connections and related behaviors.
Methods: We performed whole-cell patch clamp recordings from spiny projection neurons (SPNs) 6 weeks after α-synuclein pre-formed fibrils (PFFs) inoculations into the striatum or directly into M2. The optogenetics construct Chrimson-R was used to record light-elicited M2-striatal projection specific evoked glutamate release. Expansion Microscopy (ExM) was utilized to assess for abnormalities in synaptic morphology in presence of α-synuclein pathology. Additionally, Y maze and Erasmus ladder we used to assess for motor impairments and executive dysfunction.
Results: We show impaired evoked corticostriatal glutamate release onto SPNs in striatal and M2 PFF-injected animals compared to controls. Additionally, we found significant impairments of SPN excitability in the PFF group. M2 PFF injections caused robust layer 5 pathology throughout M2 and adjacent cortical areas and neuritic pathology overlapping with cortical terminal markers in the striatum. Using ExM superresolution imaging, we show a decrease of corticostriatal glutamatergic synapses and and overall loss of volume of presynaptic terminals in mice with α-synuclein inclusions.
Conclusions: Our combined efforts in physiology and high-resolution imaging point to a critical dysfunction of corticostriatal synapses in neurons harboring α-synuclein inclusions and our future efforts will elucidate how our findings on corticostriatal synapse abnormalities contributes to executive dysfunction in PD and DLB.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0934 / #2228

Poster Topic: *Theme C: α-Synucleinopathies / C01.k. Disease Mechanisms, Pathophysiology: Synapse pathology, neural networks, plasticity, neurogenesis*

PARKINSON'S DISEASE DNAJC13 P.N855S KNOCK-IN MOUSE MODEL EXHIBITS GLUTAMATERGIC MACHINERY DEFICITS, ALTERED EXCITATORY SIGNALLING, AND INTACT DOPAMINERGIC NETWORKS AND KINETICS

POSTERS: C01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS

Jesse Fox
University of British Columbia, Neuroscience, Health Sciences Mall, Canada

Aims: In 2014, DNAJC13 was linked to late-onset autosomal dominant Parkinson's disease (PD) in a multi-incident kindred with post-mortem SNpc neuronal loss and Lewy body pathology. Neuronally expressed DNAJC13 localizes to endosomal compartments where it functions in protein trafficking by partitioning endosomal membranes. Interestingly, all neuronally expressed DNAJ class-III (DNAJC) members (DNAJC5/CSPα, DNAJC6/auxilin, DNAJC12/HSP40, DNAJC13/RME-8 and DNAJC26/GAK) have been implicated in parkinsonism, although with disparate synaptic-endosomal properties. Here, we examine glutamatergic and dopaminergic michinery and kinetics in Dnajc13 p.N855S knock-in (DKI or Het) mice, as well as underlying molecular mechanisms and downstream effects of observed changes in relation to the onset and progression of PD.
Methods: Animal behaviour, immunohistochemistry, fast-scan cyclic voltammetry, patch-clamp electrophysiology recording, high performance liquid chromatography, western blotting, ELISA, cell culturing, immunocytochemistry, transfections, laser-scanning confocal microscopy, electron microscopy, synaptosome isolation.
Results: We show Dnajc13 p.N855S knock-in (DKI or Het) mice exhibit significant reductions in vesicular glutamate transporter 1 and altered response to a prolonged repetitive stimulation train, but with normal basal excitatory signaling and dopamine (DA) machinery and release/reuptake kinetics. Further, synaptic vesicle organization and content are presented.
Conclusions: We show Dnajc13 p.N855S knock-in mice exhibit significant alterations to synaptic homeostatic and signaling mechanisms, thereby supporting the assignment of this mutation as disease causing in humans.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0935 / #929

Poster Topic: *Theme C: α-Synucleinopathies / C01.I. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

IMPACT OF THE MICRORNA-183/96/182 CLUSTER ON SYNAPSES IN PRODROMAL ALPHA-SYNUCLEINOPATHY

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Teodoro De Vecchi, Jeannine Widmann, Jiao Geng, Otto Windl, Jochen Herms, Felix Struebing
University of Munich, Center For Neuropathology And Prion Research, Munich, Germany

Aims: In mice overexpressing α -Synuclein (SNCA), cortical synapse loss is already evident at 3 months of age, long before the onset of motor symptoms and coinciding with translational dysfunction at the synapse. We aimed to explore the regulatory networks leading up to this phenomenon.
Methods: RNA- and micro-RNA-sequencing were used to characterize the transcriptome and regulome at the onset of SNCA-mediated synaptic loss. Human iPSCs of an α-Synuclein triplication line (AST) and its CRISPR-corrected isogenic equivalent (CAS) were differentiated to cerebral organoids as well as neurons and subjected to immunohistochemical assays, gene expression assays and translatome sequencing. Genetic manipulation of miRNA levels was performed by administration of anti-miRs and miRNA mimics. Micro-RNA target genes were identified by pulldown assays.
Results: The miRNA 183/96/192 cluster was significantly upregulated during the onset of SNCA-dependent synaptic loss, while glutamatergic synaptic markers were downregulated during this phase. Human cerebral organoids as well as iPSC-derived neurons recapitulated this phenotype. miRNA-183/96/182 target genes revealed a strong enrichment for intracellular membrane-bound organelles as well as synaptic gene ontology terms.
Conclusions: We uncovered a role for the miRNA-183/96/182 cluster in early synaptic loss during the pathogenesis of α -Synucleinopathies. Experiments on iPSC-derived cerebral organoids and neurons demonstrate this process to be conserved among humans. We hypothesize that elevated levels of miRNA 183/96/182 decrease local protein synthesis at the synapse, ultimately resulting in synapse loss. Further experiments are being performed to investigate whether this is a direct or indirect effect.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0936 / #657

Poster Topic: *Theme C: α-Synucleinopathies / C01.k. Disease Mechanisms, Pathophysiology: Synapse pathology, neural networks, plasticity, neurogenesis*

SEROTONERGIC DEFICITS IN PARKINSON DISEASE

POSTERS: C01.K. DISEASE MECHANISMS, PATHOPHYSIOLOGY: SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS

Rebecca Miller[1], Jennifer O'Shea[1], Annie Winings[1], Erin Franklin[2], Nigel Cairns[3], Richard Perrin[1], Meghan Campbell[1], Joel Perlmutter[1], Paul Kotzbauer[1]
[1]Washington University School of Medicine, Neurology, St. Louis, United States of America, [2]Washington University at Saint Louis, The Charles F. And Joanne Knight Alzheimer Disease Research Center, St. Louis, United States of America, [3]University of Exeter, Neuropathology, Exeter, United Kingdom

Aims: Parkinson disease (PD) is defined by the accumulation of aggregated alpha synuclein (asyn) in Lewy bodies and neurites. As high as 80 percent of PD patients eventually develop dementia, which is associated with neocortical accumulation of asyn. However, neuronal loss and asyn accumulation also occur in multiple subcortical nuclei, including serotonergic neurons in the dorsal raphe nuclei, which have widespread projections to cortical and limbic regions. We utilized measurements of a marker for serotonergic axons to evaluate whether the loss of serotonergic projections to cortical and limbic regions contribute to the development of cognitive impairment in PD.
Methods: In this study, we analyzed markers of serotonergic innervation in 8 different brain regions from PD autopsy cases. For comparison, we also analyzed the same 8 brain regions from control autopsy cases. We used a sandwich ELISA to analyze each brain region for serotonin transporter (SERT), which mediates serotonin reuptake in serotonergic neurons.
Results: We observed significantly lower SERT levels in PD compared to control cases for three of the five cortical regions analyzed. The sum of SERT levels in the five cortical regions inversely correlated with the Clinical Dementia Rating (CDR) sum of boxes score, a measure of global cognitive impairment. These results indicate a role for the loss of serotonergic projections to cortical regions in the development of cognitive impairment in PD. Analysis of relationships between SERT levels and additional neuropsychological measures is ongoing.
Conclusions: These results indicate a role for the loss of serotonergic projections to cortical regions in the development of cognitive impairment in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0937 / #953

Poster Topic: *Theme C: α-Synucleinopathies / C01.l. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

THE PLATELET TRANSCRIPTOME CHANGES DURING THE DEVELOPMENT OF SYNUCLEINOPATHIES STARTING AT PRODROMAL STAGE AND DEFINING PHENOCONVERSION

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Laura Arnaldo[1,2], Jorge Mena[2], Dolores Vilas[3], Ramiro Álvarez[3], Pau Pastor[3], Alex Iranzo[4], Katrin Beyer[1,2]
[1]Universitat Autònoma de Barcelona, Biochemistry, Molecular Biology And Biomedicine, Bellaterra, Spain, [2]Research Institute Germans Trias i Pujol, Neuroscience, Badalona, Spain, [3]Germans Trias i Pujol Research Institute, Neurogenerative Diseases, Badalona, Spain, [4]Hospital Clínic de Barcelona, IDIBAPS, CIBERNED, Neurology Service, Sleep Disorders Center, Barcelona, Spain

Aims: We have studied the platelet miRNome in dementia with Lewy bodies (DLB) compared to controls and found a biosignature of diminished miRNAs. As consequent alterations in the platelet transcriptome can be expected, we analyzed it in DLB, Parkinson disease (PD), as another synucleinopathy, and isolated REM sleep behaviour disorder (IRBD), which is considered a prodromal stage of synucleinopathies. Thus, we aimed to identify the earliest changes associated with the development of synucleinopathies, and changes resulting in the phenoconversion to either DLB or PD.
Methods: Platelets were obtained from patients diagnosed with IRBD, PD or DLB (n=12, each) and 14 control individuals (CTRLs). Total platelet-RNA samples were pooled pairwise. Libraries were prepared using Illumina Stranded Total-RNA Prep-kit and sequenced with a NovaSeq-6000 (Illumina). RNA expression was analyzed using DESeq2-package in R (version 4.3.0), comparing DLB, PD and IRBD with CTRLs, and DLB and PD with IRBD. Pathway analysis was performed with String.
Results: Compared to CTRLs, 4206 genes were expressed differentially in IRBD, 24 in PD and 5970 in DLB platelets. Whereas 1241 of these genes were specifically deregulated in IRBD, 2950 genes were similarly expressed in IRBD and DLB, and 14 genes in IRBD and PD. Only 3 genes were deregulated in all three, IRBD, DLB and PD. Pathway analyses revealed that the most deregulated genes in IRBD were related with immune response. Comparing with IRBD, 137 genes differentially expressed in DLB were mainly associated with the ribosome pathway, and 1064 genes differentially expressed in PD with mitochondrial function.
Conclusions: Altered immune response in IRBD could be an early change during the development of synucleinopathies. Subsequent phenoconversion could be driven by ribosomal dysfunction in DLB and to by mitochondrial dysfunction in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0938 / #2423

Poster Topic: *Theme C: α-Synucleinopathies / C01.l. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

DEFECTIVE PROTEIN O-GLCNACYLATION IN BRAIN AND BLOOD CELLS OF PARKINSON'S DISEASE PATIENTS

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Michele Mario Gennari[1], Vanessa Porrini[1], Andrea Pilotto[2], Marika Vezzoli[1], Edoardo Parrella[1], Marina Benarese[1], Gaia Faustini[1], Francesca Longhena[1], Arianna Bellucci[1], Angelo Antonini[3], Alessandro Padovani[2], Marina Pizzi[1]
[1]University of Brescia, Department Of Molecular And Translational Medicine, Brescia, Italy, [2]University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy, [3]University of Padua, Department Of Neuroscience, Padova, Italy

Aims: NF-kB transcription factors family is a transcriptional regulator of inflammation that contributes to pathological processes associated with neurodegeneration. We previously reported that NF-κB/c-Rel deficient mice develop a late-onset parkinsonism. Recently, we demonstrated that post-mortem brain and peripheral blood mononuclear cells (PBMCs) of PD patients displayed a significant reduction of NF-kB/c-Rel DNA-binding activity when compared with age-matched healthy controls (HC) ones, although no differences in NF-kB/c-Rel protein level were observed. NF-kB/c-Rel DNA-binding activity has been shown to depend on post-translational modifications (PTMs) such as O-linked-β-N-acetylglucosamine (O-GlcNAc), a nutrient-sensing PTM. Interestingly, altered O-GlcNAc glycosylation (O-GlcNAcylation) has been found in multiple neurodegeneration-related pathway.
Methods: PBMCs from PD patients and HC were isolated from blood samples drawn in both fasting and postprandial conditions and NF-kB/c-Rel activity was assessed in protein extracts by customized DNA-based ELISA. The extent of total protein and NF-kB/c-Rel-specific O-GlcNAcylation was evaluated by western blot and co-immunoprecipitation assays, respectively. The impact of O-GlcNAcylation on NF-kB/c-Rel activity was assessed *in vitro* on primary culture of PBMCs from selected PD and HC subjects stimulated with high glucose concentration. Finally, O-GlcNAc transferase (OGT) and hydrolase (OGA) mRNA levels were analysed by RT-qPCR.
Results: NF-kB/c-Rel DNA-binding in PBMCs is enhanced after food intake in HC but not in PD subjects, while only stimulated HC PBMCs displayed an increase in NF-kB/c-Rel DNA-binding activity when compared with not stimulated ones. Fresh and cultured PBMCs from PD patients were characterized by lower levels of total protein and NF-kB/c-Rel-specific O-GlcNAcylation, while higher mRNA expression of OGT and OGA highlights a dysregulated O-GlcNAcylation.
Conclusions: Taken together, these data suggest that NF-kB/c-Rel dysregulation is involved in the pathophysiology of PD, whereas an altered O-GlcNAcylation state could explain the defect in NF-kB/c-Rel DNA-binding activity.

P0939 / #1875

Poster Topic: *Theme C: α-Synucleinopathies / C01.I. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

MICRORNA EXPRESSION PROFILING IN GBA1-PARKINSON'S DISEASE AND DEMENTIA WITH LEWY BODIES BRAINS

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Anthony Klokkaris, Jonathan Mill, Anna Migdalska-Richards
University of Exeter, Department Of Clinical And Biomedical Sciences, Exeter, United Kingdom

Aims: Parkinson's disease (PD), Parkinson's disease dementia (PDD) and Dementia with Lewy bodies (DLB) are heterogeneous disorders and their causes are still incompletely understood. The most common genetic risk factor for PD (*GBA1*), shows incomplete penetrance, with only a minority of carriers developing the disease. Additional factors beyond genetics are likely to play a role and previous work has identified microRNA (miRNA) expression alterations in these disorders. We aim to start investigating whether miRNA expression in the brain varies according to *GBA1* mutation status in PD, PDD and DLB individuals.
Methods: RNA was extracted from the prefrontal cortex of 96 individuals consisting of PD, PDD, DLB and controls, with each group subdivided into individuals with and without *GBA1* mutations. Following reverse transcription to cDNA, the TaqMan OpenArray Human Advanced MicroRNA Panel was used to quantify the expression of 754 miRNAs. Analysis is currently underway, with linear regression being used to identify differentially expressed miRNAs between the different groups.
Results: The OpenArray data is currently being analysed to identify differentially expressed miRNAs, comparing PD, PDD and DLB each to controls as well as the different synucleinopathies to each other and the *GBA* vs non-*GBA* carriers within each group.
Conclusions: This is one of the first miRNA studies to subdivide synucleinopathy individuals by *GBA1* status. The findings will highlight whether miRNA expression in the brain varies according to both disease and *GBA1* mutation status. We have also generated genome-wide DNA methylation data in different brain cells types and SNP data on these samples. We plan to integrate these datasets to identify novel genes involved in these disorders and improve mechanistic understanding.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0940 / #1363

Poster Topic: *Theme C: α-Synucleinopathies / C01.I. Disease Mechanisms, Pathophysiology: Transcriptional & translational regulation, micro RNAs*

SINGLE NUCLEI RNA-SEQUENCING ACROSS DIFFERENT BRAIN REGIONS IN MULTIPLE SYSTEM ATROPHY

POSTERS: C01.L. DISEASE MECHANISMS, PATHOPHYSIOLOGY: TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS

Viktoria Ruf[1], Nils Briel[1,2], Felix Struebing[1,3], Janina Mielke[1], Sigrun Roeber[1], Thomas Arzberger[1,3,4], Otto Windl[1,3], Jochen Herms[1,5,6]
[1]University of Munich, Center For Neuropathology And Prion Research, Faculty Of Medicine, Munich, Germany, [2]University Hospital Zurich, Neurology, Zurich, Switzerland, [3]German Center for Neurodegenerative Diseases (DZNE), Translational Brain Research, München, Germany, [4]University Hospital Munich, Psychiatry And Psychotherapy, München, Germany, [5]German Center for Neurodegenerative Diseases, Translational Brain Research, Munich, Germany, [6]Munich Cluster for Systems Neurology, Synergy, Munich, Germany

Aims: Multiple System Atrophy (MSA) is a devastating rapidly progressive neurodegenerative disease histologically characterized by glial cytoplasmic inclusions (GCIs) of aggregated alpha-Synuclein in Oligodendrocytes, for which no potent symptomatic nor causal treatment is available to date. Since the underlying pathomechanisms and the contribution of the different cell types in the brain to the disease is still only poorly understood, the aim of this study is to characterize the transcriptomic profiles of different cell types in differentially affected brain regions of MSA patients and healthy controls.
Methods: Droplet-based single-nuclei RNA-sequencing and subsequent bioinformatic analysis was performed on approximately 240.000 nuclei isolated from the superior frontal cortex, frontal white matter and occipital white matter of 10 MSA patients and 5 healthy controls. In addition, RNAScope and Western blot analysis as well as immunohistochemical and immunofluorescence stainings were performed.
Results: After preprocessing and quality control, the major six brain cell types were annotated, where no significant differences or shifts in the major cell type composition could be observed. Cell type-wise differential gene expression analysis revealed numerous differentially expressed genes across all three brain regions, which were most abundantly identified in oligodendrocytes, followed by astrocytes and microglia and enriched for genes associated with other neurological and especially neurodegenerative diseases. In parallel, we were able to validate and confirm particular findings on the RNA as well as on the protein level.
Conclusions: Our study presents a large and powerful dataset helping to unravel underlying molecular mechanisms and processes in MSA and providing potential new links for molecular targets for diagnostic and/or therapeutic intervention.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0941 / #1708

Poster Topic: *Theme C: α-Synucleinopathies / C01.m. Disease Mechanisms, Pathophysiology: Protein aggregation, misfolding, chaperones*

A DIGITAL SEED AMPLIFICATION ASSAY FOR QUANTIFYING A-SYNUCLEIN AGGREGATES

POSTERS: C01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Tal Gilboa[1], Zoe Swank[2], David Walt[1]
[1]Harvard Medical School, Wyss Institute, Brookline, United States of America, [2]Brigham and Women's Hospital, Pathology, Boston, United States of America

Aims: This study aimed to to develop digital Seed Amplification Assays (SAAs) to quantify α-synuclein aggregates in patient biofluids and monitor the aggregation process in-vitro.
Methods: We developed digital SAAs by compartmentalizing the aggregation reaction into microwells, droplets, and hydrogel microcapsules. We used pre-formed α-synuclein fibrils as reaction seeds and explored various reaction conditions, including pH, temperature, and salt concentration, to optimize the assay sensitivity. Additionally, we introduced a bead-based digital SAA where pathological seeds were captured with antibody-coated magnetic beads before compartmentalization. We also implemented image analysis techniques to quantify aggregate growth and structural changes in the presence of aggregation inhibitors.
Results: The digital SAAs that we developed were capable of quantifying α-synuclein aggregates at concentrations as low as 4 pg/mL, with the hydrogel microcapsule SAA exhibiting the best sensitivity. The bead-based SAA significantly increased the sample volume that can be analyzed, albeit with a bias toward larger aggregates. We successfully multiplexed the bead-based SAA using different colored beads to detect various α-synuclein aggregate conformations. Furthermore, we characterized the effect of aggregation inhibitors on α-synuclein aggregation using custom image analysis pipeline.
Conclusions: Our study presents a promising advancement in quantifying α-synuclein aggregates in patient biofluids using digital SAAs. These assays offer potential applications in early PD diagnosis, disease staging, and therapeutic screening. The digital SAAs provide a platform for further research into α-synuclein aggregation and its interaction with therapeutic compounds, paving the way for a better understanding of Parkinson's disease and related synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0942 / #290

Poster Topic: *Theme C: α-Synucleinopathies / C01.m. Disease Mechanisms, Pathophysiology: Protein aggregation, misfolding, chaperones*

FICD-MEDIATED AMPYLATION MODULATES ALPHA-SYNUCLEIN PATHOLOGY: NOVEL INSIGHTS INTO PARKINSON´S DISEASE MECHANISM

POSTERS: C01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Aron Koller[1], Laura Hoffmann[2], Martin Weidenfeller[3], Alexandra Bluhm[4], Tobias Becker[2], Verena Schmitt[3], Maike Hartlage-Rübsamen[4], Steffen Roßner[4], Friederike Zunke[3], Stephan Von Hörsten[5], Jürgen Winkler[3], Pavel Kielkowski[2], Wei Xiang[3]
[1]University Hospital Erlangen, Department Of Molecular Neurology, Erlangen, Germany, [2]LMU Munich, Institute Of Chemical Epigenetics Munich (icem), Munich, Germany, [3]University Hospital Erlangen, Molecular Neurology, Erlangen, Germany, [4]University of Leipzig, Paul Flechsig Institute For Brain Research, Leipzig, Germany, [5]University Hospital Erlangen, Department Of Experimental Therapy And Preclinical Experimental Animal Center, Erlangen, Germany

Aims: FICD, the predominant human AMP transferase, is implicated in neuronal integrity targeting key proteins of the lysosome and endoplasmic reticulum (ER). However, the role of FICD-mediated AMPylation in neurodegeneration is unclear. Considering the crucial role of protein dyshomeostasis in Parkinson´s disease (PD), we explored the interplay between the FICD-AMPylation pathway and alpha-synuclein (aSyn) pathology.
Methods: To examine the pathological relevance of FICD, we analyzed human post-mortem PD brains, brains from transgenic PD rats expressing human aSyn (BAC-SNCA), and iPSC-derived dopaminergic (DA)-neurons from a PD patient with SNCA duplication ($SNCA^{Dupl}$). For mechanistic insights, we employed H4 neuroglioma cells overexpressing aSyn and FICD variants, including the constitutively active FICD-E234G variant. To identify AMPylated proteins, we applied click chemistry-based mass spectrometry.
Results: Analysis of human and rat brains unveiled a predominant FICD expression within DA-neurons in the substantia nigra (SN). Notably, in BAC-SNCA rats, FICD levels were decreased in the striatum and SN, but increased in the cortex. This distinct topographical difference suggests that FICD levels are particularly reduced in regions characterized by a severe neuronal and synaptic DA loss. Mass spectrometry-based AMPylation profiling revealed a remarkable increase in AMPylation within $SNCA^{Dupl}$ neurons when compared to isogenic neurons with corrected SNCA dosage. Notably, lysosomal and ER proteins were identified as especially susceptible targets to this modification. Mechanistically, AMPylation of lysosomal cathepsins, key enzymes for aSyn degradation, was associated with reduced peptidase activity in H4 cells overexpressing both aSyn and FICD-E234G. Moreover, FICD-E234G overexpression increased levels of aSyn aggregation and apoptosis.
Conclusions: Our findings provide mechanistic insights into the modulatory role of the FICD-AMPylation pathway in lysosomal and ER impairment, aSyn pathogenesis, and ultimately apoptosis, suggesting pathological significance of this pathway in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0943 / #957

Poster Topic: *Theme C: α-Synucleinopathies / C01.m. Disease Mechanisms, Pathophysiology: Protein aggregation, misfolding, chaperones*

EFFECTS OF INDUCTION OF CHAPERONE-MEDIATED AUTOPHAGY IN THE OLFACTORY SYSTEM IN A TRANSGENIC RAT SYNUCLEINOPATHY MODEL

POSTERS: C01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Zoe Petraki[1], Sofia Dimopoulou[1], Olaf Reiss[2], Maria Xilouri[1], Leonidas Stefanis[1,3]
[1]Biomedical Research Foundation, Academy of Athens, Clinical- Experimental Surgery & Translational Research, Athens, Greece, [2]University of Tuebingen, Institute Of Medical Genetics And Applied Genomics, Tübingen, Germany, [3]National and Kapodistrian University of Athens, School Of Medicine, athens, Greece

Aims: Examine the evolution of α-synuclein (AS) accumulation in the olfactory system of WT human AS overexpressing BAC transgenic rats and investigate whether AAV-mediated overexpression of LAMP2A, the lysosomal transmembrane receptor which represents the rate-limiting step in the Chaperone-Mediated Autophagy (CMA) pathway, could counteract and/or reverse the aberrant AS deposition and its resultant behavioural effects both in early and later stages.
Methods: We used immunohistochemistry as well as Western immunoblotting with various AS antibodies in material derived from various areas within the olfactory system, such as the olfactory bulb (OB), the anterior olfactory nucleus (AON) and the piriform cortex (Piri) of WT and BAC Tg rats. We also performed behavioral experiments assessing olfaction using an odor descrimination task (Habituation/Cross Habituation test). We injected AAV-HA-Lamp2a or AAV-GFP in the AON in 3 or 5 month-old BAC Tg rats and assessed AS pathology and behavioral effects 2 months later in each case.
Results: In BAC transgenic rats there was accumulation of total, human and phosphorylated AS in the OB, AON and Piri in all time points examined (4, 8 and 12 weeks of age) and an olfactory dysfunction at the age of 12 weeks. AAV-HA-Lamp2a injection at both time points led to a modest (around 20%) amelioration of AS accumulation in olfactory regions and a mild improvement of the olfactory behavioral deficit, compared to AAV-GFP-injected rats.
Conclusions: Induction of CMA activity led to partial amelioration of incipient and established synucleinopathy in the olfactory system of hAS BAC Tg rats and a slight amelioration of the olfactory deficit. Relatively limited transduction of the olfactory system may be responsible for the lack of a more pronounced effect.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0944 / #1833

Poster Topic: *Theme C: α-Synucleinopathies / C01.m. Disease Mechanisms, Pathophysiology: Protein aggregation, misfolding, chaperones*

PATHOLOGICAL INTERACTION OF OLIGOMERIC ALPHA-SYNUCLEIN AND TAU IN SYNUCLEINOPATHIES

POSTERS: C01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Sudipta Senapati, Nicha Puangmalai, Nemil Bhatt, Sagar Gaikward, Mauro Montalbano, Cynthia Jerez, Kenya Moore, Rakez Kayed
University of Texas Medical Branch, Department Of Neurology, Galveston, United States of America

Aims: Accumulation of α-synuclein aggregates in large inclusion bodies is a hallmark of synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Several studies indicate that oligomers are the primary toxic species that disrupt neuronal functions and contribute to the progression of disease pathologies. Our lab has previously shown that PD and DLB pathologies exhibit elevated levels of oligomers of both α-synuclein and tau proteins, with these diseases frequently showing a concurrent presence of both proteins. Oligomeric α-synuclein polymorphs, different oligomeric forms exhibiting strain-specific biochemical profiles, and morphologies, interact differentially with tau, resulting in oligomeric tau polymorphs that differ from those associated with fibrillar synuclein. However, little is known about brain-derived α-Syn oligomeric (BDSO) polymorphs, their structural, morphological, and biological characteristics, and their role in tau aggregation, propagation, and polymorphisms.
Methods: We isolated BDSO polymorphs from human synucleinopathy cases of AD (Alzheimer's disease), PD, and DLB using sucrose gradient separation and immunoprecipitation techniques. Size, morphology, and structural characteristics were detected using Cryo-EM and AFM. Proteolytic stability profile of BDSO polymorphs was performed to identify distinct conformation. Interaction of BDSOs and tau in tau aggregation and propagation was investigated using various biochemical, biophysical, immunological, and cell-based assays.
Results: We observed differences in immunological properties, morphology, and sensitivity to proteolysis among the BDSOs. Using molecular and cellular techniques, we found that the tau aggregates cross-seeded with BDSO polymorphs had distinct biochemical and biological properties, indicating the formation of tau polymorphs.
Conclusions: The oligomeric polymorphs of α-Syn can trigger polymorphism in tau, which might play a role in the neurodegeneration associated with synucleinopathy. Therefore, targeting α-Syn or tau polymorphs, or a combination of both, can lead to effective therapeutics for synucleinopathy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0945 / #1843

Poster Topic: *Theme C: α-Synucleinopathies / C01.m. Disease Mechanisms, Pathophysiology: Protein aggregation, misfolding, chaperones*

UNVEILING NEW LINKS BETWEEN TYPE-2 DIABETES AND NEURODEGENERATIVE DISEASES: IDE DYSFUNCTION AS A PROMOTER OF COGNITIVE AND MOTOR IMPAIRMENTS

POSTERS: C01.M. DISEASE MECHANISMS, PATHOPHYSIOLOGY: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Luís Sousa, Rita Machado De Oliveira, Bruna Luzio, Soraia Chôcho, Mariana Guarda, Ana Chegão, Inês Sousa-Lima, Maria João Meneses, Paula Macedo, Hugo Vicente Miranda
NOVA Medical School, Nms Research, Lisbon, Portugal

Aims: The causal association between type-2 diabetes and neurodegenerative diseases is gaining new views and perspectives. Our team is focusing on this relationship, and we recently observed that diabetes drives to the loss of Insulin-Degrading Enzyme (IDE) in the brain. The main aim of this work was to investigate if IDE KO mice develop neurodegenerative outcomes.
Methods: Eight-week-old wild-type (WT) and IDE KO mice were subjected to a 16-week High Fat Diet (HFD) regimen, anestablished model of prediabetes. Metabolic assessments, including glucose and insulin tolerance tests, were conducted at 8 and 22 weeks of age. We evaluated cognitive, motor, and olfactory performance at 23 weeks. Brain tissue was collected at 25 weeks and subdivided into various regions. aSyn and IDE levels were measured.
Results: Our findings revealed dysregulated glucose metabolism in IDE KO mice, exacerbated by HFD. Both WT and IDE KO HFD-fed mice displayed impaired motor performance. Moreover, IDE KO mice exhibit heightened anxiety-like behavior, particularly under HFD conditions. Importantly, IDE protein levels decreased in most brain regions, except the hippocampus, while aSyn levels increased in the hippocampus and cerebellum. Notably, an inverse correlation between aSyn and IDE levels was observed in the cerebellum and brain stem.
Conclusions: This study unveils that the loss of IDE in brain may lead to behavioral dysfunction, a phenotype aggravated by prediabetes. Furthermore, the inverse correlation between aSyn and IDE levels, recapitulating observations in the pancreas of diabetic patients, strengthens a potential link between IDE dysfunction and aSyn pathogenesis. Our findings suggest that IDE failure may trigger neurodegenerative outcomes, leading to the main question if IDE failure compensation could be an important therapeutic target for neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0946 / #2202

Poster Topic: *Theme C: α-Synucleinopathies / C01.n. Disease Mechanisms, Pathophysiology: Metal ions*

SYNCHROTRON X-RAY ANALYSIS OF NANOSCALE METAL DISTRIBUTIONS IN HUMAN OLFACTORY BULB

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METAL IONS

Jake Brooks[1], James Everett[2], Naomi Visanji[3], Christopher Morris[4], Peter Sadler[5], Neil Telling[2], Joanna Collingwood[1]
[1]University of Warwick, School Of Engineering, Coventry, United Kingdom, [2]Keele University, School Of Pharmacy And Bioengineering, Stoke-on-Trent, United Kingdom, [3]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [4]Newcastle University, Newcastle Brain Tissue Resource, Newcastle-upon-Tyne, United Kingdom, [5]University of Warwick, Department Of Chemistry, Coventry, United Kingdom

Aims: Chronic exposure to air pollution is a recognised risk-factor for both Alzheimer's and Parkinson's disease, however the role of the smallest airborne particles is poorly understood. The olfactory bulb is amongst the first brain regions affected by hallmark protein pathology in both disorders, whilst also being vulnerable to the deposition of inhaled metal-rich particulates. The objective of this work was to better characterise nanoscale metal distributions in human olfactory bulb.
Methods: In situ characterisation of nanoscale metal deposits with relation to the surrounding biological milieu requires a unique combination of spatial resolution, sensitivity, and specificity, crucially without disrupting the native tissue chemistry. Synchrotron x-ray spectromicroscopy was used for this purpose. Post-mortem fresh-frozen olfactory bulb tissue from two Parkinson's disease, one Alzheimer's disease and one neurologically healthy control case were resin embedded, microtome-sectioned and examined using nanoscale x-ray fluorescence (XRF) and scanning transmission x-ray microscopy (STXM) at Diamond Light source beamlines I14 and I08, respectively. Careful measures were taken to prevent metal contamination, avoiding any metal contact with tissue during sample preparation.
Results: Multi-element XRF maps revealed evidence of titanium- and chromium-rich sub-micron sized deposits in all four cases studied, as well as nanoscale deposits of iron, nickel, copper, and manganese. STXM analysis revealed iron-rich deposits consistent with the iron oxide mineral maghemite in one Parkinson's case, with additional magnetic characterisation required to confirm iron speciation.
Conclusions: Findings from this work raise intriguing questions regarding the origin of observed metal-rich deposits, particularly for titanium which has no recognized biochemical function, suggesting an environmental origin. Ongoing investigation using advanced chemical imaging techniques will advance crucial understanding of the biochemical environment in human olfactory bulb, with relevance to burgeoning associations between neurodegeneration and air pollution.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0947 / #1949

Poster Topic: *Theme C: α-Synucleinopathies / C01.n. Disease Mechanisms, Pathophysiology: Metal ions*

DISTINCT REGIONAL AND CELLULAR PATTERNS OF IRON DEPOSITION DISTINGUISH CLINICAL SUBTYPES OF MULTIPLE SYSTEM ATROPHY

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METAL IONS

Seojin Lee[1,2], Ivan Martinez-Valbuena[2], Anthony Lang[3], Gabor Kovacs[1,2,4,5]
[1]University of Toronto, Department Of Laboratory Medicine And Pathobiology, Toronto, Canada, [2]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [3]Toronto Western Hospital, University Health Network And The University Of Toronto, Toronto, Canada, [4]University Health Network, Krembil Brain Institute, Toronto, Canada, [5]Toronto Western Hospital, Movement Disorders Clinic, Toronto, Canada

Aims: Multiple system atrophy (MSA) is a primary oligodendroglial synucleinopathy, characterized by pronounced iron deposition in the early-affected subcortical nuclei. Due to the complex involvement of iron in compounding neurodegenerative pathways, the exact role of iron in MSA pathogenesis is yet undefined. For elucidation, evaluation of iron deposition at the cellular level is critically needed, especially in relation to α-synuclein cytopathology.
Methods: Using a unique histology method which combines iron staining with immunohistochemistry, we performed the first cellular characterization of subcortical iron deposition in post-mortem human MSA brains (α-synuclein-affected and -unaffected neurons, oligodendrocytes, astroglia, and microglia), distinctly in MSA-parkinsonian (MSA-P) and cerebellar (MSA-C) subtypes. We examined mRNA expression changes in key iron- and closely related oxygen-homeostatic genes for insight into underlying mechanisms.
Results: MSA-P and MSA-C showed distinct regional patterns of subcortical iron deposition. We identified microglia as key iron-accumulating cell population in MSA-affected brains, which was more distinct in MSA-P. MSA-C showed relatively heterogenous deposition which astroglia showed greater or similar accumulation. Notably, iron deposition was also observed outside cellular bodies and cellular iron deposition minimally associated with α-synuclein cytopathology. Hierarchal cluster analysis revealed pattern of cellular vulnerability to iron accumulation, rather than of α-synuclein pathology load in the subtype-related systems, to distinguish MSA subtypes. Our gene expression analysis further highlighted dysregulation of oxygen homeostasis in the same regions.
Conclusions: Our study reveals cellular vulnerability pattern to iron deposition as a novel pathophysiological feature that distinguishes MSA subtypes, further reinforcing the involvement of iron dysregulation in disease progression at subtype-specific levels. Our findings support the role of iron dysregulation as an early affecter of disease pathology rather than consequent of synuclein pathology. We inform iron chelation therapies at the disease and cellular-specific levels.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0948 / #1630

Poster Topic: *Theme C: α-Synucleinopathies / C01.n. Disease Mechanisms, Pathophysiology: Metal ions*

USING METALLOMIC PROFILES TO DISTINGUISH DEMENTIA WITH LEWY BODIES, PARKINSON'S, AND ALZHEIMER'S DISEASE BRAINS

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METAL IONS

Melissa Scholefield[1], Stephanie Church[1], Jingshu Xu[2], Garth Cooper[1]
[1]University of Manchester, Division Of Cardiovascular Sciences, Manchester, United Kingdom, [2]University of Auckland, School Of Biological Sciences, Auckland, New Zealand

Aims: Dementia with Lewy bodies (DLB) is a neurodegenerative disease characterised by cognitive decline followed by Parkinsonian motor dysfunction. Due to its many clinical and neuropathological similarities with both Alzheimer's disease (AD) and Parkinson's disease dementia (PDD), the correct diagnosis of DLB remains difficult. Previous studies have shown multiple metallomic alterations in AD and PDD brains, including widespread copper deficiencies; here, we aimed to ascertain whether these changes were also present in DLB, or whether metallomic profiles could distinguish post-mortem DLB, AD, and PDD brains.
Methods: Fifteen clinically diagnosed and neuropathologically characterised DLB cases and fifteen controls were obtained from the NIH NeuroBioBank. Using inductively-coupled plasma mass spectrometry, the levels of eight essential metals (Na, Mg, K, Ca, Mn, Fe, Cu, and Zn) and Se were measured across ten regions of the case and control brains. Mann-Whitney U tests were used to determine case-control differences. Results were compared to those obtained in previous analyses of the AD and PDD brain, and PCA plots were used to determine whether metallomic profiles could successfully distinguish DLB from AD and PDD brains.
Results: DLB cases showed several metallomic changes, including Na increases and Cu decreases in five of the ten investigated regions, as well as more localised alterations in Mn, Fe, Ca, and Se. Using data from the cingulate gyrus and middle temporal gyrus, DLB and AD cases could be successfully separated using PCA. DLB and PDD cases could be successfully separated using only data from the primary visual cortex.
Conclusions: Copper deficiencies appear to be widespread throughout the DLB, PDD, and AD brain. However, despite such similarities, DLB can be distinguished from either AD or PDD at post-mortem using their respective metallomic profiles.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0949 / #1147

Poster Topic: *Theme C: α-Synucleinopathies / C01.n. Disease Mechanisms, Pathophysiology: Metal ions*

INVESTIGATING THE INVOLVEMENT OF POLLUTION EXPOSURE AND HEAVY METAL REGULATION PATHWAYS IN COGNITIVE DECLINE IN PARKINSON'S DISEASE.

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METAL IONS

Holly Spence[1], Fergal Waldron[1], Fiona Read[1], Hamish Johnson[2], Jenna Gregory[1]
[1]Institute of Medical Sciences, University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom, [2]School of Geosciences, University of Aberdeen, School Of Geosciences, Aberdeen, United Kingdom

Aims: Air pollution has been identified as an emerging risk factor for both Parkinson's disease and dementia. Due to the established associations between increased brain iron and progression of cognitive symptoms in Parkinson's disease, we hypothesise that heavy metal changes resulting from exposure to ambient air pollution underly the association between air pollution and dementia in Parkinson's disease.
Methods: Here, dwelling based pollution data are compared with post-mortem assessment of heavy metal metabolism, lipid metabolism and inflammation in post-mortem tissue from the motor cortex and putamen of a unique cohort of PD and control subjects stratified into the following groups (i) PD with dementia (n=19), (ii) PD without dementia (n=13), (iii) Controls with dementia (n=2), (iv) controls without dementia (n=9).
Results: Preliminary findings show that comparison of Ferritin and Glutathione peroxidase 4 staining in the motor cortex identifies 3 groups, 1) PD with Dementia, 2) Healthy controls, and 3) PD without dementia - an intermediate group. These results suggest that disruption of the iron-mediated lipid peroxidation pathway is associated with dementia in PD rather than universally observed in PD.
Conclusions: This study characterises the links between air pollution, PD and dementia, evaluating potential mechanisms that underly these relationships to identify potential biomarkers of increased risk of dementia in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0950 / #2212

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

MONITORING PARKINSON'S DISEASE SYMPTOM PROGRESSION WITH WEARABLE DEVICES

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Ro'Ee Gilron, Aiden Arnold, Tiffany Jansen, Witney Chen
Rune Labs, Neuroscience, San Francisco, United States of America

Aims: Assess long term trends in wearable data to characterize symptom progression.
Methods: In 900+ subjects with Parkinson's disease with wearable data, we assessed long term trends in tremor, dyskinesia, gait, vitals, and sleep. For metrics with high daily variability, such as tremor and dyskinesia, we used windowing functions and statistical aggregation to assess changes across time. We applied an algorithm to identify statistical changes in metric trajectory, which we compared against known therapeutic interventions such as medication changes or deep brain stimulation programming updates. Further, we applied a normative modeling approach to identify patient-specific deviations in the progression rate of different symptoms. In a subcohort with data prior to disease diagnosis, we explored wearable data trends during the prodromal period.
Results: We found highly variable trends across subjects, including instances of worsening symptoms and improving symptoms. In patients with worsening trends, increases in double support time and decreases in walking speed and step length were observed. Longitudinal tracking of sleep metrics showed that decreasing sleep time was also associated with increases in sleep fragmentation. Normative modeling provides a structure to help distinguish between the effects of clinical interventions and symptom progression across multiple modalities.
Conclusions: Worsening symptoms can be identified and characterized with wearable devices, reflecting inadequate therapeutic maintenance and/or worsening disease. Conversely, subjects with improved metrics may indicate good symptom management. Data-driven approaches for assessing longitudinal symptom change and how individual patients deviate from one another in progression patterns may yield insights on disease progression phenotypes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0951 / #2340

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

MIRNA AND GLYCOSPHINGOLIPIDS AS A PATTERN SIGNATURE OF PARKINSON'S DISEASE

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Bilal El Waly[1], Adrien Chabert[1], Delphine Hardy[1], Benoit Quentin[1], Esther Steidl[2], Philippe Poindron[2], Alexandre Henriques[2], Noëlle Callizot[2]
[1]Vivo, Neuro-sys, Gardanne, France, [2]Neuro-sys SAS, Neuropharmacology Dpt, Gardanne, France

Aims: Parkinson's disease (PD) is characterized by α-synuclein (α-syn) aggregates, mitochondrial dysfunction, and lysosomal impairment. We recently highlighted the importance of aging and lysosomal defects in the sensitivity of dopaminergic neurons to α-syn toxicity in an aged mouse model of Parkinson disease injured with α-syn protofibrils (PFF) and conduritol-B-epoxide (CBE, an irreversible inhibitor of GCase). In this model mimicking main PD features, we monitored miRNA and complex lipids, at different disease stages in order to establish pattern signature of the disease.
Methods: RT-qPCR was used to assess miRNA expression profiles in the brain of young mice, aged mice, and aged α-syn/CBE mice. LC-MS/MS was used to quantify circulating complex glycosphingolipids, known markers of lysosomal dysfunction.
Results: We identified a panel of several miRNAs in young versus aged mice, and versus α-syn/CBE mice changing over the time. Dysregulated miRNAs are involved in lysosomal functions, α-syn expression, neuronal survival, mitochondrial dysfunction, oxidative stress, and inflammation, all critical pathways implicated in PD. Simultaneously, lipidomic profiling revealed parallel accumulation of glucosylsphingosine in the PD model, emphasizing lipid dysregulation. We extended our analysis to plasma and CSF, enabling the identification of circulating miRNAs biomarkers for disease monitoring.
Conclusions: In conclusion, our study unveils a multimodal approach to understanding PD and following disease progression, by monitoring miRNAs in tissues and fluids and lipid biomarkers. miRNAs, pivotal post-transcriptional regulators, are informative on the regulation of specific pathways, illuminating the multifaceted pathophysiology of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0952 / #2126

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

CAROTID SINUS NERVE ABLATION MITIGATES NEURODEGENERATIVE OUTCOMES INDUCED BY DYSMETABOLISM IN A PREDIABETES RAT MODEL

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Inês Ferreira De Almeida, Adriana Capucho, Ana Chegão, Fátima Martins, Joana Sacramento, Sílvia Vilares Conde, Hugo Vicente Miranda
NOVA Medical School, Nms Research, Lisboa, Portugal

Aims: The carotid bodies (CBs) were recently described as metabolic sensors. While in type-2 diabetes mellitus (T2D), this organ is hyperactive, its ablation was demonstrated to lessen T2D outcomes. Knowing the association between T2D and neurodegenerative diseases, we aim to investigate if blocking CBs activity via resection of the carotid sinus nerve (CSN), its sensitive nerve, can prevent neurodegenerative outcomes induced by dysmetabolism in a prediabetic rat model.
Methods: Male Wistar rats aged three months were fed a normal-chow (NC) or a high-fat high-sucrose diet (HFHSu) for 15 weeks, followed by random assignment to CSN resection or sham surgery. After 22 weeks, proteins from the frontal cortex and hippocampus were analysed using Western blot to assess insulin resistance, neurodegeneration, inflammation, and synaptic markers.
Results: HFHSu diet promoted a decrease in Insulin receptor (IR) and Protein kinase B (AKT) levels in the cortex. In the prefrontal cortex, HFHSu animals exhibit a significant increase in the levels of the glutamate receptor, N-methyl-D-aspartate (NMDA) receptor 2, alpha-synuclein (αSyn), and β-Amyloid precursor protein (APP). Interestingly, in HFHSu-CSN resected animals, the increase of NMDA2, αSyn and APP was ameliorated.
Conclusions: Our findings suggest that HFHSu contributes to a brain insulin-resistance phenotype and to the accumulation of αSyn and APP, which are proteins associated with neurodegenerative diseases such as Parkinson's and Alzheimer's. Significantly, CSN ablation can reduce the levels of αSyn and APP, thus suggesting that the CBs can be therapeutic targets for mitigating neurodegenerative outcomes induced by dysmetabolic conditions. We consider exploring the underlying molecular mechanisms connecting CBs and neurodegeneration essential. Moreover, we aim to evaluate the long-term outcomes and the potential therapeutic interventions stemming from CB modulation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0953 / #658

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

RE-WEIGHTING MDS-UPDRS MOTOR ITEMS FOR OPTIMAL SENSITIVITY TO PARKINSON'S DISEASE PROGRESSION IN UNTREATED PATIENTS USING PARKINSON'S PROGRESSION MARKERS INITIATIVE DATA

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Gil L'Italien[1], Sam Dickson[2], Basia Rogula[3], Jordan Dubow[4], Nick Kozauer[5], Lauren Powell[3], Michele Potashman[1], Kim Crimin[6], Patrick O'Keefe[2], Ellen Korol[3], Madeline Crabtree[3], Fernanda Nagase[3], Vlad Coric[7], Suzanne Hendrix[8]
[1]Biohaven Pharmaceuticals, Inc, Clinical Outcomes Assessments And Health Economics, New Haven, United States of America, [2]Pentara Corporation, Statistics, Millcreek, United States of America, [3]Broadstreet HEOR, Health Economics & Outcomes Research, Vancouver, Canada, [4]Clintrex, LLC, Chief Medical Officer, Sarasota, United States of America, [5]Biohaven Pharmaceuticals, Inc, Clinical Development & Regulatory Strategy, New Haven, United States of America, [6]Biohaven Pharmaceuticals, Inc, Biostatistics, New Haven, United States of America, [7]Biohaven Pharmaceuticals, Inc, Ceo, New Haven, United States of America, [8]Pentara Corporation, Ceo, Millcreek, United States of America

Aims: As a complex degenerative disease, Parkinson's disease (PD) affects motor abilities across diverse domains, even prior to initiation of dopaminergic therapy (DT). This work demonstrates how composite scores (CS) consisting of re-weighted combinations of the items from MDS-UPDRS Parts II and III can better detect meaningful changes in motor progression.
Methods: This study analyzed the Parkinson's Progression Markers Initiative MDS-UPDRS data Parts II and III in subjects with confirmed PD naïve to DT. Patients were censored from the analysis once DT was initiated. The sensitivity of individual items to disease progression was assessed using partial least square regression. Selected items were weighted using the model coefficients and summed to create the CS. CS responsiveness to change was assessed using a 1-year mean-to-standard-deviation ratio (MSDR).
Results: CS were generated for untreated subjects (n=428) across items from Parts II and III individually, and as a combined motor composite score (MCS). The three most responsive items (with their combined weights) were: turning in bed, getting out of bed/car/chair, and tremor (45%) for Part II, and leg agility (left) and rest tremor amplitude – left and right (34%) for Part III. The MSDRs increased from 0.5431 to 0.5647, and 0.6341 to 0.7040, which increases power 3% and 8%, respectively. Items from Part II and III contributed to 37.4% and 62.6% of the weighed MCS. Similar items were retained in the MCS as in the individual CSs, and the MSDR increased from 0.7615 to 0.8591, increasing power 8%.
Conclusions: Endpoints derived from the CS reflecting items from combined domains can measure clinically meaningful progression of motor symptoms and the impacts with greater sensitivity compared to using the totality of items from existing tools.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0954 / #2347

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

EXPLORING THE POTENTIAL OF POLYPHENOL METABOLITES IN A PARKINSON'S DISEASE BRAIN-CHIP MODEL

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Inês Figueira[1], Inês Silva[1], Daniela Marques[1], Rafael Carecho[1,2], Alexander Mosig[3], Cláudia Nunes Dos Santos[1,2,4]
[1]NOVA Medical School, Molecular Nutrition And Health Lab, Lisboa, Portugal, [2]ITQB, Itqb, Oeiras, Portugal, [3]Center for Sepsis Control and Care, Jena University Hospital, Institute Of Biochemistry Ii, Jena, Germany, [4]iBET, Ibet, Oeiras, Portugal

Aims: Polyphenols, abundant in fruits and vegetables, have emerged as pleiotropic compounds against PD. We identified gut-derived polyphenol metabolites (PMs) as abundant in the bloodstream [1], capable of crossing the blood-brain barrier (BBB), protective against neurodegeneration and neuroinflammation [2], particularly in a 3D neuronal model [3]. However, PMs' mechanisms in a comprehensive/translatable model of the full brain for Parkinson's disease (PD) have never been explored. By taking advantage of a new microphysiological system (MPS) of a brain-on-a-chip, we will disclose PMs' molecular potential against PD.
Methods: The new two-compartment model will employ a dopaminergic insult applied into human brain microvascular endothelial cells (HBMEC), at the blood site, and dopaminergic neurons (LUHMES) [3], with astrocytes (HASTR/ci35) and microglia (HMC3), at the brain site. PMs (individually or as a mixture) will be infused from the blood site and alterations in the different cell types monitored.
Results: Full system differentiation status will be unveiled. The response of brain cells to the dopaminergic neurotoxicant in the MPS will be disclosed. PMs/PMs mixture role in tackling PD-related hallmarks will be uncovered, including their benefits in BBB impairment, dopaminergic cell death, oxidative stress, neuroinflammation, cell crosstalk, and a-synuclein phosphorylation.
Conclusions: In the end, we hope to provide physiologically relevant insights for the nutritional management of PD by unveiling PMs' physiologic mode of action in an avant-gard cell model of the pathology, bypassing the need for animal experimentation. **References:** 1.Pimpão BrJNutr 2015; 2.Figueira SciRep 2017; 3.Carecho MolNutrFoodRes 2022 **Acknowledgments:** to EU, for ERC - Grant No. 804229; to FCT, for financial support of R.C. (PD/BD/135492/2018), D.M. (2021.05505.BD), I.F. (2022.00151.CEECIND) through PeX – 2022.02127.PTDC (PERCEPT) and through the R&D unit iNOVA4Health (LISBOA-01-0145-FEDER-007344; UIDB/04462/2020), and LS4FUTURE Associated Laboratory (LA/P/0087/2020).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0955 / #1285

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

INVESTIGATING THE GENERATION OF ALPHA-SYNUCLEIN PRE-FORMED FIBRILS USING THIOFLAVIN T STAINING, FLUORESCENCE MICROSCOPY AND MOTOR SKILLS EVALUATION

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Rayanne Guimarães, Miguel Mesquita, Márcia Renata Mortari
University of Brasília, Department Of Physiology, Brasília, Brazil

Aims: This work aims to compare and describe a protocol for the generation of alpha-synuclein pre-formed fibrils (PFFs) from monomers, establish a cost-effective pre-infusion quality control methodology for the identification of successful PFFs generation and report early deficits in the motor behavior of mice after PFFs administration into striatum.
Methods: All procedures were approved by local ethics committee (CONCEA/CEUA-UnB nº23106.124642/2021-53). Monomers (1.25 mg/ml) were incubated at 37 ºC, shaking at 400 or 1000 rpm for 7 days, followed by sonication. Thioflavin T (ThT) staining and epifluorescence microscopy were used to confirmed fibril presence. Transmission electron microscopy (TEM) validated ThT staining and epifluorescence microscopy as pre-surgery quality control. PD models were established by intracerebral PFF injection (n=8), control group received vehicle (n=4). Motor skills were assessed through weekly rotarod tests (4 to 40 rpm in 300 seconds).
Results: The shaking process at 1000 rpm was shown to be more effective for the formation of PFFs. Images obtained using epifluorescence microscopy point to the presence of fluorescent bodies, indicating the interaction between ThT and amyloid-like fibrils. TEM results provide evidence for the presence of PFFs. PFFs decreased latency to fall 5 weeks ($p=0.0005$ vs. PFFs pre-surgery) and 8 weeks ($p<0.005$ vs. vehicle) after infusion.
Conclusions: ThT assay and visualization of fibrils using epifluorescence microscopy can be used as quality control to prove the presence of aSYN PFFs before infusion into rodent brains for the generation of an animal model of PD. PFFs are capable of causing early motor deficits in mice 5 weeks after administration. This study offers valuable insights into PD modeling and assessment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0956 / #280

Poster Topic: *Theme C: α-Synucleinopathies / C01.n. Disease Mechanisms, Pathophysiology: Metal ions*

HEPATIC COPPER OVERLOAD INDUCING TAUOPATHY AND SYNUCLEINOPATHY VIA OVEREXPRESSION OF MITOCHONDRIAL LIPOYLTRANSFERASE 1 IN NEURODEGENERATIVE LIVER-BRAIN AXIS

POSTERS: C01.N. DISEASE MECHANISMS, PATHOPHYSIOLOGY: METAL IONS

Van Thi Ai Tran[1,2], Minsun Song[3,4], Soongweon Hong[3,4], Yen N. Diep[1,2,5], Luke P. Lee[1,2,3,4], Hansang Cho[1,2,5]
[1]Sungkyunkwan University, Department Of Biophysics, Suwon, Korea, Republic of, [2]Sungkyunkwan University, Institute Of Quantum Biophysics, Suwon, Korea, Republic of, [3]Brigham's Women Hospital, Division Of Engineering In Medicine And Renal Division, Department Of Medicine, Boston, United States of America, [4]Harvard University, Harvard Medical School, Boston, United States of America, [5]Sungkyunkwan University, Department Of Intelligent Precision Healthcare Convergence, Suwon, Korea, Republic of

Aims: Hepatolenticular degeneration in which copper metabolic dysfunction leads to copper accumulation in the midbrain region, which causes neurological manifestations. However, how excess copper damages the midbrain is unknown. This study aimed to elucidate the intracellular mechanisms by which overload copper-induced mitochondrial lipoylation in the tricarboxylic acid cycle, which promotes both of tauopathy and synucleinopathy.
Methods: In this study, we used human embryonic stem cell-derived midbrain organoids for in vitro modeling of copper accumulation-induced degenerative liver-brain axis. Comprehensive genetic and proteomic analyses of cellular RNA and exosomal miRNA enable mechanism exploration and biomarker discovery.
Results: We observed that copper-stimulation reduced the viability of neurons and astrocytes evidenced with MAP2 and tyrosine hydroxylase by 20% while promoting the reactivity of astrocytes evidenced with GFAP by 25%. Also, we elucidated the upregulation of neurotoxic proteins, including phosphorylated alpha-synuclein and phosphorylated tau by 25%, in addition to reducing synaptic function evidenced with synapsin I by 20% upon copper-stimulation. Then, we discovered the upregulation of ferredoxin-1 (FDX1) and lipoyltransferase-1 (LIPT1) as a mediator of copper-induced mitochondrial lipoylation promoting neurodegeneration. In addition, we confirmed that copper-stimulation induces neurodegenerative (APP, MAPT, SNCA) and neuroinflammatory genes (NF-kB and mTOR) in both human cell and exosome samples.
Conclusions: Overall, this study clarifies the contribution of copper to neurodegenerative diseases suggesting a potential for future research and therapeutic development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0957 / #261

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

A NEW PARKINSON'S DISEASE MODEL - INTRACOLONIC ROTENONE CAUSES ALTERATIONS OF GUT MICROBIOTA AND INDUCES A-SYNUCLEIN AGGREGATION IN THE BRAIN

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Yoon-Seong Kim, Minkyung Song
Robert Wood Johnson Medical School at Rutgers, Neurology, Piscataway, United States of America

Aims: This study aimed to establish the Gut-Brain model of Parkinson's disease by inducing α-synuclein pathology and microbiome changes in the gut by intracolonic gavage of rotenone for 6 weeks.
Methods: C57B6 mice were treated with rotenone (30 mg/kg, 100-150ul) or vehicle (4 % carboxymethyl cellulose) by intracolonic gavage every day for 6 weeks. Fecal samples were collected before, immediately after, and 28 weeks after rotenone or vehicle administrations. 28 weeks after rotenone or vehicle injection, a rotarod test was carried out. All mice were sacrificed the next day, and the proximal colon and brain were extracted for the analysis of α-synuclein pathology, gut inflammation, and neurodegeneration. Fecal microbiomes were analyzed using 16S rRNA sequencing.
Results: We observed that intracolonic administration of rotenone induced impaired intestinal barrier and gut inflammation. α-synuclein expression and pS129 were increased in the gut mucosal layer and myenteric plexus, respectively, right after 6 weeks of rotenone administration and remained until 28 weeks. α-synuclein aggregations were limited in the DMV region at 12 weeks after the last rotenone administration, but it was significantly increased in the SN after 28 weeks, which suggests that α-synuclein pathology in the gut eventually leads to dopaminergic neuronal death in the SN. The motor deficit was observed in the rotenone-treated group. The changes in gut microbiome persist even 28 weeks after rotenone administration. Firmicutes/Bacteroidetes ratio was significantly increased by rotenone and a negative correlation between Lactobacillus and the number of dopaminergic neurons was found.
Conclusions: Our novel gut-brain PD model successfully demonstrates that α-synuclein pathology originated in the colon propagates to the brain, leading to dopaminergic neuronal loss in the SN, and dysbiosis of the gut microbiota might contribute to this process.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0958 / #1736

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

COGNITIVE PROFILES AT PRESENTATION AND SUBSEQUENT COGNITIVE DECLINE IN PARKINSON'S DISEASE

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Saira Mirza[1], Sarah Duff-Canning[2], Mark Mapstone[3], Susan Fox[4], Mario Masellis[5], Connie Marras[6]
[1]Sunnybrook Research Institute, Medicine, Toronto, Canada, [2]University of Toronto, Psychology, Toronto, Canada, [3]University of California, Department Of Neurology, Institute For Memory Impairments And Neurological, Irvine, United States of America, [4]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [5]Sunnybrook Research Institute, Hurvitz Brain Sciences Program, Toronto, Canada, [6]Toronto Western Hospital, Krembil Research Institute, Toronto, Canada

Aims: To determine cognitive profiles in Parkinson's disease and study the relationship between baseline cognitive profiles and subsequent cognitive decline in two cohorts
Methods: We included PD patients with or without cognitive impairment(CI) from the Toronto Western Hospital(TWH) and Ontario Neurodegenerative Diseases Research Initiative(ONDRI) cohorts [TWH cohort:138 persons followed up annually for 5 years;ONDRI:96 persons with an annual follow-up of 2 years;combined N=234]. In both cohorts, a comprehensive neuropsychological test battery was administered at all visits; PD-MCI was diagnosed by MDS Task Force Level 2 criteria. Eight neuropsychological tests(equivalent across cohorts) assessing attention and processing speed, executive functions, memory, language, and visuospatial function were used to create cognitive profiles at baseline by cluster analyses. We calculated a global cognitive z-score at all visits by averaging z-scores for all tests. Cognitive decline was determined by change in global cognitive z-score using a linear mixed-effects model, including age, sex, education, time from baseline(TFB), interaction between cognitive profiles and TFB, and random intercept clustered over subjects
Results: Sample demographics: Mean age=69.4±6 years, mean education=15.6±2.8 years, women=30%. We identified 4 cognitive profiles at baseline: 1.Normal cognition(n=108), 2.Lower memory score(n=47), 3.Lower memory and executive function scores(n=59), and 4.Global CI(n=20). Compared to cluster 1, all clusters had lower global scores at baseline, and showed greater cognitive decline over time (β=difference in slope)(cluster 2: = β-0.4, 95% CI=-0.5,-0.2; cluster 3: β= -0.96, 95% CI=-1.1,-0.8; cluster 4: β=-2.0, 95% CI: -2.3,-1.7). Cluster 3(β=-0.6, 95% CI=-0.8,-0.4) and 4(β=-1.6, 95%CI=-1.9,-1.3) showed greater decline than cluster 2 and cluster 4 showed a greater decline than cluster 3(β=-1.0, 95% CI=-1.3,-0.7).
Conclusions: Identification of cognitive profiles in PD patients may help predict their cognitive trajectory and guide therapeutic interventions to improve the natural pathologic course.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0959 / #2093

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

DOSE-DEPENDENT EFFECT OF ALPHA-SYNUCLEIN OVEREXPRESSION ON DOPAMINERGIC CELLS

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Miraj Ud Din Momand, Karolína Albertusová, Diana Mjartinová, Ľubica Fialová, Dominika Fričová
Slovak Academy of Sciences, Institute Of Neuroimmunology, Bratislava, Slovak Republic

Aims: Despite the identification of alpha-synuclein (a-Syn) as a pivotal player in Parkinosn's disease (PD), the precise molecular mechanism that leads to its aggregation and related neurodegeneration remains a mystery. In this study, we aim to create a novel approach to understanding the complexity of a-Syn-induced pathological changes at the cellular level in the ReNVM neural progenitor cells, that can readily differentiate into dopaminergic neurons. Additionally, we aim to analyze in greater detail intracellular changes and differences in extracellular signaling induced by a-Syn in a dosage-dependent manner.
Methods: We created novel neuronal cell models of PD in ReNVM cells background, stably overexpressing GFP-tagged a-Syn either wild type (WT) or its A53T mutant version via lentivirus transduction. Cells were then sorted into three sub-populations based on GFP expression and analyzed for a-Syn levels and intracellular distribution comparing sub-populations among themselves, between WT and A53T as well as with cells not overexpressing a-Syn. We then qualitatively profiled various species of a-Syn including its phosphorylated or aggregated forms along with investigating the effects on cell viability, and mitochondrial morphology and function. Excitingly, we started to investigate the intercellular spreading of a-Syn-related signaling through extracellular vesicles (EVs) isolated from these cell models.
Results: We successfully characterized novel cellular models for the investigation of the role of a-Syn. Our study revealed differences in cellular responses based on a-Syn levels, along with comparative investigation of the effects of WT and A53T a-Syn overexpression. Moreover, we analyzed the differences in the spreading of pathological a-Syn signals mediated by EVs depending on the a-Syn level.
Conclusions: Findings from this study clarify the complex cellular processes that underlie a-Syn-related pathologies in PD. This study was supported by: APVV-20-0331, SASPRO 2_1085/01/02, ICGEB CRP/SVK22-04_EC, APVV-20-0447

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0960 / #1540

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

NF-KB/C-REL DEFICIENT MOUSE AS A MODEL OF BODY-FIRST PARKINSON'S DISEASE

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Vanessa Porrini, Edoardo Parrella, Michele Mario Gennari, Marina Benarese, Giulia Abate, Mariachiara Pucci, Daniela Uberti, Arianna Bellucci, Marina Pizzi
University of Brescia, Department Of Molecular And Translational Medicine, Brescia, Italy

Aims: A growing body of evidence links Parkinson's disease (PD) to the gastrointestinal tract. Borghammer and colleagues proposed that PD pathology first appears in the enteric nervous system and spreads to the brain. According to this theory, the vagal nerve plays a crucial role in gut-to-brain propagation of alpha-synuclein (AS) pathology. The resection of gastric vagal nerve (vagotomy) decreases PD pathology in animal models. Finally, epidemiological studies show that vagotomy is associated with a decreased risk for PD in humans. NF-κB/c-Rel deficient (c-rel$^{-/-}$) mice develop a progressive PD-like phenotype, presenting both prodromal and motor symptoms as well as nigrostriatal dopaminergic neurons degeneration and progressive caudo-rostral brain deposition of AS. Aims of this study were: 1) the characterization of intestinal pathology and 2) the role of vagal nerve in the gut-to-brain spreading of AS, by assessing monolateral vagotomy (hemivagotomy), in c-rel$^{-/-}$ mice.
Methods: Progressive intestinal pathology as well as hemivagotomy effect on AS spreading were evaluated by confocal microscopy, biochemical analysis and behavioral tests in c-rel$^{-/-}$ and wt mice from 2 to 12 months of age.
Results: c-rel$^{-/-}$ mice display early and progressive accumulation of both native and phosphorylated AS in the myenteric plexus of proximal colon, accompanied by an increase in oxidative stress and inflammation markers. Moreover, AS deposition was prevented in the ipsilateral side of the dorsal motor nucleus of the vagus in hemivagotomized c-rel$^{-/-}$ mice at 12 months of age. However, hemivagotomy did not rescue anxiety-like behavior and motor deficits.
Conclusions: Taken together, these results indicate that the c-rel$^{-/-}$ mice develop a progressive PD pathology at intestinal levels. Furthermore, the vagal nerve is involved in the gut-to-brain spreading of AS in this PD mouse model.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0961 / #1010

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

MODELING OF PARKINSON'S DISEASE PROGRESSION AND IMPACT OF ENDPOINT SELECTION ON PROBABILITY OF STUDY SUCCESS

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Benjamin Ribba[1], Tanya Simuni[2], Ken Marek[3], Cheikh Diack[1], Philippe Pierrillas[1], Annabelle Monnet[4], Benedicte Ricci[1], Tania Nikolcheva[5], Gennaro Pagano[1]
[1]F. Hoffmann La Roche Ltd., Pharma Research And Early Development, Basel, Switzerland, [2]Northwestern University, Neurology, Chicago, United States of America, [3]Institute for Neurodegenerative Disorders, N/a, New Haven, United States of America, [4]F. Hoffmann-La Roche Ltd., Product Development Data Sciences, Data And Statistical Sciences, Basel, Switzerland, [5]F. Hoffmann-La Roche Ltd., Product Development Neuroscience, Basel, Switzerland

Aims: To characterize the natural history of Parkinson' disease (PD) progression and evaluate the impact of clinical endpoint selection on the probability of success of clinical trials for disease-modifying treatments in PD.
Methods: Longitudinal data from 401 individuals with early-stage PD from the Parkinson's Progression Markers Initiative (PPMI) were used to characterize disease progression of non-motor aspects of experiences of daily living (MDS-UPDRS part I), motor aspects of experiences of daily living (MDS-UPDRS part II), and motor signs (MDS-UPDRS part III). Further, MDS-UPDRS progression before PD diagnosis was assessed using PPMI prodromal cohort data (65 subjects) to estimate the lag time between first motor signs onset (MDS-UPDRS part III) and development of functional impairment (MDS-UPDRS part II). A simulation framework was used to calculate the probabilities of study success with either MDS-UPDRS part III or part II as study endpoints.
Results: For early-stage PD, estimated increase in MDS-UPDRS parts I, II and III was approximately 1, 1 and 3 points per year, respectively. Backward extrapolation of MDS-UPDRS scores progression leveraging the prodromal cohort showed that, in the earliest stage of the disease, part III worsening precedes part II by about 5 years at the cohort level. Finally, the probability of success of a clinical trial, when using part II as primary endpoint, was found to be consistently lower than when using part III despite assuming the same relative disease-modifying effect on both parts.
Conclusions: Leveraging longitudinal data contributes to a better understanding of disease progression. Such a framework can support the clinical development of therapeutic strategies for PD patients by identifying endpoints that effectively measure the progression of PD and the potential clinically meaningful treatment effect of novel therapeutics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0962 / #1269

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

REGULATORY SCIENCE AND GLOBAL MULTISTAKEHOLDER COLLABORATIONS ARE KEY TO ENABLING BIOLOGICAL STAGING OF NEURONAL ALPHA-SYNUCLEIN DISEASE: PERSPECTIVES FROM CRITICAL PATH INSTITUTE

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Diane Stephenson[1], Martijn Müller[1], Klaus Romero[1], Joseph Hendrik[1], Angelica Asis[2], Clyde Campbell[3], David Dexter[4], Keith Fargo[5], Catherine Kopil[6], Karen Lee[7], Helen Matthews[8], Angela Taylor[9], Yuge Xiao[10], Billy Dunn[10], Ken Marek[11], Tanya Simuni[12]
[1]Critical Path Institute, N/a, Tuscon, United States of America, [2]parkinson's canada, Research, Mississauga, Canada, [3]Shake it up Australia, Patient Advocacy, NSW, Australia, [4]Parkinson's UK, Research, London, United Kingdom, [5]Lewy Body Dementia Association, Research, naperville, United States of America, [6]Michael J Fox Foundation, Research Partnerships, New York, United States of America, [7]parkinson's canada, Research, toronto, Canada, [8]Cure Parkinson's, Research, London, United Kingdom, [9]Lew Body Dementia Association, Research, Lilburn, United States of America, [10]Michael J. Fox Foundation, N/a, Hagerstown, United States of America, [11]Institute for Neurodegenerative Disorders, N/a, New Haven, United States of America, [12]Northwestern University, Neurology, Chicago, United States of America

Aims: Biological staging of disease represents a paradigm shift in catalyzing drug development by targeting earlier stages of the disease prior to onset of clinical symptoms. A novel biological staging framework for Neuronal alpha-Synuclein Disease (NSD) grounded in innovative advances in biomarkers and genetics is highlighted.
Methods: Regulatory agencies recommend that public private partnerships comprised of multiple stakeholders are key to advancing data driven translational tools that focus on underlying pathophysiology of the disease. Examples of biological staging frameworks with profound impact on drug development focused on early intervention include Type 1 Diabetes and Huntington's disease. The experience of Critical Path Institute as a neutral convener was key in these examples. A data driven iterative path to advancing a biological staging framework for NSD was initiated by regulatory agency leaders in 2022.
Results: Critical success factors for ensuring efficient data driven advancement of biological staging of disease are the ability to appropriately stage the disease process through the integration of translational platforms, clinical outcome assessment tools, biomarkers, genetics and quantitative solutions to optimize trial design. A series of iterative multistakeholder meetings took place in 2022-2023 to review emerging scientific advances within the Parkinson's disease (PD) and dementia with Lewy bodies (DLB) fields aimed at establishing biological definitions of disease and a new biological staging paradigm for clinical trials. The role of public private partnerships has been key in all cases to advancing the evolution and adoption of biological staging that is inclusive to regulatory agencies and has emphasis on patient centricity.
Conclusions: The precompetitive global collaboration framework pioneered by multiple stakeholders is primed to catalyze the path to the generation of disease modifying therapies targeting neuronal synucleinopathies with true promise for prevention on the horizon.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0963 / #2317

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

TO EXPLORE THE THERAPEUTIC EFFECT AND MOLECULAR MECHANISM OF ELECTROACUPUNCTURE COMBINED WITH WUZI YANZONG PILL ON PD BASED ON BDNF/TRKB/CREB

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Duo Jia, Yize Tang, Hui-Jie Fan, Si Xiang Niu, Yanrong Li, Ruirui Sun, Liran Wang, Lulu He, Cungen Ma, Xu Wang, Zhi Chai
shanxi university of chinese medicine, Shanxi University Of Chinese Medicine, shanxi province, China

Aims: Parkinson's disease is a common neurodegenerative disease in the elderly, with high disabilities. Levodopa supplement therapy is the main method in the clinic, but its side effects are large. Our previous study found that Wuzi Yanzong Pills (WYP) has a good prevention and treatment effect on PD, and its treatment mechanism is probably related to the regulation of BDNF signaling pathway. Recent studies have reported that electroacupuncture (EA) can also play a protective role in PD by regulating BDNF signaling molecules. We hypothesized that EA combined with WYP may play a synergistic effect on PD treatment by co-regulating BDNF signaling pathway.
Methods: C57BL/6 male mice were randomly divided into control group, model group, ANA-12 (Trk B antagonist) group, WYP group, WYP+ANA-12 group, EA group, EA+ANA-12 group, WYP+EA group, WYP+EA +ANA-12 group. The PD model of mice was established by MPTP (except normal group and ANA-12 group). At the same time, oral administration of all WYP was carried out twice a day for 14 consecutive days, EA stimulation at Baihui (GV20) and Taixi (KI3) was applied to PD mouse in all EA groups for 2 weeks, intraperitoneal injection ANA-12 (0.5mg/kg) to all ANA-12 groups. Mouse motor function was evaluated by gait, stick climbing, suspension and open field test. The expression levels of tyrosine hydroxylase (TH) was determined by immunofluorescence analysis. The expression levels of TH, BDNF, Trk B, CREB was determined by Western Blot.
Results: Following 2 weeks of WYP, EA and WYP+EP treatment, the abnormal behavioral impairment induced by MPTP was alleviated, but ANA-12 can reverse the protective effects.
Conclusions: WYP combined with EA play a synergistic effect on PD treatment by co-regulating BDNF signaling pathway.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0964 / #2297

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

PARKINSON'S DISEASE-RELATED CHANGES IN OLIGODENDROGLIAL SUBPOPULATIONS

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Eun-Jin Bae, Dayana Pérez-Acuña, Ka Hyun Rhee, Seung-Jae Lee
Seoul National University, Biomedical Sciences, Seoul, Korea, Republic of

Aims: A specific loss of dopaminergic neurons is a hallmark of Parkinson's disease (PD). Few studies have looked at changes in oligodendroglia, despite the fact that the majority of PD research to date has concentrated on neurons and, to some extent, glia.
Methods: Here, we investigated the heterogeneity of oligodendrocytes from PD patients compared with those of control cases by analyzing single-nuclei transcriptomes.
Results: These analyses revealed the presence of distinct oligodendrocyte populations in Parkinson's disease patients, indicating corresponding variations in molecular features such as inflammatory response activation, response to protein folding stress, and myelination abnormalities. In α-synuclein preformed fibril-injection mouse model of Parkinson's disease, we confirmed myelination defects and responses to protein folding stress.
Conclusions: These findings imply that in Parkinson's disease, oligodendrocytes acquire disease-associated characteristics and may contribute to the subsequent neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0965 / #459

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

RE-WEIGHTING MDS-UPDRS PART II ITEMS FOR OPTIMAL SENSITIVITY TO PARKINSON'S DISEASE PROGRESSION USING PARKINSON'S PROGRESSION MARKERS INITIATIVE NATURAL HISTORY DATA

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Sam Dickson[1], Basia Rogula[2], Jordan Dubow[3], Nick Kozauer[4], Lauren Powell[2], Michele Potashman[5], Kim Crimin[6], Patrick O'Keefe[1], Ellen Korol[2], Madeline Crabtree[2], Fernanda Nagase[2], Vlad Coric[7], Suzanne Hendrix[8], Gil L'Italien[5]
[1]Pentara Corporation, Statistics, Millcreek, United States of America, [2]Broadstreet HEOR, Health Economics & Outcomes Research, Vancouver, Canada, [3]Clintrex, LLC, Chief Medical Officer, Sarasota, United States of America, [4]Biohaven Pharmaceuticals, Inc, Clinical Development & Regulatory Strategy, New Haven, United States of America, [5]Biohaven Pharmaceuticals, Inc, Clinical Outcomes Assessments And Health Economics, New Haven, United States of America, [6]Biohaven Pharmaceuticals, Inc, Biostatistics, New Haven, United States of America, [7]Biohaven Pharmaceuticals, Inc, Ceo, New Haven, United States of America, [8]Pentara Corporation, Ceo, Millcreek, United States of America

Aims: Parkinson's disease (PD) clinical trials require careful planning to progress beyond Phase 2. Many in the PD community recognize the need for improvements in communication, education, funding, recruitment, and compliance, but the need to measure disease with optimized outcome is underappreciated. This work demonstrates how composite scores (CS) of re-weighted combinations of the MDS-UPDRS PART II items can better detect meaningful changes and increase success for efficacious disease-modifying treatments.
Methods: This study analyzed Parkinson's Progression Markers Initiative data in subjects with confirmed PD. Three cohorts were defined based on use of levodopa or dopamine agonists (lev/DA) and presence of motor complications: untreated, early-lev/DA (motor complications absent), and later-lev/DA with motor complications (≥25% time of waking day in OFF-state and/or dyskinesia assessed on MDS-UPDRS). Sensitivity of individual items to disease progression was assessed using partial least square regression. Selected items were weighted using model coefficients and summed to create the CS. CS responsiveness to change was assessed using a 2-year mean to standard deviation ratio (MSDR) for treated and 1-year for untreated (due to data limitations).
Results: CS were generated for untreated (n=428), early-lev/DA (n=424), and later-lev/DA (n=536) cohorts separately. The three most responsive items (with their combined weights) were: turning in bed, getting out of bed/car/chair, tremor (45%); turning in bed, getting out of bed, and speech (56%); and turning in bed, speech, and handwriting (53%) respectively. The MSDRs increased from 0.5431 to 0.5647, 0.4265 to 0.4994, and 0.3128 to 0.3849, respectively. Corresponding sample size decreases were ~7%, 27%, and 34%, reflecting powering improvements of ~3%, 11% and 13%.
Conclusions: Endpoints derived from the three CS presented can measure clinically meaningful progression with greater sensitivity compared to existing tools.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0966 / #145

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

COGNITIVE PERFORMANCE AND DYNAMIC ORGANIZATION OF LEG'S MOTOR ACTS IN PARKINSONIAN PATIENTS

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Yacov Balash[1], Riyad Idries[1], Evelin Mate[1], Amos Korczyn[2]
[1]Kaplan Medical Center, Neurology, Rehovot, Israel, [2]Tel Aviv University, Departments Of Neurology And Physiology And Pharmacology, Tel Aviv, Israel

Aims: Dynamic organization of leg movements has been insufficiently studied in Parkinson's disease (PD). Its links to mental changes that developed in PD remain unclear. Aims: To detect subclinical mental changes enforced to bipedal vs. one-legged monopedal motor performance in PD patients.
Methods: Eighteen non-demented PD patients and 12 age and sex matched controls performed MoCA and two types of probes characterizing the dynamic organization of leg movements. As bipedal tests, a reciprocal coordination of heels and toes (Oseretzky, 1931) and its timed variation – the speed of putting on inverted sneakers were investigated. As monopedal tests, alternate tapping of the right and left foot (Luria, 2000), motor programming for each foot as a change of three consecutive positions "heel-edge-toes" (Luria-leg), conflicting instructions, and Go–no-Go (Dubois et al, 2000) were studied. The results of the cognitive bi-and monopedal tests were video registered and compared between PD patients and healthy individuals.
Results: The mean scores of the MoCA verbal fluency and both bipedal tasks were statistically significantly worse in PD (Mann–Whitney U=0.039, 0.041 and 0.012). Negative Pearson's correlation between the number of generated words and reciprocal coordination of heels-toes scores was –0.647 ($p<0.05$). As PD worsened, the patients avoided a bipedal and preferred the monopedal strategy when performing inverted sneakers test, which slowed down it's velocity. Pearson's correlation between the speed of putting on inverted sneakers and UPDRS III was severe (0.742, $p<0.05$).
Conclusions: In PD, the worst bipedal performance is associated with disorder in the word fluency domain and related to disruption of the premotor systems of the brain and the corpus callosum, so they may be useful to detect early mental changes.

P0967 / #335

Poster Topic: *Theme C: α-Synucleinopathies / C01.o. Disease Mechanisms, Pathophysiology: Modeling of disease progression*

MODELING LEWY BODY DISEASE WITH SNCA TRIPLICATION IPSC-DERIVED CORTICAL ORGANOIDS AND IDENTIFYING THERAPEUTIC DRUGS

POSTERS: C01.O. DISEASE MECHANISMS, PATHOPHYSIOLOGY: MODELING OF DISEASE PROGRESSION

Na Zhao
Mayo Clinic, Neuroscience, Jacksonville, United States of America

Aims: Aggregated α-synuclein (α-SYN) proteins, encoded by the *SNCA* gene, are hallmarks of Lewy body disease (LBD), affecting multiple brain regions. However, the specific mechanisms underlying α-SYN pathology in cortical neurons, crucial for LBD-associated dementia, remain unclear.
Methods: In this study, we generated cortical organoids from two *SNCA* triplication iPSC lines of LBD patients and two healthy controls, including two subclones for each line. After 2 months of culture, we assessed α-SYN levels and conducted single-cell RNA sequencing (scRNA-seq) to identify relevant molecular pathways. Organoid functionality was verified through mitochondrial stress tests and neuronal activity measurements. Furthermore, we performed single-nucleus RNA sequencing (snRNA-seq) on human brain cortices, comparing molecular pathways with our organoid models. In addition, we employed real-time quaking-induced conversion (RT-QuIC) to screen 1,280 FDA-approved compounds for their ability to inhibit α-SYN seeding, using human brain lysates. Promising drugs were subsequently evaluated on *SNCA* triplication organoids, with computational modeling exploring their mechanism of inhibiting α-SYN aggregation.
Results: We found that *SNCA* triplication iPSC-derived organoids had increased soluble total and phosphorylated α-SYN levels and high-molecular-weight insoluble α-SYN aggregates. ScRNA-seq and functional validation revealed synaptic and mitochondrial dysfunction in excitatory neurons with high *SNCA* expression, mirroring the findings from the autopsy-confirmed LBD human brains cortices. Four FDA-approved drugs (Entacapone, Tolcapone, Phenazopyridine hydrochloride, and Zalcitabine) showed strong capacity of inhibiting α-SYN seeding in RT-QuIC assays, reduced α-SYN aggregation and improved mitochondrial function in *SNCA* triplication organoids and excitatory neurons. Computational modeling suggested drug binding at specific α-SYN sites, involving Lys43 and Tyr39 residues, causing structural shifts that disrupted protein interactions and aggregation propensity.
Conclusions: Our findings establish human cortical LBD models and suggest novel therapeutic drugs targeting α-SYN aggregation for LBD and its associated dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0968 / #615

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

IDENTIFICATION OF FREEZING OF GAIT IN PARKINSON'S DISEASE DURING 360° TURNING – CNN-BASED APPROACH

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Sang-Myung Cheon[1], Young Jin Jeong[2], Jae Woo Kim[1]
[1]Dong-A University School of Medicine, Neurology, BUSAN, Korea, Republic of, [2]Dong-A University School of Medicine, Nuclear Medicine, BUSAN, Korea, Republic of

Aims: To verify the modeling approach using visual images for identification of gait freezing in Parkinson's disease.
Methods: The subjects of this study were each 30 PD patients with and without freezing of gait and 30 healthy control subjects. Subjects patients performed the 360° turning tasks in an off state of medication. Position and acceleration time-series data were converted into new imaging and trained with a classification modeling approach using visual images (Convolutional Neural Network, CNN algorithm) technique. The performance of the three-group classification model was evaluated using accuracy.
Results: The body segments with the highest performance in classifying freezers, non-freezers, and controls were the left elbow at 61%, right tibia at 60%, and right ankle at 60% in the image-based position time-series data when using the Recurrence Plot (Rec) algorithm and were the left upper arm at 60% and left knee at 60% when using the Gramian Angular Summation Field (GASF) algorithm. In addition, the left toe at 62% and right toe at 58% were found in the image-based acceleration time-series data when using the Rec algorithm.
Conclusions: The time-series gait pattern was useful for identification of gait freezing during 360º turning. And these results suggest uncoordinated gait pattern and troubled automatic movement of turning in freezers. Therefore, the CNN technique based on time-series gait data imaging might be used as an objective indicator and an effective research tool for revealing pathophysiology of gait freezing in PD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0969 / #1071

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

NOVEL 3D CELL CO-CULTURE MODEL REVEALED PARKINSON'S DISEASE MIDBRAIN ORGANOIDS TO BE VULNERABLE TO T CELL MIGRATION

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Elizaveta Gerasimova[1], Veronika Sigutova[1], Pavel Shelyganov[2], Sebastian Zundler[3], Beate Winner[1], Iryna Prots[4]
[1]University Hospital Erlangen, Stem Cell Biology, Erlangen, Germany, [2]University of Windsor, Department Of Chemistry And Biochemistry, Windsor, Canada, [3]University Hospital Erlangen, Department Of Medicine 1, Translational Research Center, Erlangen, Germany, [4]University Hospital Erlangen, Dental Clinic 1 - Restorative Dentistry And Periodontology, Erlangen, Germany

Aims: Recent studies indicate that adaptive immune system plays a role in neurodegenerative disorders, including Parkinson's disease (PD), and T cells are emerging as potential mediators of this pathology. T cells are suggested to migrate into brain and play a crucial role in PD pathogenesis by mediating cell death and neuroinflammation. To study T cell migration mechanisms into central nervous system (CNS) and investigate spatial interactions of T cells and neurons we aim to develop a co-culture system of peripheral blood T cells and stem cell-derived human midbrain organoids (hMOs). Moreover, we compared T cell infiltration and impact on hMOs of PD patients and controls, hypothesizing that PD hMOs are more vulnerable to T cell migration and T cell driven effects.
Methods: hMOs were differentiated from induced pluripotent stem cells derived from PD patients with α-syn gene locus duplication and controls. hMOs were co-cultured with T cells or left untreated, and assessed for neuronal, immunological, cell migration and cell adhesion markers, and cell death.
Results: We determined that T cell migrate into hMOs and localize in the proximity of MAP2-positive neurons. Indeed, neurons express lymphocytes adhesion molecules such as ICAM1 and VCAM1. Differential T cell migration into control and PD hMOs was demonstrated pointing to the relevance of T cells in PD pathogenesis. Moreover, T cell presence was shown to increase cell death within hMOs tissue and decrease MAP2 signal, suggesting that T cells cause neuronal cell loss. This pathology was enhanced in hMOs harboring PD phenotype.
Conclusions: Our work suggests a novel 3D cell co-culture model as a promising tool to investigate peripheral immune cell impact on CNS and delineates the neurotoxic effect of T cells in PD pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0970 / #1059

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

INVESTIGATION OF THE NOSE-TO-BRAIN TRANSPORT OF EXOGENOUS MICROPARTICLES USING MANGANESE CONTRAST-ENHANCED MRI TECHNIQUE

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Yasuyoshi Kimura[1], Makoto Osanai[2], Yuji Komaki[3], Hideki Hayakawa[1], Yuki Uemura[2], Chika Matsushita[3], Naoki Hasegawa[4], Kensuke Ikenaka[1], Kousuke Baba[1], Takafumi Seto[5], Hajime Mushiake[6], Rikinari Hanayama[7], Hideki Mochizuki[1]
[1]Osaka University Graduate School of Medicine, Department Of Neurology, Osaka, Japan, [2]Osaka University Graduate School of Medicine, Department Of Medical Physics And Engineering, Osaka, Japan, [3]Central Institute for Experimental Animals, Live Imaging Center, Kanagawa, Japan, [4]Tohoku University Graduate School of Medicine, Department Of Radiological Imaging And Informatics, Miyagi, Japan, [5]nstitute of Science and Engineering, Kanazawa University, Faculty Of Frontier Engineering, Ishikawa, Japan, [6]Tohoku University Graduate School of Medicine, Department Of Physiology, Miyagi, Japan, [7]Kanazawa University, Nanolsi, Ishikawa, Japan

Aims: Exposure to ambient fine particulate matter is considered a risk factor for neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease, but the mode of propagation to the brain and the biological response have not been fully elucidated. In this study, we investigate the nose-to-brain transport of exogenous microparticles using manganese contrast-enhanced MRI technique.
Methods: (1) Manganese chloride (MnCl2), manganese oxide nanoparticles (MnO2), or solvent were intranasally administered to mice, and imaging was performed by manganese contrast enhanced MRI over time (N=6~7/group, 9.4 Tesla MRI). (2) MnO2 or solvent was repeatedly administered intranasally to the mice and imaging was performed in the same manner (N=6~8/group, 7 Tesla MRI). Statistical analysis was performed using Student's t test.
Results: (1) MnCl2-treated group showed significant signal changes in the olfactory bulb and pisiform cortex at 26 hours ($p<0.01$), and some signals in the pisiform cortex remained after 1 week ($p<0.05$); MnO2-treated group showed significant signal changes in the thalamus and substantia nigra at 26 hours, and midbrain signals remained after 1 week ($p<0.05$). (2) When MnO2 was repeatedly administered, signal changes were detected in deep brain regions includiing the amygdala, hippocampus, thalamus, and substantia nigra in addition to the olfactory bulb and pisiform cortex at 24 hours ($p<0.01$). Signals in the hippocampus and thalamus remained even after 2 weeks ($p<0.01$).
Conclusions: The results suggest that insoluble exogenous microparticles may reach to the deep brain at an early stage, and accumulate at least for 2 weeks. Our result support that ambient fine particulate matter can be a risk for neurodegenerative disorders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0971 / #1015

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

DOES LOW DOSE INJECTIONS OF TETANUS TOIXIN INTO THE RAT BASAL GANGLIA INDUCE PARKINSON'S-LIKE MOTOR IMPAIRMENTS?

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Patrik Meglić, Petra Šoštarić, Ivica Matak
School of Medicine University of Zagreb, Pharmacology, Zagreb, Croatia

Aims: The onset of movement disorders like dystonia and parkinsonism is primarily linked to abnormalities in basal ganglia activity. The basal ganglia and associated nuclei are crucial for motor control. Tetanus toxin (TeNT) disrupts normal neuronal inhibition by selectively blocking inhibitory GABA or glycinergic synapses. This study's objective was to investigate does neuronal disinhibition in the basal ganglia, induced by low, non-convulsive doses of TeNT, produces Parkinson's like motor impairments.
Methods: Male Wistar rats underwent unilateral stereotaxic injections of tetanus toxin into the caudate putamen (CPu), globus pallidus internus (GPi), and substantia nigra (SN). The effects of tetanus toxin (TeNT) were evaluated on the 7th, 10th, and 14th day post-injection. Various motor and behavioral tests were conducted to analyze the impact of TeNT-induced disinhibition on normal motor function. On the 10th day following the injection, the animals were subjected to an amphetamine-induced rotation test.
Results: Following unilateral injection of TeNT into the CPu, animals exhibited contralateral hind paw misplacement during the beam-walk test. Animals receiving injections in the CPu and GPi displayed a propensity for circling behavior towards the injected side in both the open field and swimming tests, a tendency that was further highlighted during the amphetamine-induced rotation test. In the CatWalk analysis, animals injected in the CPu and GPi demonstrated increased stride frequency and reduced swing time.
Conclusions: Animals injected in GPi and CPu exhibit Parkinson's-like motor impairments, showing comparable rotational behavior and gait-related issues. CPu injections also reveal a proprioceptive deficit. This highlights the interplay between inhibitory and dopaminergic transmission in the basal ganglia, crucial for motor control and function. Further investigation is needed to pinpoint the affected transmission pathways, potentially explaining tetanus-induced Parkinson-like motor impairments?

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0972 / #1116

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

FINANCING DRUG DISCOVERY AND DEVELOPMENT FOR PARKINSON'S BY PATIENT ORGANISATIONS

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Arthur Roach
Parkinson's UK, Parkinson's Virtual Biotech, London, United Kingdom

Aims: The Parkinson's Virtual Biotech is a patient community led and financed Seed and Series A funder dedicated to enabling early companies to develop compelling drug candidates for the treatment of Parkinson's. We aim to provide over $50m in funding over the coming ten years, with a strong focus on meeting important unmet needs of patients, and the sustainability of programmes based on strong science, clinical insight and credible teams.
Methods: The Parkinson's Virtual Botech obtains its funds from patient organisations in the US and Europe. Companies and entrepreneurs request funding for their projects by application to virtualbiotech@parkinsons.org.uk or through encounters at scientific and partnering meetings. Aspects reviewed include target validation, technical approach, probability of technical success, patient involvement, strength of team, stability of company, commitment to Parkinson's drug development, budget and prospects for follow-on funding. Typical investments are of $1m-$4m over one to three years, and may be followed by further rounds. We have a track record of investing solo, and alongside other non-profit and private investors. Investment terms are designed to provide to the Parkinson's community a financial return similar to that which a private early-stage investor might expect.
Results: Over seven years we have invested over $25m in 12 projects. The full portfolio is shown at **www.parkinsonsvirtualbiotech.co.uk**. Funded projects include: - disease-modifying and symptomatic drugs - drug discovery projects - IND enabling studies - phase 2 clinical trials - registration trials in exceptional cases. Five of the first 12 projects have received a second round of funding from the Parkinson's Virtual Biotech following successful completion of their research plan.
Conclusions: Through the Parkinson's Virtual Biotech the patient community is helping innovative companies create new treatments for Parkinson's.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0973 / #1592

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

EXTRACELLULAR VESICLES AND THEIR RENIN-ANGIOTENSIN CARGO AS A LINK BETWEEN METABOLIC SYNDROME AND PARKINSON'S DISEASE

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Ana Isabel Rodríguez Pérez[1,2], Maria A. Pedrosa[1], Carmen M. Labandeira[3], Nerea Lago-Baameiro[4,5], Rita Valenzuela[1,2], María Pardo[4,5], José Luis Labandeira-García[1,2]
[1]Cellular and Molecular Neurobiology of Parkinson´s disease, Research Center for Molecular Medicine and Chronic diseases (CIMUS), Idis, Santiago de Compostela, Spain, [2]CIBERNED, Networking Research Center On Neurodegenerative Diseases, Madrid, Spain, [3]Neurology Service, University Hospital Of Ourense., Oursense, Spain, [4]CIBER Fisiopatología Obesidad y Nutrición,,, Instituto De Salud Carlos Iii, Madrid, Spain, [5]Grupo Obesidómica, Área de Endocrinología, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complexo Hospitalario Universitario De Santiago De Compostela/sergas), Santiago de Compostela, Spain

Aims: Several studies have shown an association between metabolic syndrome (MetS) and Parkinson's disease (PD). The linking mechanisms remain to be clarified. MetS promotes low-grade peripheral oxidative stress and inflammation, and dysregulation of adipose renin-angiotensin system (RAS). Interestingly, brain RAS dysregulation is involved in the progression of dopaminergic degeneration and PD. Circulating extracellular vesicles (EVs) from MetS fat tissue can cross brain-blood barrier and may act as linking signals. However, the possible effects of MetS EVs RAS cargo on dopaminergic degeneration and astrocytic function are not known. In the work reported here, we studied whether EVs from MetS show RAS dysregulation cargo and if it could be a major link between MetS and PD development and progression.
Methods: We isolated and characterized EVs from MetS and control rats, and analyzed their mRNA and protein cargo using RT-PCR and the single particle interferometric reflectance imaging sensor platform ExoView R200, respectively. Furthermore, cultures of N27 dopaminergic neurons and C6 astrocytes were treated with EVs from MetS rats.
Results: EVs were highly increased in MetS rat serum, which was inhibited by treatment with the angiotensin type-1 receptor blocker candesartan. Furthermore, EVs from MetS rats showed increased prooxidative/proinflammatory and decreased anti-oxidative/anti-inflammatory RAS components, which was inhibited in candesartan-treated MetS rats. In cultures, EVs from MetS rats increased the dopaminergic neuron death and modulated the astrocytic function, upregulating markers of neuroinflammation and oxidative stress, which were inhibited by pre-treatment of cultures with candesartan.
Conclusions: In conclusion, our results show, for the first time, that the MetS may generate circulating EV_{MetS} that may increase the progression of neuroinflammation and dopaminergic neurodegeneration through RAS dysregulation in recipient cells, and that this process can be inhibited by treatment with AT1 receptor blockers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0974 / #2133

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

AUTOANTIBODIES ACTING ON ANGIOTENSIN TYPE-1 RECEPTORS AND ACE2 INDUCE PROGRESSION OF DOPAMINERGIC DEGENERATION

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Ana Isabel Rodríguez Pérez[1,2], Carmen M. Labandeira[3], Maria A. Pedrosa[1], Aloia Quijano[1], Rita Valenzuela[1,2], Pablo Garrido-Gil[1,2], José Luis Labandeira-Garcia[1,2]
[1]Cellular and Molecular Neurobiology of Parkinson´s disease, Research Center for Molecular Medicine and Chronic diseases (CIMUS), Idis, Santiago de Compostela, Spain, [2]CIBERNED, Networking Research Center On Neurodegenerative Diseases, Madrid, Spain, [3]University Hospital of Ourense, Neurology Service, Ourense, Spain

Aims: The role of autoimmunity in neurodegeneration has been increasingly suggested. The renin-angiotensin system (RAS) autoantibodies play a major role in several peripheral inflammatory processes. Dysregulation of brain RAS has been involved in neuroinflammation and neurodegeneration. We aimed to know whether angiotensin type-1 receptor autoantibodies (AT1-AA; AT1 agonists) and angiotensin-converting enzyme 2 autoantibodies (ACE2-AA; ACE2 antagonists) may be involved in Parkinson's disease (PD) progression and constitute a new therapeutical target.
Methods: Serum levels of AT1-AA, ACE2-AA, cytokine LIGHT; IL-6; IL-17 and 27-hydroxycolesterol were measured in PD patients and in controls. Possible mechanisms involved in neoantigen production were analyzed in an animal model of PD induced by injection of the neurotoxin 6-OHDA. Possible enhancement of dopaminergic death and proinflammatory effects mediated by AT1-AA were measured in rat primary neuron-glia mesencephalic cultures.
Results: AT1-AA and ACE2-AA serum levels were higher in PD patients (n=117) than in controls (n=106). Serum AT1-AA levels correlated with several cytokines, particularly with LIGHT, and with 27-hydroxycholesterol. Serum ACE2-AA correlated with AT1-AA. In the cerebrospinal fluid (CSF) of four PD patients, both autoantibodies were identified. Consistent with these results in patients, dopaminergic degeneration induced by 6-hydroxydopamine, increased levels of autoantibodies in serum and CSF in rats, as well as LIGHT levels and transglutaminase activity in rat substantia nigra. In primary mesencephalic cultures, administration of AT1-AA promoted a significant increase in dopaminergic degeneration and in neuroinflammation markers that were inhibited by the administration of the AT1 antagonist, candesartan.
Conclusions: The results suggest dysregulation of RAS autoantibodies as a new mechanism that can contribute to PD progression. Therapeutical strategies blocking the production, or the effects of these autoantibodies may be useful for PD treatment. The results further support repurposing AT1 blockers (ARBs) as a treatment against PD progression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0975 / #2034

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

RNA SEQUENCING OF OLFACTORY BULB IN PARKINSON'S DISEASE REVEALS GENE ALTERATIONS ASSOCIATED WITH OLFACTORY DYSFUNCTION.

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Cécilia Tremblay, Sidra Aslam, Jessica Walker, Anthony Intorcia, Ileana Lorenzini, Thomas Beach, Geidy Serrano
Banner Sun Health Research Institute, Brain And Body Donation Program, Sun City, United States of America

Aims: The olfactory bulb is involved early in the pathophysiology of Parkinson's disease (PD), which is consistent with the early onset of olfactory dysfunction. Identifying the molecular mechanisms through which PD affects the olfactory bulb could lead to a better understanding of the etiology of olfactory dysfunction and the pathophysiology of PD. We specifically aimed to assess gene expression changes and affected pathways by whole transcriptomic profiling of the olfactory bulb of subjects with clinicopathologically defined PD in comparison to controls.
Methods: Bulk RNA sequencing was performed on frozen human olfactory bulbs of 20 PD and 20 controls without dementia or any movement disorder, from the Arizona Study of Aging and Neurodegenerative disorders (AZSAND) and the Brain and Body Donation Program (BBDP).
Results: Differential expression analysis revealed a total of 2164 significantly differentially expressed genes (DEGs). Significantly downregulated pathways included neurodegeneration, Parkinson's disease, oxidative phosphorylation, and olfactory transduction. Upregulated pathways were involved in the immune and inflammatory responses as well as cellular death. An overrepresentation of microglial and astrocytes related genes was observed amongst upregulated genes, and excitatory neurons related genes amongst downregulated genes. UPSIT olfactory identification score correlated with gene expression of genes coding for G-coupled protein, calcium binding protein including proteins expressed in glial olfactory ensheathing cells, neuropeptides expressed in GABAergic granule neurons such as neurogranin and somatostatin, and dopaminergic, GABAergic and cholinergic receptors. Co-expression network analysis revealed LAIR1 and PPARA as hub genes with a high discriminative power between PD and controls
Conclusions: This this work reveals gene alterations associated with neuroinflammation, multi-neurotransmitter dysfunction and disruptions of factors involved in the initiation of olfactory transduction signaling that may be involved in PD-related olfactory dysfunction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0976 / #481

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

LOWERING OF ALPHA-SYUCLEIN TOXICITY BY TARGETING AGGREGATION-PRONE ALPHA SYNUCLEIN TO LIPID DROPLETS

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Andreas Müller-Schiffmann[1], K Paulvannan[2], Deben Dey[2], N Deyarman[2], Suganyah Selvarajah[2], Vishwanath Lingappa[2], Carsten Korth[1]
[1]Heinrich Heine University of Düsseldorf, Neuropathology, Düsseldorf, Germany, [2]Prosetta Biosciences, Chemistry, San Francisco, United States of America

Aims: Hijacking the cellular autophagy system is a common strategy of viruses to drive efficient replication. However, disrupting autophagy leads to aberrant proteostasis that can ultimately promote protein aggregation and the development of neurodegenerative diseases. We recently reported that influenza virus infection led to the aggregation of alpha-synuclein, a major molecular hallmark for Parkinson´s disease, by interfering with the autophagic pathway. Here, we hypothesized that small molecule anti-influenza compounds that specifically target the autophagy system could also be identified to benefit for alpha-synuclein (aSyn) homeostasis independent of infection.
Methods: A library of novel antiviral drugs that are directed against cellular factors, was screened in human neuroblastoma cells and differentiated LUHMES cells showing aSyn aggregation after influenza infection or rotenone treatment. The cellular targets were identified by Drug-resin-affinity-chromatography (DRAC).
Results: We identified several drugs that abolished both influenza infectivity and aSyn aggregation, including in the absence of infection. One subseries increased the association of aSyn to lipid droplets, while diminishing aSyn aggregates. This also led to a rescue of dopamine and rotenone mediated synapto- and neurotoxicity. DRAC identified several target proteins involved in autophagy, especially autophagosome maturation. The lead compound increased the association of the autophagy marker LC3 to aSyn loaded lipid droplets, inducing autophagic flux and increasing alpha-synuclein clearance.
Conclusions: We indirectly confirmed a connection between influenza infection and aSyn aggregation by identifying a drug that inhibits both by targeting a protein of the autophagy system. Interestingly, this involved facilitating the turn-over of aSyn by targeting it to lipid droplets and the induction of macroautophagy.

P0977 / #566

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

TARGETING TAU, AMYLOID AND A-SYNUCLEIN IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE: DRUG DEVELOPMENT.

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Ravi Pratap Barnwal
Panjab University, Biophysics, Chandigarh, India

Aims: In this work, we would present work in our lab targeting these three proteins. And any molecule inhibiting the aggregation of these proteins will open new avenues for treatment. The research will provide new opportunities to investigate pharmaceutical treatment for neurodegenerative diseases associated with these proteins.
Methods: Small molecule inhibitors are gaining popularity among well-known treatments in this field of medicine, so, we aim to design a few small molecules that could efficiently reduce or delay the aggregation process of these proteins. For this, in brief, the methodology will be. **1) *In-silico* studies**- **2) In-vitro work a) Expression and purification of the proteins**- **b) Structural and biophysical studies**- **3) Cell culture studies**
Results: *In-silico* work has been performed for three proteins using the in-house library of molecules (200+). A few molecules have demonstrated a greater binding affinity against them.
Conclusions: In the last several decades, there has been progress in developing a medicine to treat AD and PD, for symptomatic relief, no proper cure for this disease is available, so there is an urgent need for novel therapeutic discoveries for fighting against AD. Despite several promising treatment ideas for PD and AD in clinical trials, there are still several challenges that need to be addressed before these drugs can be widely used in patients. One challenge is that it is difficult to deliver drugs to the blood-brain barrier. It is likely that a combination of therapeutic approaches will be needed to effectively treat these diseases. The development of drugs that target tau, Aβ, and α-synuclein has the potential to revolutionize the treatment of these devastating diseases. Our proposed drugs will pave the way for new regime of treatment for these diseases in future.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0978 / #2017

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

TURMERIC ENHANCED PHENOTYPICAL CHARACTERISTICS AND REDUCED ALPHA-SYNUCLEIN AGGREGATION IN MUTANT STRAIN NL5901 CAENORHABDITIS ELEGANS.

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Fernanda Fajardo[1], Ruth Melida Sanchez Mora[2]
[1]Universidad Colegio Mayor de Cundinamarca, Bogotá, Bogotá, Colombia, [2]Universidad Colegio Mayor de Cundinamarca, Bogota, Bogotá, D.C., Colombia

Aims: Turmeric decreases protein aggregation on muscle wall of NL5901 Caernohabditis elegans mutant strain. NL5901 strain shows a decline on mobility and reproduction due to protein aggregation on muscle wall.Turmeric solution shown an effect on a dependent manner on characteristics such as life span, mobility and reproduction. Protein aggregation on the muscle wall leads to Matricidal effect, due to the lack of muscle contractions that result on the Matricidal effec
Methods: Maintenance and cultivation of C elegans mutant strain Longevity assay Worms on stage L4, after bleaching adults, were taken and placed on a new plate. Locomotion assay Reproduction assay Quantifying protein aggregates Statistical Analysis
Results: Our findings indicate that Turmeric affects alpha-synuclein aggregation by reducing the amount of its aggregates and the effects on phenotypic characteristics. Turmeric shown to decrease protein aggregation in a dose-dependent manner, by treating worms under 1.5 mg/ml protein aggregates decreased by 50% in relation to the Control strain. Life span increased from 18 Days (Control strain) to 26 under 1.0 mg/ml of turmeric solution. Reproduction and mobility increased on higher concentrations of Turmeric solution, Reproduction assay showed an increase in offspring on overall life cycle, 116 Worms against 43 (Control Strain). As protein aggregation is conducted to the nematode worm and by decreasing protein aggregation mobility increases 19 bends per minute under 1.5 mg/ml Turmeric solution against 8 angles (Control strain)
Conclusions: Reduction of protein aggregates

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0979 / #1080

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

A BRAIN-SHUTTLED ANTIBODY TARGETING ALPHA SYNUCLEIN AGGREGATES FOR THE TREATMENT OF SYNUCLEINOPATHIES

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Sungwon An[1], John Mcinnis[2], Dongin Kim[1], Ozge Yilmaz[2], Jinhyung Ahn[1], Yi Tang[3], Jinwon Jung[1], Julia Bonner[2], Hyesu Yun[1], Simon Dujardin[2], Donghwan Kim[1], Laurent Pradier[2], Sumin Hyeon[1], Jinyoung Park[1], Weon-Kyoo You[1], Pablo Sardi[2], Sang Hoon Lee[1], Can Kayatekin[2]
[1]ABL Bio Inc, Abl Bio, Seongnam-si, Korea, Republic of, [2]Sanofi, Rare And Neurologic Diseases, Cambridge, United States of America, [3]Sanofi, Large Molecule Research, Cambridge, United States of America

Aims: Synucleinopathies, which include Parkinson's disease and multiple systems atrophy, are a class of devastating neurodegenerative diseases characterized by the presence of alpha-synuclein (aSyn) rich aggregates in the brains of patients. Passive immunotherapy targeting these aggregates is an attractive disease-modifying strategy. Such an approach must not only demonstrate target selectivity towards aSyn aggregates, but also achieve appropriate brain exposure to have the desired therapeutic effect.
Methods: SAR446159/ABL301 is a bispecific antibody composed of an aSyn-binding IgG and an engineered insulin-like growth factor receptor (IGF1R) binding moiety acting as a shuttle to transport an antibody across blood-brain barrier (BBB). We tested SAR446159 binding to various forms of aSyn to demonstrate selectivity for aggregates. Then, we used cell-based assays, a transgenic mouse model, and a preformed-fibril (PFF) induced synucleinopathy mouse model to demonstrate the efficacy of this molecule.
Results: SAR446159 bound tightly to aSyn aggregates and prevented their uptake *in vitro* and seeding *in vivo*. In wild type (WT) mice injected in the striatum with aSyn PFFs, treatment with SAR446159 reduced aSyn pathology and lowered the severity of motor phenotypes. Additionally, in 9-month-old transgenic mice overexpressing aSyn, SAR446159 reduced pSer129 aSyn levels in the brain. The potent activity of this antibody was enabled by the engineered IGF1R binding moiety, which enhanced brain exposure by shuttling the antibody across the BBB, and by its high selectivity for aggregated conformers of aSyn over monomeric aSyn. Moreover, the IGF1R-binding shuttle enabled greater uptake into the endo-lysosomal trafficking pathway of neurons, potentially allowing this antibody to engage aSyn aggregates both intracellularly and extracellularly.
Conclusions: The *in vitro* and *in vivo* properties of SAR446159 supported the clinical translation of this next-generation immunotherapeutic molecule. Phase I clinical trials were started in late 2022.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0980 / #2279

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

BLEBBISTATIN ALLEVIATED HYPERLOCOMOTION IN A53T A-SYNUCLEIN PARKINSON'S DISEASE MODEL

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Seong-Ryeong Lim[1], Yujeong Lee[2], Taesub Jung[1], Jin-A Lee[3], Chany Lee[2], Kipom Kim[4], Jeongyeon Kim[1]
[1]Korea Brain Research Institute, Emotion, Cognition & Behavior Research Group, Cheomdan-ro, Dong-gu, Daegu, Republic of Korea, Korea, Republic of, [2]Korea Brain Research Institute, Cognitive Science Research Group, Cheomdan-ro, Dong-gu, Daegu, Republic of Korea, Korea, Republic of, [3]Hannam University, Department Of Biological Science And Biotechnology, Daejeon, Korea, Republic of, [4]Korea Brain Research Institute, Research Strategy Office, Daegu, Korea, Republic of

Aims: Parkinson's disease (PD) is a common neurodegenerative disorder associated with misfolding and aggregation of α-synuclein protein (α-syn). Recently, it has been strongly suggested that A53T mutated α-syn represents the different phenotype of the PD model. However, it is still unclear how different effects of each period induced by A53T mutated α-syn involve neurodegeneration and whether targeting this pathway has therapeutic potential.
Methods: A53T-α-syn overexpressed transgenic mice (line G2-3) is widely used as a PD animal model (Lee et al., 2002). Mice (7 mo, 12 mo A53T TG and littermate WT) were administrated with blebbistatin (BLEB, 10 mg/kg, i.p.) daily once for two weeks. Also, we developed the in vitro PD model, A53T overexpression in cultured cortical neuron by adeno associated viral vector system. We investigated how BLEB treatment influences transgenic mouse models by mediating molecular changes in cortex region using quantitative real-time polymerase chain reaction (qRT-PCR), western blot, immunohistochemical, and behavioral analysis.
Results: We demonstrated that the treatment of BLEB, a non-muscle myosin II inhibitor, improves mitochondrial dysfunction and hyperlocomotion caused by A53T-α-syn in the in-vitro and in-vivo model. After α-syn overexpression, dynamin-related protein 1 (Drp1, mitochondrial fission marker) level significantly increased in PD model, whereas the elevated Drp1 level was suppressed in the BLEB co-treated groups. Also, Similarly, peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1-α, mitochondrial homeostasis marker) and sirtuin 1 (Sirt-1, mitochondrial homeostasis marker) levels significantly decreased in PD model, whereas the decreased levels were suppressed in the BLEB co-treated groups. The behavioral showed hyperlocomotion in transgenic mice model was rescued by BLEB.
Conclusions: Our study reveals that BLEB could play a role in alleviating the symptoms of PD in A53T PD model.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0981 / #1334

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

SMALL MOLECULE INHIBITORS FOR PRECISE INHIBITION OF A-SYNUCLEIN OLIGOMER GENERATION IN PARKINSON'S DISEASE (PD)

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Kelvin Luk[1], Andrew Cridland[2], Nora Bengoa-Vergniory[3], Sarah Ball[2], Marta Cruz[2], Xiangyu Teng[2], Georg Meisl[2], Alexander Dear[2], Isaac Kitchen-Smith[2], Johnny Habchi[2], Bochong Li[4], John Thomson[2]
[1]University of Pennsylvania, Pathology And Laboratory Medicine, Philadelphia, United States of America, [2]Wavebreak Therapeutics, Discovery Research, Cambridge, United Kingdom, [3]UPV/EHU, Achucarro Basque Center For Neuroscience, Leioa, Spain, [4]Wavebreak Therapeutics, Discovery Research, Boston, United States of America

Aims: Develop small molecule therapeutics for PD that inhibit production of toxic α-synuclein oligomers, reduce aggregate formation, and improve neuronal functions, by targeting all sources of oligomer generation. α-synuclein oligomers bind membranes, receptors and organelles, and disrupt metabolic and neuronal pathways, resulting in dysfunction and neurotoxicity. We harness biophysics-based analytics to target two source mechanisms that produce these transient intermediates with high precision: (i) primary nucleation, catalysed by lipid membranes, and (ii) secondary nucleation, catalysed by α-synuclein fibrillar aggregates.
Methods: Precision *in vitro* protein aggregation assays using recombinant α-synuclein along with advanced biophysics-based analytics were used to profile small molecule compounds, supported by analyses in multiple disease-relevant cellular and animal models, including iPSC-derived dopaminergic neurons, and seeded M83 transgenic mice. We leveraged a variety of oligomer and aggregate biomarker technologies to measure target engagement and disease progression.
Results: Wavebreak's compounds significantly inhibited both primary and secondary nucleation of α-synuclein oligomer formation, blocking catalytic sites on fibrils with low stoichiometry. Lead optimisation further enhanced potency, oral pharmacokinetics and brain penetration. First generation inhibitors demonstrated efficacy across cell and mouse models, reducing oligomers and aggregates. Second generation inhibitors were even more potent in inhibiting the oligomer source mechanisms and demonstrated significant efficacy in aggressive seeded models in cells and in vivo. Importantly, second generation inhibitors also effected neuronal protection and attenuated atrophy in fibril-seeded M83 mice.
Conclusions: Wavebreak's small molecule α-synuclein oligomer inhibitors delivered robust *in vitro*, cellular and *in vivo* efficacy, demonstrating potent inhibition of oligomer production and aggregate formation. We are advancing these first-in-class molecules for the treatment of PD, initially, along with oligomer biomarker technology to measure both target engagement and the impact of oligomer inhibition on disease progression in human clinical trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0982 / #236

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

DISCOVERY OF A SMALL-MOLECULE COMPOUND INHIBITING THE FORMATION OF TWO TYPES OF BIOLOGICALLY RELEVANT, NON-AMYLOIDOGENIC OLIGOMERS OF ALPHA-SYNUCLEIN

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Pedro Martins[1], Zsuzsa Sárkány[1], Joana Saavedra[2], Marina Oliveira Da Silva[3], Rosa Perez-Gregorio[4], Fernando Rocha[5], Pablo Taboada[6], Márcia Liz[3], Sandra Macedo-Ribeiro[1], Isabel Cardoso[2]
[1]Instituto para a Investigação e Inovação em Saúde - i3S, Biomolecular Structure And Function Group, Porto, Portugal, [2]i3S - Instituto de Investigação e Inovação em Saúde, Molecular Neurobiology Group, Ibmc, Porto, Portugal, [3]i3S - Instituto de Investigação e Inovação em Saúde da Universidade do Porto – Associação, Neurodegeneration Team, Nerve Regeneration Group, Ibmc, Porto, Portugal, [4]Faculty of Sciences-University of Vigo, Department Of Analytical And Food Chemistry. Nutrition And Bromatology Area, Ourense, Portugal, [5]FEUP - Faculdade de Engenharia da Universidade do Porto, Lepabe - Laboratory For Process Engineering, Environment Biotechnology And Energy, Porto, Portugal, [6]Universidade de Santiago de Compostela, Colloids And Polymer Physics Group, Santiago de Compostela, Spain

Aims: Using a novel biophysical assay developed by us, the first small molecule inhibitor of nonamyloidogenic α-synuclein (aSyn) oligomerization was discovered. This compound was identified in a chemical library of drug-repurposing compounds but was never used in the context of neurodegenerative diseases. Dopamine-induced oligomers (DOIOs) and spontaneous oligomers (SPOs) formed upon incubation of 10 μM aSyn are the two species targeted by our compound.
Methods: Both DOIOs and SPOs were characterized using a combination of biophysical techniques, including Transmission Electron Microscopy, Dynamic Light Scattering, SDS-PAGE, Size-Exclusion Chromatography and immunochemistry. Oligomer toxicity in SH-SY5Y cells was quantified from the observations of labelled F-actin and using MTT and caspase-3 activity assays. The presence of the compound in the cerebrospinal fluid (CSF) of SV129 mice was measured using High-Resolution Electrospray Ionization Mass Spectroscopy (ESI-MS).
Results: Compound concentrations <5 μM suppress the formation of both DOIOs and SPOs *in vitro*. Of the two oligomeric species, only SPOs increased cell death and induced cytoskeleton disruption in SH-SY5Y cells. None of the oligomers has morphological or tinctorial properties resembling amyloid fibrils. The toxicity of SPOs is rescued if aSyn is incubated in the presence of the inhibitor. Our preliminary pharmacokinetic studies confirm the presence of the compound in the CSF of SV129 mice after intraperitoneal injection.
Conclusions: DOIOs and SPOs of aSyn are two species produced under physiologically relevant conditions and strongly implicated in PD pathogenesis. We identified a potent inhibitor of DOIOs/SPOs oligomerization and characterized its mechanism of action. As a drug-repurposing small molecule, this compound has favourable pharmacokinetic and toxicological profiles that were confirmed in our preliminary preclinical tests. These results warrant further investigation towards a novel therapy preventing the formation and proliferation of neurotoxic aSyn aggregates.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0983 / #2908

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

NANOBODY-BASED TARGETING OF PATHOGENIC ALPHA-SYNUCLEIN AS A PROMISING DIAGNOSTIC AND THERAPEUTIC APPROACH IN PARKINSON'S DISEASE

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Nishant Vaikath[1], Issam Hmila[1], Indulekha Sudhakaran[1], Simona Ghanem[1], Vijay Gupta[1], Nour Majbour[1], Ilham Abdi[1], Hoauri Abdesselem[1], Daniel Erskine[2], Omar El-Agnaf[1]
[1]Qatar Biomedical Research Institute, Qatar Foundation, Neurological Disorder Research Center, Doha, Qatar, [2]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom

Aims: α-Synuclein (α-syn) aggregates are central to the pathology of Parkinson's disease and represent a promising target for therapeutic intervention. Nanobodies, characterized by their small size, epitope accessibility, stability, solubility, ease of labeling, scalability, and engineering adaptability, offer an ideal tool for selectively targeting pathogenic α-syn.
Methods: We constructed nanobody phage display libraries using RNA isolated from camels immunized with α-syn monomers or fibrils. Following multiple rounds of panning and selection, we successfully isolated nanobodies and subjected to thorough characterization using a range of biochemical techniques and assays.
Results: Three nanobodies that specifically target α-syn were identified and subsequently engineered into bivalent formats to enhance their binding affinity. Notably, these nanobodies exhibited remarkable specificity, as they recognized α-syn aggregates while showing no cross-reactivity with aggregates or monomers of other amyloid proteins. Epitope mapping revealed distinct binding regions: two nanobodies targeted the C-terminal region, while the third recognized a region containing numerous mutations associated with early-onset Parkinson's disease. Additionally, these nanobodies displayed variations in their conformational specificity. One nanobody recognized α-syn oligomers with a beta-sheet conformation, while another recognized oligomers with and without beta-sheet structure. Importantly, all three nanobodies effectively inhibited α-syn aggregation in an in vitro seeding assay. Furthermore, in an in-vitro cell model using HEK cells expressing α-syn, the nanobodies successfully inhibited seed-dependent aggregation and reduced the formation of insoluble phosphorylated α-syn at Ser 129. Lastly, all identified nanobodies detected Lewy bodies pathology in post-mortem brain tissues from Parkinson's disease cases, underscoring their potential value as research tools.
Conclusions: These nanobodies hold significant promise for both diagnostic and therapeutic applications in Parkinson's disease and associated disorders, with their unique characteristics and specificities making them valuable candidates for further exploration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0984 / #157

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

IN CELLULO LIBRARY-DERIVED PEPTIDE-BASED INHIBITORS OF ALPHA-SYNUCLEIN AGGREGATION AND TOXICITY

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Jody Mason, Richard Meade, Robert Williams
University of Bath, Department Of Life Sciences, Bath, United Kingdom

Aims: A major group focus is the design and selection of peptides that target amyloidogenic proteins involved in age-related diseases. Amyloid proteins are known to be important in a number of such diseases that include Alzheimer's, Parkinson's, Lewy Body Dementia, Huntington's, and CJD.
Methods: We use a novel *in cellulo* library-screening platform to select peptides that can bind amyloidogenic target proteins to sequester and detoxify them. Utimising a Protein-fragment Complementation approach (PCA), we have identified both strand and helix-based peptide antagonists of α-synuclein proteins implicated in PD and related synucleinopathies. PCA is multiplexed, making no mechanistic assumptions about the target oligomeric state or conformer populated. Rather, library members must bind to and reduce associated toxicity to become selected.
Results: Peptides that either generate, or fail to prevent formation of a toxic species, result in cell death or retarded cell growth rates relative to effective binders. Library members that confer the most rapid bacterial growth are then selected from the PCA by increased stringency during further competition selection.
Conclusions: Our antagonists have been characterised using a range of biophysical and cell-based approaches and been downsized / refined using truncation, alanine-scanning, and incorporation of structure-inducing constraints and non-natural sequences. Our work in this area is currently funded by an Alzheimer's Research UK Major Project Award.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0985 / #2218

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

TRKB MODULATOR OT-003 REDUCES DOPAMINERGIC CELL LOSS, MITOCHONDRIAL STRESS, ALPHA-SYNUCLEIN AGGREGATION AND MOTOR DYSFUNCTION IN PARKINSON'S DISEASE MODELS

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Thomas Pfeiffer, Man-Ling Ho, Edward Duckworth, Louise Tear, Zdravko Zahariev, Lila Khederlarian, Alleyn Plowright
Pangea Botanica Ltd, R&d, Sevenoaks, United Kingdom

Aims: To assess the cellular efficacy and potency of proprietary lead compound OT-003, an orally available small molecule Tropomyosin receptor kinase B (TrkB) modulator, in preclinical Parkinson's disease models.
Methods: OT-003 was tested at a broad range of concentrations in separate experiments on primary rat neuronal cell cultures of dopaminergic neurons either injured with MPP+ or alpha-synuclein preformed fibrils (PFF), respectively. To enable this, rat mesencephalic neuronal cultures enriched in dopaminergic neurons were prepared from embryos obtained from pregnant female Wistar rats. In both experimental settings, OT-003 and positive control agents were pre-incubated on day 6 of culture for 1h before MPP+ and alpha-synuclein PFF exposure, respectively. Subsequently, the number of TH-positive neurons, complexity of the neurite network, mitochondrial ROS and alpha-synuclein levels were assessed using immunostaining and quantified using automated image analysis. Statistical significance was tested using one-way ANOVA followed by Fisher's LSD test. $p<0.05$ was considered significant.
Results: In the MPP+ assay, OT-003 significantly reduced mitochondrial ROS generation in dopaminergic neurons after 4h of MPP+ application. After 48h of MPP+ application, OT-003 significantly increased the survival of TH-positive neurons, protected the neurite network and reduced the aggregation of alpha-synuclein. In the alpha-synuclein PFF experiments, OT-003 significantly and dose-dependently reduced TH-positive neuronal cell loss, loss of neurite network and alpha-synuclein aggregation 96h after addition of the alpha-synuclein PFFs. This positive cellular data was reproduced in a Parkinson's disease mouse model in vivo, where chronic oral dosing of OT-003 significantly reduced PD pathologies and improved motor function.
Conclusions: These results in conjunction with additional compelling in vitro and in vivo data are supportive of OT-003's potential to be a novel disease-modifying therapy for patients suffering from Parkinson's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0986 / #1333

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

EXPLORING A-SYNUCLEIN POST-TRANSLATIONAL MODIFICATIONS AS BIOMARKERS AND THERAPEUTIC TARGETS FOR PARKINSON'S DISEASE

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Shaohua Qi, Li Yang, Michael Chan, Bill Chan, Zheng Yin, Stephen Wong
Houston Methodist Academic Institute, T. T. & W. F. Chao Center For Brain, Houston, United States of America

Aims: Parkinson's disease (PD) is a challenging neurodegenerative disorder characterized by abnormal clumps of α-synuclein (α-Syn) in the brain. Post-translational modifications (PTMs) of α-Syn contribute to its misfolding and aggregation, triggering inflammation in the brain and exacerbating PD pathology. Understanding the role of α-Syn PTMs and utilizing a systematic screening approach is crucial for identifying potential biomarkers and therapeutic targets of PD.
Methods: We summarized different types of α-Syn PTMs and developed a comprehensive library of α-Syn point mutation vectors to mimic or block specific PTMs, facilitating *in vitro* 3D cell culture experiments. The GFP-labeled α-Syn was captured with a high content screening scanner (ImageXpress Micro, Molecular Devices) to assess conformations and aggregation. We explored biomarkers and therapeutic targets by matching compounds with the drug library using automated screening, followed by drug toxicity assessment and pharmacokinetics in a PD mice model.
Results: PTMs play a key role in generating distinct toxic forms across synucleinopathies, resulting in various types of misfolding of α-Syn and influencing α-Syn conformation and aggregation. Phosphorylated α-Syn emerged as a biomarker during the synucleinopathic process of PD. The ubiquitin-dependent proteasome degradation system mediated α-Syn phosphorylation, modulating α-Syn interchange between the nucleus and cytoplasm. The drug screening system successfully identified and confirmed 4 novel drug candidates that maintained α-Syn biological activity while reducing toxic forms.
Conclusions: Post-translational modifications of α-Syn significantly contribute to the formation of toxic α-Syn aggregation, affecting its misfolding and cellular translocation. Modulating or reversing these PTMs through targeted drug intervention holds promise in mitigating α-Syn pathogenesis, potentially leading to functional and protective outcomes. Our research paves the way for further investigations and therapeutic strategies targeting α-Syn PTMs in Parkinson’s disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0987 / #209

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

ELECTROCONVULSIVE SEIZURES (ECS) RESCUE MOTOR IMPAIRMENTS AND PROMOTE A-SYNUCLEIN CLEARANCE IN A MOUSE MODEL OF PARKINSON'S DISEASE

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Alysia Ross, Sophie Bechkos, Delenn Hills, Jeff Correa, Stephanie Hobbs, Shawn Hayley, Hongyu Sun
Carleton University, Neuroscience, Ottawa, Canada

Aims: Recent work has highlighted the potential of electroconvulsive therapy (ECT) in relieving motor symptoms in Parkinson's Disease (PD) patients. While this suggests that modulation of neuronal excitability influences motor severity, the mechanisms behind this improvement remains unknown. The aggregation and accumulation of toxic alpha synuclein (a-Syn) fibrils represent a key trigger for neurodegeneration. As such, targeting the mechanisms regulating and clearing a-Syn is a promising disease-modifying strategy. Thus, we sought to assess the impact of neuroexcitability on aggregation, accumulation and localization of a-Syn. This information is critical for informing clinical practices around the use of ECT in PD.
Methods: We presently assessed whether electroconvulsive seizures (ECS), the mouse model of ECT, either early or late in disease progression, would influence PD pathology and motor symptoms provoked by the well-established A53T PFF mouse model.
Results: We found that ECS, regardless of timing, rescued deficits on rotarod, horizontal ladder and wire hang tests. ECS did not have any significant effects on TH or DAT levels, but reduced levels of phosphorylated a-Syn at s129 and modestly reduced degenerative effects on dopamine neurons in the substantia nigra. In fact, ECS markedly increases activation of relevant basal ganglia structures, consistent with motor deficit improvements. ECS also seems to alter the localization of a-Syn, with most s129 positive inclusions moving from intra-nuclear to cytoplasmic following ECS treatment.
Conclusions: These data suggest that the beneficial effects of ECT on PD motor symptoms may be due in part to alterations in basal ganglia excitability and a-Syn aggregation and accumulation that may be relevant for informing clinical practices and, at the very least, suggestive of novel mechanisms that should be further explored.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0988 / #1712

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

ROBUST DCAS9-MEDIATED ALPHA-SYNUCLEIN DOWNREGULATION: A PROMISING THERAPEUTIC APPROACH FOR PARKINSON'S DISEASE AND ALPHA-SYNUCLEINOPATHIES

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Birgitt Schuele[1], C. Morato Torres[1], Faria Zafar[1], De'Angelo Hermesky[1], Jocelyn Palafox Vazquez[1], Desiree Piper[2], Danuta Sastre[3], Stanley Qi[4], Laurie Sanders[5], Deniz Kirik[6]
[1]Stanford University, Pathology, Stanford, United States of America, [2]San Jose State University, Biological Sciences, San Jose, United States of America, [3]SRI International, Biossciences, Menlo Park, United States of America, [4]Stanford University, Engineering, Stanford, United States of America, [5]Duke University, Neurology And Pathology, Durham, United States of America, [6]Lund University, Experimental Medical Science, Lund, Sweden

Aims: Parkinson's disease and related alpha-synucleinopathies are increasingly prevalent due to an aging population, lacking effective disease-modifying therapies. Alpha-synuclein, a key player in Parkinson's disease, forms aggregates in Lewy bodies and is linked to neurodegeneration in hereditary conditions. This study introduces a nuclease-dead S. aureus Cas9 (sadCas9) CRISPR interference (CRISPRi) system for alpha-synuclein downregulation, both in vitro and in vivo.
Methods: In vitro, we screened 32 single guide RNAs (sgRNAs) targeting the human SNCA promoter. In vivo, we assessed a lead sgRNA in a humanized alpha-synuclein mouse model by delivering it through an all-in-one AAV9 construct, co-expressing sadCas9 and the sgRNA via unilateral stereotactic injections into the substantia nigra of four-month-old mice.
Results: In vitro, several sgRNAs effectively downregulated alpha-synuclein in HEK cells and human iPSC models. Cas9-mediated alpha-synuclein downregulation in patient iPSC-derived neuronal cultures reduced oxidative stress and mitigated mitochondrial DNA damage. In vivo, we observed sustained sadCas9 expression and substantial reduction in alpha-synuclein mRNA and protein levels at one and six months post-surgery. Initial microglia activation subsided over time, with no significant differences in microglia markers Iba1 and CD16/32 between the groups at the six-month mark.
Conclusions: This study showcases the efficacy of Cas9 interference technology in reducing alpha-synuclein mRNA and protein levels in both in vitro and in vivo settings. These promising pre-clinical results suggest the potential for advancing towards a disease-modifying genetic therapy for Parkinson's disease and related alpha-synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0989 / #1259

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

INSULIN-DEGRADING ENZYME PLAYS A NEUROPROTECTIVE ROLE IN AN IN VITRO MODEL OF SYNUCLEINOPATHIES

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Luís Sousa, Mariana Guarda, Ana Rita Marçal, Ana Chegão, Paula Macedo, Hugo Vicente Miranda
NOVA Medical School, Nms Research, Lisbon, Portugal

Aims: Recent findings suggests that Insulin Degrading Enzyme (IDE) suppresses alpha-synuclein (aSyn) oligomerization and accumulation *in vitro*. In addition to its insulin degradation role, IDE plays chaperone, heat-shock protein, and proteasome modulator functions. Herein, we aimed to explore the therapeutic potential of genetically modulating IDE against aSyn pathology using an H4 cell culture model.
Methods: H4 cells were co-transfected 24 hours post-seeding with aSyn or SynT, an aSyn aggregation-prone variant, together with IDE-WT or IDE-E111Q, a catalytically inactive variant. At 48 hours post-transfection, we collected cells and evaluated cytotoxicity via lactate dehydrogenase release, aSyn levels, and aSyn solubility at 1% Triton-X100. We evaluated the impact of IDE's degradative activity for its interaction with aSyn through co-immunoprecipitation and characterized SynT aggregates by immunocytochemistry.
Results: We observed that IDE reduces aSyn-dependent neurotoxicity. IDE-E111Q exhibits reduced efficacy, suggesting that while aSyn is not a direct degradative substrate of IDE, degradative active IDE has a higher suppressing capacity. Furthermore, we observed a stronger interaction between aSyn and IDE-WT compared to the degradative-inactive IDE. Cells overexpressing IDE present higher levels of aSyn, and bigger aSyn aggregates, although aSyn solubility remained unaltered.
Conclusions: This study showcases IDE's potential to attenuate aSyn-induced neurodegeneration in an activity-dependent manner. Notably, the observed reduction in toxicity, coupled with an increase in aSyn aggregate size but no solubility alterations, suggests IDE's potential chaperone role, possibly favoring monomer or high-weight aSyn fiber formation over oligomeric species. Future research should explore targeting brain IDE as a therapeutic avenue for Parkinson's disease (PD) progression. Given IDE's relevance in type 2 diabetes (T2D), a crucial PD risk factor, repurposing existing IDE-targeted drugs may hold promise in PD treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0990 / #2298

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

NON-INVASIVE DOWN-REGULATION OF ENDOGENOUS MURINE ALPHA-SYNUCLEIN VIA AAV.PHP.EB-GFP CAPSIDS AS A NOVEL THERAPEUTIC APPROACH FOR ALPHA-SYNUCLEINOPATHIES

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Leonidas Stefanis[1,2], Maria Fouka[1], Iraklis Tsakogias[1], Elena Gialinaki[1], Athanasios Stavropoulos[1], Ronald Melki[3], Louis De Muynck[4], George Tofaris[5], Maria Xilouri[1]
[1]Biomedical Research Foundation, Academy of Athens, Clinical- Experimental Surgery & Translational Research, Athens, Greece, [2]National and Kapodistrian University of Athens, School Of Medicine, athens, Greece, [3]Institut Francois Jacob (MIRCen), Cea And Laboratory Of Neurodegenerative Diseases, Fontenay-Aux-Roses cedex, France, [4]University of Oxford, Nuffield Department Of Clinical Neuroscience, Oxford, United Kingdom, [5]University of Oxford, Nuffield Department Of Clinical Neurosciences, Oxford, United Kingdom

Aims: Accumulation of alpha-Synuclein (aSyn) aggregates in specific brain regions is a hallmark of Parkinson's disease (PD) and related synucleinopathies. The propagation of aSyn has been suggested to be the underlying mechanism by which aggregates spread throughout the brain. The human aSyn preformed fibril (PFF) striatal injection model is a widely used animal PD model that recapitulates key disease characteristics, including aSyn aggregation, propagation, dopaminergic cell loss, and behavioral deficits. Herein, we investigated the potential beneficial role of non-invasive endogenous aSyn down-regulation via AAV.PHP.eB-GFP capsids on the spreading of aSyn-related pathology *in vivo*.
Methods: PHP.eB-GFP AAVs carrying either short hairpin RNA (shRNAs) or microRNA sequences, both targeting endogenous murine *Snca* encoding for aSyn, or respective scrambled control sequenceswere intravenously administered to 8-week-old male C57/Bl6 mice. One week post-injection, human aSyn PFFs were unilaterally injected into the right dorsal striatum. Three months post-injection,behavioral and histochemical analyses were performed to evaluate the effects of endogenous aSyn down-regulation on the haSyn PFF-mouse model.
Results: Intravenous administration of both types of PHP.eB-GFP AAVs was accompanied by widespread GFP transduction throughout the brain, including the substantia nigra, the area mainly affected in PD. Importantly, both *Snca*-targeted approaches (shRNA and microRNA), resulted in a significant reduction of endogenous aSyn levels within the transduced dopaminergic neurons, decreased the levels of pathology-related Ser129-phosphorylated aSyn and mitigated the dopaminergic celland terminal loss in the nigrostriatal axis. This amelioration of dopaminergic system degeneration was notably reflected in motor phenotype
Conclusions: Our approaches employing thePHP.eB-GFP-shRNA- or microRNA-targeted *Snca* capsids enabled the efficient downregulation of endogenous aSyn and hampered the propagation of aSyn-related pathology, setting the stage for novel, non-invasive therapeutic interventions for PD and related synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0991 / #1556

Poster Topic: *Theme C: α-Synucleinopathies / C01.p. Disease Mechanisms, Pathophysiology: Other*

CONVERGENCE OF POST-TRANSLATIONAL MODIFICATIONS OF TAU AND _-SYN MAY INFLUENCE THE TOPOGRAPHICAL DISTRIBUTION OF PATHOLOGICAL PROTEIN AGGREGATES IN DLB.

POSTERS: C01.P. DISEASE MECHANISMS, PATHOPHYSIOLOGY: OTHER

Lauren Walker[1], Ahmad Khundakar[2], Kirsty Mcaleese[1], Johannes Attems[1]
[1]Newcastle University, Translational And Clinical Reserch Institute, Newcastle upon Tyne, United Kingdom, [2]Teeside University, National Horizons Centre, Darlington, United Kingdom

Aims: Dementia with Lewy bodies (DLB) is neuropathologically defined by inclusions of α-synuclein (α-syn). However, concomitant Alzheimer's disease (AD) pathologies, hyperphosphorylated tau (HP-*T*) and β amyloid, are observed frequently at *post-mortem* examination, with 50-70% of DLB cases found to have medium to high- level of AD neuropathologic change. Mixed pathologies are associated with an accelerated cognitive decline, which can make diagnosis challenging. An increased burden of all three pathologies in end- stage dementia suggests a potential synergistic interaction between these proteins and is supported by studies that demonstrate α-syn and HP-*T* are co-localised. Proteins can undergo numerous alterations, which can affect their structure and enhance toxicity, however little is known regarding which post-translational modifications (PTMs) of α-syn and tau are co-localised, and are associated with specific clinical symptoms.
Methods: Tissue microarray (TMA) slides that incorporate 15 anatomically distinct brain regions from DLB cases with high and low AD neuropathology were double immunolabelled with PTMs of α-syn and tau (i.e α-syn phosphorylated at serine 129 (α-syn pS129), MC1, CP13, Alz 50 and PHF-1) and topographical distribution of pathological protein aggregates investigated.
Results: Co-localisations between α-syn pS129 and all tau markers were observed in multiple brain region in particular the amygdala and topographical distributions differed between DLB cases with low and high levels of concomitant AD related neuropathology.
Conclusions: The interaction between α-syn and tau has to be further elucidated and clincal trials should explore the feasibility of combination therapies targeting both α-syn and tau pathologies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0992 / #1552

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

EVALUATING NUCLEAR RECEPTOR LIGANDS AS POTENTIAL THERAPEUTICS IN CELLULAR MODELS OF PARKINSON'S DISEASE

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Arati Tripathi, Heba Alnakhala, Lisa Brontesi, Dennis Selkoe, Ulf Dettmer
Brigham and Women's Hospital/Harvard Medical School, Department Of Neurology, Boston, United States of America

Aims: Disease-modifying strategies for Parkinson disease (PD), the most common synucleinopathy, represent a critical unmet medical need. Accumulation of the neuronal protein alpha-synuclein (αS) and abnormal lipid metabolism have each been implicated in PD pathogenesis. Nuclear receptors are ligand-activated transcription factors that regulate gene expression linked to lipid metabolism and cellular fitness. Here, we identify and elucidate how nuclear receptor signaling impacts PD-associated αS and lipid alterations.
Methods: Pharmacological and genetic approaches in cellular PD models were used to investigate the impact of nuclear receptor signaling on fatty acid metabolism and αS homeostasis.
Results: We show that nuclear receptor agonists ameliorate cytotoxicity elicited by αS expression. Our data demonstrate that nuclear receptor agonism regulates fatty acid desaturase, SCD, and influences lipid droplets. Activation of these receptors normalizes alpha-synuclein homeostasis in cellular models of Parkinson's Disease. The effect of nuclear receptor activation on lipid droplets, fatty acid desaturase, and alpha-synuclein is reversed by an RXR antagonist, supporting pathway specificity.
Conclusions: Nuclear receptor activating ligands can alter fatty acid metabolism and correct perturbation in αS homeostasis to alleviate cytotoxicity and confer benefit in cellular models of PD. Our study offers a new paradigm to investigate nuclear receptor ligands for therapeutic potential in synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0993 / #873

Poster Topic: *Theme C: α-Synucleinopathies / C02.a. Therapeutic Targets, Mechanisms for Treatment: a-synuclein*

PHARMACOLOGICAL INHIBITION OF O-GLCNAC HYDROLASE REDUCES PS129 ALPHA-SYNUCLEIN AGGREGATION IN THE SUBSTANTIA NIGRA OF MTHY1-HSNCA MICE

POSTERS: C02.A. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: A-SYNUCLEIN

Jefferey Yue[1], Bryan Jones[2], Kim Tran[2], Matthew Deen[3], Viktor Holicek[3], Wai Hang Cheng[4], Mateusz Michalik[2], Sarah Power[2], Cheryl Wellington[4], Ralph Mistlberger[2], Neil Watson[2], David Vocadlo[1,3]
[1]Simon Fraser University, Molecular Biology And Biochemistry, Burnaby, Canada, [2]Simon Fraser University, Psychology, Burnaby, Canada, [3]Simon Fraser University, Chemistry, Burnaby, Canada, [4]The University of British Columbia, Pathology And Laboratory Medicine, Vancouver, Canada

Aims: Phosphorylation of α-synuclein at serine-129 (pS129) is generally accepted as a marker of neurotoxic Lewy Bodies deposition within defined regions of the brain, the primary pathological hallmark of Parkinson's disease (PD). Moreover, pS129 α-synuclein is considered an aggregation-prone form that exacerbates disease progression. Phosphorylation can be blocked by O-GlcNAcylation, the addition of beta-D-*N*-acetylglucosamine (GlcNAc) to serine to form O-linked N-acetylglucosamine (O-GlcNAc). Here, we investigated whether increasing brain O-GlcNAc levels by using Thiamet-G, a potent inhibitor of the enzyme O-GlcNAc hydrolase (OGA) that removes this modification from cellular proteins, could perturb pS129 α-synuclein aggregation.
Methods: Two-month-old wild type α-synuclein transgenic mice (mThy1-hSNCA) were administered vehicle, or Thiamet-G at low (200 mg/kg/day) or high (500 mg/kg/day) doses for 10 months. Locomotive and cognitive assessments were conducted throughout the treatment period to profile the longitudinal effects on behavior. Brain tissue was collected at the study end to quantitate deposition of pS129 α-synuclein aggregates.
Results: Thiamet-G treatment at both doses increased brain O-GlcNAc levels by approximately 5 folds. Both treatments also led to large and significant reductions of pS129 α-synuclein aggregates within dopaminergic brain regions. There was no significant reduction of total α-synuclein, indicating strong specificity in depleting α-synuclein aggregates. As early as one month of treatment, mice demonstrated improved locomotion in open field and pole descending tests with no observable cognitive abnormalities.
Conclusions: Our findings align with the beneficial effects of OGA inhibitors observed in various neurodegenerative diseases including PD and support pursuing OGA inhibitors, which have now advanced into the clinic, as a novel disease modifying treatment for slowing progression of PD. Further research on the mechanism of action by which OGA inhibitors act in PD may uncover precise neuroprotective effects of this pharmacological approach.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0994 / #2930

Poster Topic: *Theme C: α-Synucleinopathies / C02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

A NOVEL DISEASE MODIFYING THERAPY FOR PARKINSON'S DISEASE

POSTERS: C02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Ish Khanna, Sivaram Pillarisetti, Marcus Malkmus, Kathrin Kortschak
NeuroPn Therapeutics, Drug Discovery, Peachtree Corners, United States of America

Aims: Neuroinflammation and mitochondrial dysfunction with associated oxidative/endoplasmic reticulum (ER) stress work synergistically to accelerate Parkinson's disease (PD) progression. Epoxyeicosatrienoic acids (EETs) are the endogenous mediators that stimulate the inflammation resolution pathway and attenuate mitochondrial stress and neurotoxicity. The EETs are, however, degraded rapidly by the soluble epoxide hydrolase (sEH) to inactive metabolite. Recent studies in PD patients confirm that sEH expression in the human brain increases in tandem with rising synuclein aggregates and correlates with a reduction in dopaminergic neurons. The animal studies also confirm that sEH plays crucial role in driving neurodegeneration in PD. Collectively, these data suggest sEH as an important target for pharmacological intervention in PD. We envisaged that a brain penetrating, oral sEH inhibitor could block neurodegeneration and arrest PD progression. The efficacy of **NP-319** in alpha-synucleinopathy PD model will be presented as a potential breakthrough therapy for Parkinson's disease.
Methods: NP-319 was evaluated in alpha-synucleinopathy PD model in aged mice that reproduces neuropathological features of human PD (motor function defects, loss of dopaminergic neurons, a-syn aggregation). **NP-319** was dosed (*oral, q.d.*) both in a preventive (starting day -1) and therapeutic setting (starting day +7) post stereotaxic injection of a-syn fibrils in the brain. The motor coordination was evaluated after 3-weeks while impact on neuroprotection, a-syn aggregation, and neuronal inflammation was evaluated at the sacrifice of animals after 4-weeks of **NP-319** treatment.
Results: NP-319 therapy given in a preventive or therapeutic setting fully rescues motor function (mobility, motor coordination and slips), shows complete protection of dopaminergic neurons, prevents a-syn aggregation in the substantia nigra and blocks neuronal inflammation (microgliosis) and the mitochondrial dysfunction.
Conclusions: NP-319 has potential to be the *first* disease-modifying therapy in Parkinson's Disease

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0995 / #1988

Poster Topic: *Theme C: α-Synucleinopathies / C02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

NOVEL WISIT PLATFORM-BASED NEOGLUCOCONJUGATE VACCINES AGAINST ALPHA-SYNUCLEINOPATHIES: PRECLINICAL EVALUATION OF IMMUNOGENICITY AND THERAPEUTIC EFFICACY AS PRELUDE FOR CLINICAL STUDIES

POSTERS: C02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Markus Mandler[1], Sabine Schmidhuber[1], Sandra Scheiblhofer[1], Richard Weiss[2], Mihály Cserepes[3], Jozsef Tóvári[3], Erwan Bezard[4]
[1]Tridem Bioscience, Tridem Bioscience, Vienna, Austria, [2]Paris Lodron University Salzburg, Department Of Biosciences And Medical Biology, Salzburg, Austria, [3]KINETO Lab Ltd, Na, Budapest, Hungary, [4]Univ. de Bordeaux, CNRS, IMN, UMR 5293,, 1inst. Of Neurodegenerative Dis, Bordeaux, France

Aims: Synucleinopathies, including Parkinson's disease (PD), are believed to be primarily caused by the continuous build-up of misfolded alpha-Synuclein (aSyn) in the brain. Vaccines targeting aSyn represent a promising, innovative approach to treating these disorders. However, the immunogenicity of the current generation of PD vaccines remains a limiting factor. To enhance effectiveness and specificity of PD vaccination, we have developed a highly potent and adaptable platform termed WISIT (Win the Skin Immune System Trick). This novel class of neoglucoconjugate vaccines is designed to harness the capabilities of skin immune cells by targeting their C-type lectin receptors. This approach resulted in the production of several vaccine candidates with unprecedented immunological efficacy.
Methods: The leading WISIT candidates, differing in B cell - and T helper epitopes, are evaluated in comparison for their immunological (titer, specificity for aggregated aSyn) and therapeutic potential (inhibition of in vitro and in vivo aSyn propagation). The objective is to identify the top three candidates for progression into clinical testing as part of the Nexgen-PD project funded by Horizon Europe.
Results: The leading PD vaccine candidates from WISIT elicit robust and highly specific Ab responses with exceptional avidity for aSyn aggregates. Consequently, they significantly outperform conventional benchmark vaccines. Antibodies induced by chosen WISIT candidates have been demonstrated to inhibit aSyn aggregation in a dose-dependent manner, both in vitro and in vivo. The top candidates identified are set to undergo preclinical safety and tolerability studies. Additionally, their production process is currently being upgraded to GMP standards.
Conclusions: Our studies validate the concept for our top three aSyn WISIT vaccine candidates, demonstrating their immunological and in vivo efficacy, as well as safety. These findings provide substantial support for their translation towards clinical development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0996 / #1513

Poster Topic: *Theme C: α-Synucleinopathies / C02.b. Therapeutic Targets, Mechanisms for Treatment: Immunotherapy*

ACI-7104.056, AN ACTIVE IMMUNOTHERAPY FOR SYNUCLEINOPAHTIES, INDUCES A STRONG AND SUSTAINED ANTIBODY RESPONSE AGAINST ALPHA SYNUCLEIN IN NON-HUMAN PRIMATES.

POSTERS: C02.B. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: IMMUNOTHERAPY

Guenther Staffler[1], Rakel Carpintero[2], Emma Fiorini[2], Stefanie Siegert[2], Maelle Maelle Verardo[2], Nathalie Chuard[2], Aurélie Guillaume-Gentil[2], Lorène Aeschbach[2], Nadine Ait-Bouziad[2], Ilonka Van Hoof[3], Francesca Capotosti[2], Elpida Tsika[2], Marija Vukicevic[2], Andrea Pfeifer[1], Marie Kosco-Vilbois[1]
[1]AC Immune SA, Ac Immune Sa, Lausanne, Switzerland, [2]AC Immune SA, Research, Lausanne, Switzerland, [3]Nonclinical Insights, Nonclinical Insights, Oss, Netherlands

Aims: The accumulation of misfolded alpha synuclein (aSyn) and the cell-to-cell transmission of resulting aSyn aggregates propagate disease pathology in Parkinson's disease (PD) and other synucleinopathies. Thus, aSyn is considered a target for disease modification. ACI-7104.056, an aSyn-targeting immunotherapy currently being tested in a phase 2 clinical trial (NCT06015841), is designed to trigger an antibody response specifically binding to aSyn aggregates to halt their propagation. Here, we have assessed the safety and immunogenicity of ACI-7104.056 in non-human primates (NHP) and further characterized the quality of induced antibodies.
Methods: NHPs received multiple intramuscular injections of ACI-7104.056 and serum was collected at different time points. The animals were closely monitored for tolerability and safety throughout the entire in-life phase. Anti-aSyn aggregate-specific antibody levels in serum of immunized animals were analyzed by ELISA. The capacity of elicited antibodies to interfere with the accumulation of intracellular aSyn aggregates induced by human preformed fibrils was tested in rat primary cortical neurons using immunocytochemistry.
Results: ACI-7104.056 was safe and well tolerated in NHP with only a few transient local injection site reactions. A strong IgG response against aSyn aggregates was observed already after two immunizations and maintained at a high level until study end. Elicited antibodies reduced the number of intracellular aSyn aggregates in a primary neuron seeding assay demonstrating efficient blockage of aSyn propagation.
Conclusions: The evaluation of the phase 2 clinical stage ACI-7104.056 immunotherapy in a safety and immunogenicity study in NHP supports the use of this drug chronically in humans. The ability of elicited antibodies to interfere with the propagation of aSyn aggregates in living neurons further supports the development of ACI-7104.056 as a potential disease modifying therapy for PD and other synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0997 / #934

Poster Topic: *Theme C: α-Synucleinopathies / C02.c. Therapeutic Targets, Mechanisms for Treatment: Kinases, other enzymes*

AN ASSAY PLATFORM TO VALIDATE NOVEL DIRECT MODULATORS OF BETA-GLUCOCEREBROSIDASE

POSTERS: C02.C. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: KINASES, OTHER ENZYMES

Carla F. Bento[1], Mellissa Clark[1], Heather Weir[1], Joanna Ravenscroft[1], Juan Castro[1], James Mccarthy[1], Joe Coyle[2], Nick Palmer[3], Dominic Tisi[2], Elena Di Daniel[1], Nicola Wallis[1]
[1]Astex Pharmaceuticals, Biology, Cambridge, United Kingdom, [2]Astex Pharmaceuticals, Molecular Sciences, Cambridge, United Kingdom, [3]Astex Pharmaceuticals, Chemistry, Cambridge, United Kingdom

Aims: Mutant forms of β-Glucocerebrosidase (GCase) found in Gaucher´s Disease, Parkinson's Disease and Dementia with Lewy Bodies are less stable than wild-type (WT) GCase, which contributes to endoplasmic reticulum (ER) stress and lysosomal dysfunction due to ineffective trafficking. This leads to increased accumulation of lysosomal glucosylceramide and/or toxic α-synuclein aggregates. Therapeutics aimed at enhancing GCase trafficking and lysosomal activity are therefore of high relevance.
Methods: To this end we have established a comprehensive panel of *in vitro* and cellular assays to evaluate direct target engagement of small molecules against GCase and their mechanism of action. The assays have been validated using literature tool compounds and implemented in multi-well format enabling simultaneous multiple compounds testing.
Results: This platform includes assays to determine *in vitro* and cellular target engagement (e.g., X-ray Crystallography, Isothermal Titration Calorimetry, Cellular Thermal Shift Assay, Nano-Glo GCase-HiBiT assay), as well as assays to interrogate compound effects on GCase enzyme activity, protein stability, intracellular localisation and endogenous substrate levels in WT and mutant patient cell lines using a range of biochemical, high-content imaging and LC-MS methods. This has been applied to support fragment-based and structure-guided drug discovery against new potentially druggable sites on the protein surface.
Conclusions: We have developed a platform that enables profiling of GCase small molecule modulators. The assays can be used to assess target engagement and investigate mechanism of action. Identifying compounds that improve GCase trafficking and function may lead to the development of novel therapeutics for neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0998 / #1572

Poster Topic: *Theme C: α-Synucleinopathies / C02.d. Therapeutic Targets, Mechanisms for Treatment: Dopamine, Acetylcholine, neurotransmitters*

PRECLINICAL IN VIVO CHARACTERIZATION OF IRL1117; A NOVEL DOPAMINE D1/D2 AGONIST FOR THE TREATMENT OF PARKINSON'S DISEASE

POSTERS: C02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: DOPAMINE, ACETYLCHOLINE, NEUROTRANSMITTERS

Daniel Andersson, Sabina Brandin, Angelica Johansson, Karin Önnheim, Kristina Möller, Li Rousk, Jenny Gunnergren, Sverker Von Unge, Nicholas Waters, Clas Sonesson, Joakim Tedroff
IRLAB Therapeutics AB, Research & Development, Göteborg, Sweden

Aims: The objective of the current study was to characterize the novel dopamine D1/D2 agonist IRL1117 in the 6-OHDA-lesioned rat model of Parkinson's Disease.
Methods: The methods employed in the current studies were a combination of tests assessing motor function (cylinder test for motor asymmetry and the induced rotations assay) and the standard AIMs test for assessing extent of treatment-induced dyskinesias. Both acute and chronic studies have been performed, with the longest study following a 16 days once-daily treatment protocol.
Results: indicate that IRL1117 induces a long-lasting behavioral effect in the induced rotations assay (>12h) after a single oral dose, and that the restorative effect on motor function (as measured by the cylinder test) are maintained during chronic once-daily oral IRL1117 treatment for 16 days. In parallel, no or minimal induction of treatment-induced dyskinesias was observed during chronic treatment with IRL1117. Furthermore, when substituting L-DOPA with IRL1117 in rats with established L-DOPA induced dyskinesias, the dyskinesias were gradually diminished until largely absent while a functional motor response as measured by the cylinder test appears instead. Of note is also that these effects attained during chronic treatment with IRL1117 occur without the development of D1-related tachyphylaxis.
Conclusions: In conclusion, the data show that chronic treatment of 6-OHDA-lesioned rats with IRL1117 results in a robust effect on motor function without the simultaneous development of treatment-induced dyskinesias or the development of D1-mediated tachyphylaxis. Consequently, IRL1117 may constitute a novel chemical entity for once-daily treatment of the motor symptoms in Parkinson's disease, providing robust efficacy without the development of treatment-induced dyskinesia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P0999 / #833

Poster Topic: *Theme C: α-Synucleinopathies / C02.d. Therapeutic Targets, Mechanisms for Treatment: Dopamine, Acetylcholine, neurotransmitters*

THERAPEUTIC TARGETING OF SYNAPTIC VESICLE GLYCOPROTEIN 2C (SV2C) IN PARKINSON'S DISEASE

POSTERS: C02.D. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: DOPAMINE, ACETYLCHOLINE, NEUROTRANSMITTERS

Meghan Bucher[1], Farhad Forouhar[2], Gary Miller[1]
[1]Columbia University Irving Medical Center, Environmental Health Sciences, New York, United States of America, [2]Columbia University Irving Medical Center, Herbert Irving Comprehensive Cancer Center, New York, United States of America

Aims: Dopamine mishandling has been a recognized feature of Parkinson's disease (PD) since the 1960s when decreased dopamine was observed in post-mortem PD brain tissue and it was discovered that L-DOPA supplementation rescued motor deficits. Our work suggests *synergistic action* between vesicular monoamine transporter 2 and synaptic vesicle glycoprotein 2C (SV2C) to regulate vesicular dopamine homeostasis. Several SNPs in SV2C have been implicated for PD including variants that modify differential responses of PD patients to L-DOPA. There is precedent for therapeutically targeting SV2 proteins demonstrated by the efficacy of the SV2A modulator Levetiracetam for epilepsy treatment. We believe a pharmacotherapeutic modulator of SV2C may improve motor symptoms for PD patients either as a monotherapy or by improving L-DOPA efficacy. We sought to use theoretical modeling approaches and functional assays of SV2C activity to identify and test putative SV2C-targeted pharmacotherapeutics.
Methods: Induced-Fit docking (Schrödinger software) of small molecules against a reliable Alpha-Fold model of the full-length SV2C were used to evaluate interactions between SV2C and therapeutic compounds containing -racetam moieties. Compounds with high docking scores were tested in an *in vitro* plate-reader based assay utilizing a fluorescent dopamine analogue (FFN206) for effects on SV2C activity.
Results: Functional assays identified inhibitory effects (-39%) of the -racetam compound Padsevonil on FFN206 uptake at high (e.g., 100μM) dose, although no effects were identified with Levetiracetam. Additional compounds identified by theoretical modeling were prioritized for analysis resulting in the identification of "compound 29," which increased FFN206 uptake (+8%) at low (e.g., 0.001μM) dose.
Conclusions: Theoretical modeling can be paired with functional assays to identify and test putative compounds for SV2C activity. Future studies will expand this catalogue of potential SV2C-modifying compounds for translation into *in vivo* models of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1000 / #801

Poster Topic: *Theme C: α-Synucleinopathies / C02.e. Therapeutic Targets, Mechanisms for Treatment: Cell transplantation*

BENEFICIAL AND ADVERSE OUTCOMES FROM BDNF SUPPLEMENTATION IN BDNF-DEFICIENT PARKINSONIAN RATS WITH STRIATAL DOPAMINE GRAFTS.

POSTERS: C02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: CELL TRANSPLANTATION

Carlye Szarowicz[1,2], Kathy Steece-Collier[2], Molly Vander Werp[2], Jennifer Stancati[2], Caryl Sortwell[2], Margaret Caulfield[2]
[1]Michigan State University, Pharmacology And Toxicology, East Lansing, United States of America, [2]Michigan State University, Translational Neuroscience, Grand Rapids, United States of America

Aims: Mechanisms underlying graft-induced dyskinesia (GID), a potential side effect in individuals with Parkinson's disease (PD) and striatal dopamine (DA) grafts, remain controversial. One potential genetic contribution to this therapeutic outcome is a common single nucleotide polymorphism (SNP), rs6265, found in the gene for brain-derived neurotrophic factor (BDNF), a SNP which results in decreased BDNF release. Using rs6265 knock-in rats, we previously demonstrated that homozygous rs6265 (Met/Met) parkinsonian rats engrafted with wild-type (WT; Val/Val) DA neurons uniquely developed GID. Based on the necessity of BDNF for DA neuron maturation, we hypothesize that decreased BDNF release in rs6265 carriers impairs maturation and synaptogenesis of grafted DA neurons, leading to GID, and that infusion of exogenous BDNF will allow for graft maturation, normalization of graft-derived synaptic innervation, and GID prevention.
Methods: Male parkinsonian Met/Met rats were transplanted with intrastriatal embryonic WT DA neurons. Infusion cannulas were stereotaxically inserted 3μm dorsal to grafted cells with a 28-day Alzet™ osmotic minipumps containing BDNF or vehicle phosphate buffered saline (PBS). Pumps were removed after four weeks. Levodopa-induced dyskinesia (LID) and GID severity were evaluated over 10 weeks post-engraftment.
Results: DA-grafted animals infused with PBS or BDNF exhibited significant amelioration of LID compared to non-grafted animals, demonstrating successful engraftment. Contrary to our hypothesis, BDNF infusion in grafted animals increased amphetamine- and levodopa-mediated GID behavior in Met/Met hosts. BDNF infusion also increased contralateral amphetamine-induced rotational behavior.
Conclusions: Behavioral results are indicative of excess DA in the grafted striatum, a phenomenon reported in some grafted individuals with PD and GID. Histological and molecular analyses of graft neurochemical phenotypes are ongoing. These data highlight the necessity of careful therapeutic tailoring for optimization of clinical outcomes for individuals with PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1001 / #1627

Poster Topic: *Theme C: α-Synucleinopathies / C02.e. Therapeutic Targets, Mechanisms for Treatment: Cell transplantation*

THERAPEUTIC EFFECT OF NEURAL-INDUCED HUMAN ADIPOSE TISSUE-DERIVED STEM CELL EXOSOME ON ROTENONE-INDUCED PARKINSON'S DISEASE IN RATS

POSTERS: C02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: CELL TRANSPLANTATION

Mahesh Ramalingam[1], Jinsu Hwang[1], Jin Yoo[1], Byeong C. Kim[2], Hyong Ho Cho[3], Sujeong Jang[4], Han-Seong Jeong[1,4]
[1]Chonnam National University Medical School, Physiology, Hwasun-gun, Korea, Republic of, [2]Chonnam National University Medical School & Hospital, Neurology, Gwangju, Korea, Republic of, [3]Chonnam National University Medical School, Otolaryngology, Gwangju, Korea, Republic of, [4]StemCell Bio Inc., Stem Cell Bio, Hwasun, Korea, Republic of

Aims: Parkinson's disease (PD) trigger protein misfolding associated with accumulation of a-synuclein (a-syn) aggregation and neurodegeneration. Rotenone (ROT), a mitochondrial complex I inhibitor, trigger protein aggregation in the pathogenesis of PD. Mesenchymal stem cells treating neurodegenerative diseases mainly attributed their beneficial effects from their secretome during differentiation mainly consist of extracellular vesicles, proteasomes, microRNA, and neurotropic factors. In this study, we examined the exosomes isolated from neurogenic differentiation of human adipose tissue-derived stem cells (NI-hADSC-Exo) against ROT-induced PD model in rats
Methods: Male Sprague-Dawley rats (200-250 g; 8~9 weeks old) were obtained, Rotenone in a dose of 1 mg/kg b.wt. daily for 28 d for induction of PD. NI-hADSC-Exo were suspended in PBS slowly injected into the tail vein at 500 mg/kg b.wt. at days 15, 18, 21, 24, and 27. At end of the experimental period, rats were sacrificed by terminal anesthesia and transcranially perfused, brains were rapidly removed, midbrain and striatum were located, and lysates were prepared for Western blotting. Whole brains were used for immunohistochemistry.
Results: The results obtained in the present study revealed that ROT toxicity significantly reduced tyrosine hydroxylase expression in midbrain and striatum regions. ROT also increased the phospho-Ser129-a-syn in Triton X-100-soluble and -insoluble cell lysate fractions from midbrain and stratum subregions along with increased total a-syn except in midbrain Triton X-100-insolbule fraction. However, NI-hADSC-Exo induced increase in TH expression and TH-positive cells also reduced the phospho-Ser129-a-syn in Triton X-100-soluble and -insoluble cell lysate fractions from midbrain and stratum.
Conclusions: These results suggest that NI-hADSC-Exo involved in improving neurological functions in rats, thus, may presents critical insight in future studies on PD and other neurodegenerative disorders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1002 / #1611

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

SELECTIVE, POTENT, BRAIN-PENETRANT KV1.3 BLOCKADE ABROGATES INFLAMMATORY PROCESSES IN BLOOD AND BRAIN

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Marianne Pedersen[1], Ivana Geric[2], Lucas Baltussen[2], Jorge Valadas[2], Leen Wolfs[3,4], Anke Misbaer[2], Negin Afrang[2], Laura Sans[1], Maria Dalby[1], Anja Koustrup[1], Dorota Kuczek[1], Lars Roenn[1], Rita Balice-Gordon[1], Bart De Strooper[3,4,5], Niels Plath[1]
[1]Muna Therapeutics, Discovery Biology, Copenhagen, Denmark, [2]Muna Therapeutics, Discovery Biology, Heverlee, Belgium, [3]KU Leuven, Department Of Neurosciences And Leuven Brain Institute, Leuven, Belgium, [4]Flanders Institute for Biotechnology (VIB), Centre For Brain And Disease Research, Leuven, Belgium, [5]University College London, Dementia Research Institute, London, United Kingdom

Aims: Microglia are key players in neuroinflammation linked to neurodegenerative diseases such as AD and PD. Several studies suggest that pharmacological blockade of Kv1.3 in rodent microglia reduces neuroinflammation and enhances neuroprotection, indicating its potential as a novel therapeutic approach. A lack of selective, small molecule Kv1.3 blockers with CNS exposure has however prevented the study of Kv1.3 in the context of neuroinflammation in vivo so far. We present here the effect of a potent, selective brain penetrant Kv1.3 blocker on T cells and microglia in the context of inflammatory stimulation in vitro and in vivo.
Methods: Selectivity of compounds was determined by patch-clamp electrophysiology in heterologous cells. Compounds were tested in the context of disease pathology relevant inflammatory stimuli in vitro in human PBMC derived T cells and hIPSC derived microglia and in vivo in human microglia xenografted into mice and wildtype rodent models challenged with pro-inflammatory stimuli both centrally and peripherally. Assessment of cytokine release and gene expression analyses by qPCR and/or RNA-seq were performed on T cells and microglia.
Results: We identified small molecules with low double-digit nanomolar potency for Kv1.3, high selectivity against other Kv1 family members, and excellent brain pharmacokinetics. These compounds exert anti-inflammatory effects both on human T cells and microglia in vitro and in vivo across several different pro-inflammatory stimuli. Transcriptional analyses from xenografted hIPSC microglia showed that Kv1.3 blockade in vivo normalized a pro-inflammatory gene signature.
Conclusions: These results support Kv1.3 as a novel drug target for the treatment of brain disorders with prominent neuroinflammation. Kv1.3 blockade impacts both T cells and microglia, suggesting synergistic effects in the context of neurodegenerative disorders accompanied by peripheral and central inflammation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1003 / #651

Poster Topic: *Theme C: α-Synucleinopathies / C02.e. Therapeutic Targets, Mechanisms for Treatment: Cell transplantation*

NON-MOTOR EFFECTS OF BEMDANEPROCEL FOR PARKINSON'S DISEASE: RESULTS UP TO 18 MONTHS FROM A PHASE 1 STUDY

POSTERS: C02.E. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: CELL TRANSPLANTATION

Marcus Yountz[1], Claire Henchcliffe[2], Harini Sarva[3], Andres Lozano[4,5], Alfonso Fasano[4,6,7], Suneil Kalia[4,5], Kenny Yu[8], Cameron Brennan[8], Michele York[9], Whitney Stemple[10], Nauman Abid[1], Ahmed Enayetallah[11], Antoine Lampron[1], Viviane Tabar[8]
[1]BlueRock Therapeutics LP, Clinical Development, Cambridge, United States of America, [2]University of California, Irvine, Department Of Neurology, Irvine, United States of America, [3]Weill Cornell Medicine, Department Of Neurology, New York, United States of America, [4]Toronto Western Hospital, Krembil Brain Institute, Toronto, Canada, [5]University of Toronto, Division Of Neurosurgery, Toronto, Canada, [6]Toronto Western Hospital, Edmond J. Safra Program In Parkinson's Disease, Morton And Gloria Shulman Movement Disorders Clinic, Toronto, Canada, [7]University of Toronto, Division Of Neurology, Toronto, Canada, [8]Memorial Sloan Kettering Cancer Center, Department Of Neurosurgery And Center For Stem Cell Biology, New York, United States of America, [9]Baylor College of Medicine, Section Of Neurology, Houston, United States of America, [10]BlueRock Therapeutics LP, Biostatistics, Cambridge, United States of America, [11]BlueRock Therapeutics LP, Development, Cambridge, United States of America

Aims: Bemdaneprocel is an investigational cellular therapy composed of pluripotent stem cell–derived dopaminergic neuron precursor cells under development for the treatment of Parkinson's disease (PD). At 1-year post-transplantation, bemdaneprocel was generally safe and well tolerated in all 12 participants in a phase 1 study. Here, we report data exploring the impact of bemdaneprocel on non-motor symptoms in participants with PD.
Methods: In this open-label, non-controlled study, 12 participants received 1 of 2 different doses of bemdaneprocel bilaterally to the post-commissural putamen and a 1-year immunosuppression regimen. Exploratory outcomes assessed at 12 months included the impact of bemdaneprocel on non-motor symptoms. Assessments will be repeated at 18 months, 6 months post-discontinuation of immunosuppression.
Results: At 12 months, participants receiving the higher dose of bemdaneprocel showed an improvement in non-motor symptoms, including a median (Q1, Q3) change from baseline of −28.7% (−58.5%, −1.2%) on the Non-Motor Symptom Scale total score and a median (Q1, Q3) change from baseline of −83.3% (−100%, −50.0%) on the Neuropsychiatric Inventory Questionnaire. Measures of activities of daily living and quality of life remained stable during this time, with a median (Q1, Q3) change from baseline of −9.1% (−42.9%, 11.1%) in part II of the MDS-UPDRS and a median (Q1, Q3) change from baseline of −9.9% (−55.1%, 47.4%) on the PDQ-39 summary index. Participants in the low dose cohort had a median (Q1, Q3) change from baseline of −21.9% (−46.7%, 12.5%) on the PDQ-39 summary index.
Conclusions: Overall, some participants receiving the higher dose of bemdaneprocel had improvement or no worsening from baseline in non-motor outcomes. Data from additional cognitive assessments and 18-month follow-up (6 months post-discontinuation of immunosuppression) will be presented at the congress.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1004 / #1494

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

PEA-OXA EXERTS NEUROPROTECTIVE EFFECTS BY MODULATING THE AUTOPHAGIC PATHWAY IN A MOUSE MODEL OF PARKINSON'S DISEASE

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Alessio Ardizzone[1], Irene Paterniti[2], Deborah Mannino[1], Salvatore Cuzzocrea[1], Emanuela Esposito[1]
[1]University of Messina, Department Of Chemical, Biological, Pharmaceutical And Environmental Sciences, Messina, Italy, [2]University of Messina, Chemical, Biological, Pharmaceutical And Environmental Sciences, Messina, Italy

Aims: Objective: Parkinson's disease (PD) is the second most frequent neurodegenerative disease, and it is characterized by degeneration of nigrostriatal dopaminergic neurons that cause disabling motor disorders. Growing evidences support the impairment of autophagy in PD pathogenesis, thus, its regulation has been considered an attractive therapeutic target in the development of novel PD treatments. In this framework, many scientific articles highlighted the neuroprotective properties of Palmitoylethanolamide (PEA), an endogenous lipid molecule belonging to the N-acetylethanolamines (NAEs) class. PEA is produced "on demand" by our body, in response to stressful conditions or inflammatory stimuli, thus denoting its key role in maintaining cellular homeostasis. Since the administration of PEA suffers from problems related to its metabolism, it was synthetized new derivates such as N-Palmitoylethanolamide-Oxazoline (PEA-OXA), which resulted successful in inhibiting NAAA PEA-degrading enzyme and decreasing neuroinflammation. On this basis, the aim of this study was to deep the neuroprotective effects of PEA-OXA in a murine model of PD.
Methods: Methods: Nigrostriatal degeneration was induced by intraperitoneal injection of MPTP (80 mg/kg), then PEA-OXA 10 mg/kg was administered daily by oral gavage starting from 24 h after the first administration of MPTP. Mice were killed 7 days after MPTP induction, and their brains were processed for histological evaluations and molecular biology analyses.
Results: Results: Our results demonstrated that PEA-OXA treatment significantly improved behavioral deficits and reduced the impairment of PD hallmarks such as tyrosine hydroxylase and dopamine transporter deficit as well as a-synuclein accumulation. Furthermore, PEA-OXA administration mediated a neuroprotective effect through increasing markers of autophagic pathway and modulating apoptosis.
Conclusions: Conclusions: Therefore, in the light of these findings, PEA-OXA could be considered a valuable therapeutic approach by enhancing dopaminergic neurons survival and renewal in PD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1005 / #2349

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

THE CLINICAL STAGE NLRP3 INHIBITOR RRX-001 AMELIORATES NEUROPATHOLOGY AND ACTIVATES MITOCHONDRIAL NRF2 IN MODELS OF PARKINSON'S DISEASE

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Richard Gordon[1], Nanthini Jayabalan[1], Kunal Bhatt[1], Natalia Birch[1], Yashu Balalledeo[1], Madeleine Yule[1], John O'Sullivan[1], Scott Caroen[2], Bryan Oronsky[2]
[1]Translational Research Institute, Queensland University of Technology, Faculty Of Health, Brisbane, Australia, [2]EpicentRx Inc., Therapeutic Development, San Diego, United States of America

Aims: Parkinson's disease manifests as a spectrum of motor and non-motor deficits including selective dopaminergic degeneration, alpha synuclein accumulation and inflammasome activation. Given the complex multifactorial aetiology of PD, emerging evidence suggests that targeting multiple pathological processes could be is essential to achieve disease modification. We recently confirmed that RRx-001, a Phase 3 small molecule chemoprotective and radioprotective agent, is a direct NLRP3 inflammasome inhibitor. In this study, we evaluated if RRx-001 could be developed as a novel disease-modifying therapy for PD.
Methods: For this study we used a combination of mechanistically distinct animal models of PD including the 6-OHDA model and the PFF-synuclein model. For our in vitro models, we used a combination of primary microglia, primary neurons and dopaminergic cell lines such as N27 cells.
Results: We confirmed that daily dosing with RRx-001 (10 mg/kg) reduced NLRP3 inflammasome activation markers in the 6-OHDA model. In the synuclein PFF model, RRx-001 therapy reduced markers of immune and inflammasome activation. In RRx-001 treated animals, we found activation of the neuroprotective NRF2 pathway in the nigrostriatal system. Our *in vitro* mechanistic studies with RRx-001 in dopaminergic neurons and microglia also confirmed that RRx-001 inhibits NLRP3 activation with nanomolar potency. In dopaminergic neurons, RRx-001 prevented mitochondrial fragmentation induced by the Parkinsonian neurotoxicant MPP^+. RRx-001 also improved markers of mitochondrial function and biogenesis in these studies.
Conclusions: Our results highlight RRx-001 as a unique therapeutic agent which can target multiple pathological mechanisms relevant to PD. Given the clinical safety record of RRx-001 in human studies to date, our results suggest that RRx-001 treatment could be an attractive neuroprotective strategy to slow or halt disease progression in PD. Clinical studies with RRx-001 in PD are planned for 2024.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1006 / #750

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

TIANQI PINGCHAN GRANULE PROMOTES RECOVERY OF GLYMPHATIC SYSTEM FUNCTION IN RATS MODEL OF L-DOPA-INDUCED DYSKINESIA

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Zhenguo Liu, Zhihua Liu, Shuyuan Yang, Shuwei Wang, Lu Song, Yu Zhang, Ying Wan, Jing Gan, Na Wu
Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Neurology, Shanghai, China

Aims: To explore the therapeutic effects of TPG(a traditional Chinese medicine for the treatment of Parkinson's disease with an anti-inflammatory protective effect) on the glymphatic systemfunction inparkinsonian rats with L-DOPA-induced dyskinesia (LID)
Methods: 6-hydroxydopamine-hemilesioned rats were injected with L-DOPAfor three weeks to create a model of LID. Then, rats received intragastric administrations of TPG(2.8, 5.6and 11.2 g/kg, respectively) or saline once a day for 3 weeks. The pharmacological effects of TPGonLID were investigated by behavioral test, immunofluorescence and Enzyme-linked immunosorbent assay for the functions of glymphatic system.
Results: showed that TPG (5.6 and 11.2 g/kg) significantly alleviated abnormal involuntary movements score. Moreover, TPG (5.6g/kg) treatment increased CSF tracer influx andreduce amyloid-β deposition in the cortex and striatum. In addition, TPG markedly improved the perivascular aquaporin-4 (AQP4) polarization and exhibited a decrease in glial activation and AQP4expression compared with saline treatment.
Conclusions: This study shows for the first time that glymphatic systemfunctionis impaired in LID and TPG attenuates abnormal involuntary movements in rats with LID by protectingthe glymphatic system

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1007 / #1650

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

NEUROIMMUNE MODULATION IN THE PATHOGENESIS AND THERAPEUTICS OF SYNUCLEINOPATHIES OF THE AGING POPULATION

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Eliezer Masliah[1], Michiyo Iba[2], Changyoun Kim[2]
[1]National Institute on Aging, Division Of Neuroscience And Lng, Bethesda, United States of America, [2]National Institute on Aging, Laboratory Of Neurogenetics, Bethesda, United States of America

Aims: Synucleinopathies of the aging population includes an heterogeneous group of neurodegenerative disorders with alpha-synuclein (alpha-syn) accumulation and includes Dementia with Lewy bodies (DLB), Parkinson's disease (PD) and PD dementia. We have shown that extracellular α-syn that propagates from neurons to glial cells triggers via the TLR2, LRRK2 and NFATc2 axis neuroinflammation and neurodegeneration. Aging is associated with increased accumulation of alpha-syn and neuroinflammation. These abnormal responses involve both adaptive and innate immunity leading to synaptic dysfunction and neurodegeneration involving signaling pathways such as p38MAPK. The main objective of this study is to evaluate the effcts of modulating these signaling pathways in developing novel therapeutics for DLB and PD.
Methods: We investigated the effcts of Immunotherapy with antibodies that block selected T cell populations and NKT's such as CD1d, we also investigated the effects of blocking NFAT signaling with 11R compound, p38MAPK with SKF compounds and deleting microglia with PLX in models of synucleinopathy. We evaluated neuroinflammation, neurodegeneration, transcriptomics, behaviour, signaling, flow cytometry, and proteomics effects.
Results: We have shown that passive immunization with an antibody against CD1d reduces neuroinflamation and neurodegeneration. Treatment with the anti-CD1d antibody did not have effects on CD3 (T cells), slightly decreased CD4 and increased CD8 lymphocytes in the mice. Treatment with CD1d antibody blunted this cytokine response that was associated with reduced astrogliosis and microgliosis in the CNS of the α-syn tg mice treated with CD1d antibody. We have also investigated the effects of blocking NFAT signaling with 11R compound and and targeting p38 in models of synucleinopathy and found that neuroinflammtion is an important mediator of synaptic degeneration
Conclusions: These results suggest that reducing inflammation might be a potential therapeutical approach for DLB/PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1008 / #1463

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

SAFFRON (CROCUS SATIVUS L.) IN ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Reza Mosaddeghi-Heris[1], Ali Norouzi Norouzi[2], Mahnaz Talebi[1], Sarvin Sanaie[1], Amirreza Naseri[3]
[1]Tabriz university of medical sciences, Neurosciences Research Center (nsrc), Tabriz, Iran, [2]Tabriz University of Medical Sciences, Tabriz, Iran, Student Research Committee, Tabriz, Iran, [3]Tabriz university of medical sciences, Student Research Committee, Tabriz, Iran

Aims: Animal studies have provided evidence of saffron antidiabetic, anti-inflammatory, anti-atherosclerotic, antitumor, immunomodulatory, and antioxidant effects. Besides, human studies have brought saffron consumption in Alzheimer's disease (AD) patients to a challenge and the outcomes are not the same and can be discussed. This systematic review aims to evaluate the literature on the effect of saffron, as the main therapeutic agent or as the supplementation on AD.
Methods: This systematic review was conducted based on the methods mentioned in the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) statement. In this study, we electronically searched the databases PubMed, Embase, Scopus, and Web of Science. To be included in the systematic review, a study had to follow the next eligibility criteria: (a) designed as a randomized controlled trial, (b) human studies only; (c) subjects were given saffron orally and compared to either placebo or any approved anti-AD drug or nothing; and (d) cognitive performance was evaluated through objective standardized tests before and after the intervention.
Results: A total of 565 studies were identified in the initial comprehensive search, but only 4 met the criteria. Three studies discovered that saffron significantly improved cognitive outcomes compared to a placebo and only in one study there was no significant difference between the saffron and placebo groups in patients treated with donepezil after 12 weeks.
Conclusions: Saffron, as the main treatment, is found to be beneficial in improving cognitive functions in patients with AD which is comparable to approved drugs for AD with acceptable safety issues. Adding saffron to the main treatments as supplementation may lead to improved inflammation and oxidative stress status.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1009 / #2346

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

BERRY GOOD NEWS: (POLY)PHENOL-RICH DIET AS A PREVENTIVE STRATEGY AGAINST PARKINSON'S DISEASE

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Rafael Carecho[1,2], Ana Filipa Raimundo[1], María Ángeles Ávila-Gálvez[1,3], Hugo Lopes[1], Bernardo Rocha[1], Catarina Pinto[1], Catarina Sequeira[1], Sofia Pereira[1], Natasa Loncarevic-Vasiljkovic[1], Cláudia Nunes Dos Santos[1,2,4]
[1]NOVA Medical School, Molecular Nutrition And Health Lab, Lisboa, Portugal, [2]ITQB, Itqb, Oeiras, Portugal, [3]CEBAS-CSIC, Laboratory Of Food & Health, Research Group On Quality, Safety, And Bioactivity Of Plant Foods, Murcia, Spain, [4]iBET, Ibet, Oeiras, Portugal

Aims: The rising global burden of chronic neurodegenerative disorders, particularly Parkinson's disease (PD), prompts the need for more effective preventive strategies and treatments. (Poly)phenols, natural compounds abundant in plant-derived foods, were studied for their role in preventing or mitigating neurodegenerative diseases. This research endeavored to delve the advantages of a (poly)phenols-rich diet in countering PD's key pathological markers in mice challenged by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and to unveil the metabolic fingerprint behind these effects.
Methods: Mice were fed for 6 weeks with a mixture of (poly)phenol-rich foods (comprising blueberries, raspberries, and blackberries) before PD-like phenotype was induced following an acute protocol of MPTP. The study evaluated motor abilities, dopaminergic neurons damage, inflammatory response, and thiolome profile, aiming to develop an in-depth understanding of dietary phenolics' impact on PD brains.
Results: We demonstrated that the berry-enriched diet was able to alleviate motor deficits in the MPTP-intoxicated mice and delayed dopaminergic neuronal damage in the midbrain. Neuroinflammation was ameliorated by attenuating microglial reactivity in MPTP-treated mice fed with berries in midbrain, striatum, and motor cortex and decreasing mRNA levels of pro-inflammatory IL-6. The berry-enriched diet also interfered with the cysteine-related thiolome. Glutathione levels in MPTP-intoxicated mice fed with (poly)phenol-rich food approached those of control levels, indicating an enhanced capacity to manage the oxidative stress resulting from MPTP toxicity.
Conclusions: These results support the potential of a (poly)phenol-rich diet in delaying and alleviating PD-like symptoms. This study contributes to the broader understanding of dietary interventions' role in neurodegenerative disorders, highlighting the potential role of dietary phenolics in preventing or delaying PD progression. **Acknowledgments:** To the European Research Council (ERC) - Grant Agreement No. 804229; to FCT, for financial support of R.C. (PD/BD/135492/2018), and through the R&D unit iNOVA4Health (LISBOA-01-0145-FEDER-007344).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1010 / #1491

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

STUDY OF NEW PHARMACOLOGICAL TARGETS FOR THE TREATMENT OF PARKINSON'S DISEASE

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Irene Paterniti, Deborah Mannino, Alessio Ardizzone, Salvatore Cuzzocrea, Emanuela Esposito
University of Messina, Chemical, Biological, Pharmaceutical And Environmental Sciences, Messina, Italy

Aims: Objectives: Parkinson's disease (PD) is the second most frequent neurodegenerative disease characterized by progressive and chronic degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Considered research into the etiological mechanisms of PD has demonstrated that the accumulation of damaged proteins such as the α-synuclein protein, the main component of Lewy bodies, is closely related to the alteration of intracellular mechanisms responsible for the degradation of abnormal proteins and damaged organelles such as autophagy. Therefore, pharmacological induction of autophagy and reduction of neuroinflammation could improve the clearance of intracytoplasmic protein aggregates reducing PD progression. Recent scientific research has showed powerful anti-inflammatory and neuroprotective effects of two N-acylethanolamines: palmitoylethanolamide (PEA) and oleoylethanolamide (OEA). Based on this evidence, the aim of the study was to better test the neuroprotective effects of PEA and OEA and investigate their probable mechanism on autophagic processes in an *in vivo* model of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).
Methods: Methods: The experimental model of PD involved four intraperitoneal injections of MPTP (20 mg/kg) at two hours intervals in one day. After twenty-four hours PEA and OEA were administered (orally and intraperitoneally, respectively) both at the dose of 10 mg/kg for seven days.
Results: Results: Our results confirmed that administration of PEA and OEA significantly reduced the alteration of the hallmarks of PD, attenuating the neuroinflammatory state. Furthermore, we demonstrated that the neuroprotective effect observed following PEA and OEA treatment could be linked to the modulation of the autophagic pathway.
Conclusions: Conclusions: In conclusion, given the potent neuroprotective effect of PEA and OEA, both molecules could be considered valid therapeutic approaches for the treatment of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1011 / #659

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

ASSOCIATION OF ANTI-INFLAMMATORY THERAPY USE WITH THE INCIDENCE OF PARKINSON'S DISEASE: A PERSON-TIME ANALYSIS AMONG PATIENTS WITH AUTOIMMUNE DISEASES

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Michele Potashman[1], Jennifer Haas[2], Ambrish Pandit[3], Dana Stafkey[3], Vlad Coric[4], Wolfgang Singer[5], Gil L'Italien[1]
[1]Biohaven Pharmaceuticals, Inc, Clinical Outcomes Assessments And Health Economics, New Haven, United States of America, [2]Xcenda GmbH (Cencora Inc.), Real World Evidence, Hannover, Germany, [3]Cencora Inc., Heor, Conshohocken, United States of America, [4]Biohaven Pharmaceuticals, Inc, Ceo, New Haven, United States of America, [5]Mayo Clinic, Neurophysiology, Rochester, United States of America

Aims: Examine the association between the incidence of Parkinson's Disease (PD) and anti-inflammatory drug exposure, specifically anti-tumor necrosis factor (anti-TNF) and anti-interleukin (IL)-17, in patients diagnosed with autoimmune disease (rheumatoid arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, or psoriasis/psoriatic arthritis).
Methods: This retrospective cohort study analyzed data from the US Komodo Health claims database (2015-2022). Conditions and therapies were identified using established diagnosis and product codes. The comparative risk of PD associated with anti-TNF/anti-IL-17 exposure was examined by designing two cohorts of patients diagnosed with an autoimmune disease, exposed and unexposed to specified anti-inflammatory treatment. Person-time incidence rates of PD were calculated, and incidence rate ratios (IRRs) derived. Person-time incidence rates (per 100 person-years [PY]) by anti-TNF/anti-IL-17-exposure quintiles were derived to evaluate for a potential treatment response.
Results: Among 2,135,733 patients with an autoimmune disease, 122,319 received anti-TNF/anti-IL-17 treatment and 2,013,414 were untreated. The incidence of PD among the exposed cohort was 0.709 per 100-PY, whereas incidence in the unexposed cohort was 1.013 per 100-PY. The IRR between exposed and unexposed was 0.699 (95% CI: 0.675, 0.726). PD incidence rate by anti-inflammatory drug, anti-TNF or anti-IL-17 only respectively, was 0.713 (95% CI: 0.688, 0.739) and 0.558 (95% CI: 0.451, 0.683). The IRR between anti-IL-17 and anti-TNF therapy suggested anti-IL-17-treated patients have a lower risk of developing PD (0.782 [95% CI: 0.634, 0.965)]. Person-time incidence rates suggested a treatment-response relationship, with an incidence in the lowest and highest exposure quintiles, respectively of 6.221 (95% CI: 5.852, 6.608) and 0.153 per 100-PY (95% CI: 0.135, 0.172).
Conclusions: A lower incidence of PD among anti-TNF/anti-IL-17-treated patients with autoimmune disease was observed. This may suggest that lowering levels of systemic inflammation can reduce the risk of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1012 / #1469

Poster Topic: *Theme C: α-Synucleinopathies / C02.f. Therapeutic Targets, Mechanisms for Treatment: Anti-inflammatory, anti-oxidant*

OXIDATIVE STRESS IN MANF KO HUMAN STEM CELLS AND STEM CELL-DERIVED DOPAMINERGIC NEURONS

POSTERS: C02.F. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ANTI-INFLAMMATORY, ANTI-OXIDANT

Amanda Sandelin[1,2], Dimitri Meistermann[3], Leena Koistinen[4], Timo Otonkoski[5], Maria Lindahl[4], Mart Saarma[4], Helena Kilpinen[3], Eija Jokitalo[4], Mikko Airavaara[1,2], Vassilis Stratoulias[1,2]
[1]Drug Research Program of Pharmacology and Pharmacotherapy, Faculty Of Pharmacy, University Of Helsinki, Helsinki, Finland, [2]Neuroscience Center, Hilife, Helsinki, Finland, [3]Helsinki Institute of Life Science, University Of Helsinki, Helsinki, Finland, [4]Institute of Biotechnology, Hilife, Helsinki, Finland, [5]Stem Cell and Metabolism Research Program, University Of Helsinki, Helsinki, Finland

Aims: Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons (DNs) in the substantia nigra pars compacta (SNpc). The SNpc DNs have an exceptionally high energy demand due to high axonal arborization and autonomous pacemaker activity, which renders the SNpc DNs more vulnerable to mitochondrial dysfunction and oxidative stress. Mesencephalic astrocyte-derived neurotrophic factor (MANF) has been shown to have cytoprotective effects in DNs and other cell types. Although the neuroprotective effects of MANF show promise, MANF function at the cellular level is poorly understood. The aim of this study is to elucidate the cellular and neuroprotective mechanisms of endogenous MANF in the context of oxidative stress.
Methods: In this study, we established an in vitro model to study human dopaminergic neurons. Wildtype and MANF knockout (KO) human embryonic stem cells (hESCs) were differentiated into DNs. Wildtype and MANF KO hESCs and DNs are compared using a wide range of functional assays. We used methods such as RNA sequencing, bioenergetic measurements, and electron microscopy to study the effects of MANF knockout on cell profiles at different developmental time points.
Results: Our results show that MANF KO hESCs differentiate efficiently into DNs. However, the MANF KO hESCs and DNs show deficits in their bioenergetic and antioxidant profiles and increased vulnerability to oxidative stress. In addition, we observe ultrastructural differences between wildtype and MANF KO cells.
Conclusions: Our data on MANF KO hESCs and DA neurons indicate a role for MANF in mitochondrial respiration and protection against oxidative stress.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1013 / #1713

Poster Topic: *Theme C: α-Synucleinopathies / C02.g. Therapeutic Targets, Mechanisms for Treatment: Microglia*

NOVEL ORAL BIOAVAILABLE SMALL MOLECULES TARGETED AT BRAIN PHOSPHOLIPID DYSREGULATION FOR PREVENTION AND SLOW DOWN OF ALZHEIMER'S DISEASE PROGRESSION

POSTERS: C02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Dongming Cai[1,2,3,4], Min Huang[2], Maria Duarte[2], Li Zhu[1], Minghui Wang[5], Minghao Zhong[6], Michael Ohlmeyer[7]
[1]The University of Minnesota, Neurology, Minneapolis, United States of America, [2]Icahn School of Medicine at Mount Sinai, Neurology, And Alzheimer's Disease Research Center, New York, United States of America, [3]The Minneapolis VA Health Care System, Grecc, Minneapolis, United States of America, [4]James J Peters VA Medical Center, Research & Development, New York, United States of America, [5]Icahn School of Medicine, Genomics And Genetic Studies, New York, United States of America, [6]The University of Minnesota, Pathology, Minneapolis, United States of America, [7]Atuk Iskay LLC, Ceo, Plainsboro, United States of America

Aims: With ongoing effort to test and optimize anti-amyloid monoclonal antibodies, the evidence of a significant improvement in cognitive outcome measures without any major side effect concerns is rather limited. We have been studying a novel AD target synaptojanin 1 (synj1), a brain-specific phosphoinositol bisphosphate (PIP_2)-degrading enzyme that modulates lipid homeostasis and endo-lysosomal function. Evidence suggests by reducing synj1, multiple disease processes can be modulated at once.
Methods: We identified an FDA-approved drug, nimodipine that reduces synj1 protein expression. Nimodipine has proven human safety profiles with excellent pharmacokinetic (PK) properties and blood-brain barrier (BBB) penetrability as a starting point for drug discovery. On the other hand, nimodipine manifested some short-term benefits but failed to show any sustained cognitive benefits with chronic treatments in AD mouse models *in vivo*. We then developed nimodipine structural analogs using medicinal chemistry approaches to potentiate its synj1-lowering effects (on-target effects) and reduce its calcium channel activity (off-target effects), which resulted in the discovery of two promising synj1-lowering compounds, Cpd#9 and Cpd#6 as lead candidates.
Results: Two nimodipine derivatives (Cpd#9 and Cpd#6) showed superior beneficial effects *in vitro* and improved oral bioavailability *in vivo*. More importantly, both lead compounds manifested a sustained *in vivo* efficacy of cognitive improvement after chronic oral administration in familial and sporadic AD mouse models. Single-cell RNA-sequencing (scRNA-seq) analysis identified brain cell type-specific changes in microglial signature, reversing disease-related microglial signatures observed in AD human and mouse brains.
Conclusions: In summary, we describe key findings of two novel disease modifying small molecules targeting the brain PIP_2-synj1 pathway that could prevent and slow down cognitive decline in AD mouse models. The mechanisms of action involve changes in microglial signature and modulation of neuro-inflammation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1014 / #1038

Poster Topic: *Theme C: α-Synucleinopathies / C02.g. Therapeutic Targets, Mechanisms for Treatment: Microglia*

DEVELOPMENT OF CHIMERIC HUMAN-RODENT FUNCTIONAL AND HIGH CONTENT IN VITRO NEUROINFLAMMATORY MODELS

POSTERS: C02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Joana De Abreu Carvalho[1], Christina Nodin[2], Paul Karila[2]
[1]Apollo Therapeutics, Research, Cambridge, United Kingdom, [2]Cellectricon AB, Cellectricon Ab, Mölndal, Sweden

Aims: Neuron-glia interactions and neuroinflammation may be dysfunctional in neurodevelopmental and neurodegenerative disorders. Complex cell biology in vitro models for investigating such interactions for drug discovery are lacking. We therefore set out to establish high-capacity, high-quality in vitro assays using rodent primary cortical cultures, consisting of neurons and astrocytes with human iPSC-derived (hiPSC) microglia. Our novel assays will investigate neuronal function and cell health and are promising tools for the testing of molecules with the potential to modulate neuroinflammation.
Methods: Chimeric cultures of rodent primary cortical cultures and hiPSC microglia were generated in 384 well-format. After 10-14 days, cell cultures were treated with LPS at different concentrations and timepoints. 1-5 days after LPS addition, neuronal, astrocytic and microglial morphology and TNF-alpha release was quantified. Further, optical electrophysiology was used to investigate effects on neuronal network activity.
Results: The chimeric model resulted in well-integrated hiPSC microglia, with morphology resembling homeostatic microglia, as well as healthy neurons and astrocytes. Addition of LPS resulted in a clear shift of hiPSC microglia to an amoeboid morphology as quantified by HCA, an increased TNF-alpha secretion and an increased electric field stimulation-evoked response. Changes in microglia were aligned with an activated pro-inflammatory status.
Conclusions: The results indicate that it is possible to generate biologically relevant neuroinflammation models for drug discovery, where both morphological and functional phenotypes such as cytokine release and neuronal network activity can be investigated for the functional profiling of molecules developed for clinical use.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1015 / #2378

Poster Topic: *Theme C: α-Synucleinopathies / C02.g. Therapeutic Targets, Mechanisms for Treatment: Microglia*

ELUCIDATING THE NEUROPROTECTIVE MECHANISMS OF HUMAN MICROGLIAL REPLACEMENT THERAPY IN A MODEL OF PARKINSON'S DISEASE

POSTERS: C02.G. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: MICROGLIA

Sarah Naguib, Eileen Ruth Torres, Maitreyee Bhagwat, Li Fan, Shiaoching Gong, Li Gan
Weill Cornell Medicine, Neuroscience, New York, United States of America

Aims: Microglia are the most prevalent immune cell in the central nervous system (CNS) and interact with neurons in both physiological and pathological conditions. In multiple neurodegenerative diseases, including Parkinson's Disease (PD), microglia become activated and relocate to the site of damage. In our studies we aim to study the roles of both adaptive and innate immunity in PD pathology. Our lab and others have shown that progranulin (PGRN) is important in multiple neurodegenerative diseases, including PD. As such, we aim to implement a PGRN microglial gene therapy approach in order to protect against neurodegeneration.
Methods: We bilaterally injected α-synuclein PFFs into immunodeficient ($Rag2^{-/-}$, $IL2R^{-/-}$, human m-$CSF^{KI/KI}$) and C57Bl/6 mice. We performed behavioral analysis on these mice using the pole test to assess movement disorder phenotypes. For microglial cell replacement, we injected another cohort of immunodeficient mice with PBS or α-synuclein to induce Parkinsonian pathology in the striatum. Two weeks later, we treated mice with control or PLX-5622 diet to deplete microglia and after three weeks, we bilaterally injected PBS, wildtype HPCs, or PGRN-overexpressing HPCs. After four months, we performed similar behavioral analyses.
Results: In examining the role of adaptive immunity in α-synuclein pathology, we found that the immunodeficient mice spent significantly more time completing the pole test than their wildtype controls. After four months, we observed that the spread of α-synuclein was significantly increased in the immunodeficient mice suggesting the necessity for an adaptive immune response to prevent α-synuclein spread.
Conclusions: Using our model, we have demonstrated that microglia are an important component in the progression of neurodegeneration. Together, our results highlight the feasibility of a cell therapy approach to combat neurodegeneration in Parkinson's Disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1016 / #1917

Poster Topic: *Theme C: α-Synucleinopathies / C02.i. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, misfolding, chaperones*

BRAIN-DERIVED NEUROTROPHIC FACTOR DECREASES LEWY BODY-LIKE INCLUSIONS INDUCED BY PRE-FORMED ALPHA-SYNUCLEIN FIBRILS IN MOUSE PRIMARY NEURONS

POSTERS: C02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Airavaara Mikko Tuomas, Irena Hlushchuk, Veera Kulmala, Tomi Rantamäki, Andrii Domanskyi, Safak Er
University of Helsinki, Faculty Of Pharmacy, Helsinki, Finland

Aims: Parkinson's disease is the second most common progressive neurodegenerative disease characterized by loss of dopamine neurons in the substantia nigra and Lewy bodies - intraneuronal inclusions- as neuropathological hallmarks. The aim of this study is to investigate if brain-derived neurotrophic factor (BDNF) can reduce pre-formed fibril (PFF) induced Lewy body-like alpha-synuclein aggregation in mouse primary dopaminergic and hippocampal neurons.
Methods: Dopaminergic neurons isolated from the ventral midbrain floor of 13.5 mouse embryos were plated in 96-well plates and maintained in a culture medium without neurotrophic factors until the day *in vitro* (DIV)8. Glial cell line-derived neurotrophic factor (GDNF) was used as a positive control since it reduces the aggregation of alpha-synuclein in cultured dopaminergic neurons and the mouse brain. BDNF was added on a DIV8 1 hour after the PFF-treatment, or on DIV12. The cultures were fixed on DIV15 and stained with tyrosine hydroxylase (TH) and phosphoSer129-alpha-synuclein (pS129-alpha-syn) antibodies. Quantifying TH+ neurons and pS129-alpha-syn+ and TH+ neurons was performed with unbiased image analysis using CellProfiler™ software.
Results: and conclusions: Neither GDNF nor BDNF added at the late stages of culturing did not significantly affect the survival of TH+ neurons. Like GDNF, BDNF added either on DIV8 or DIV12 decreased pS129-alpha-syn positive aggregates in dopaminergic neurons. The effect of BDNF was slightly more pronounced when added earlier on DIV8 instead of on DIV12.
Conclusions: BDNF treatment similarly to GDNF treatment decreased the numberr of pasyn-s129-positive neurons in our model system. Research on neurotrophic factors' protective effects on multiple neuropathologies can help the development of new therapies against Parkinson's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1017 / #971

Poster Topic: *Theme C: α-Synucleinopathies / C02.i. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, misfolding, chaperones*

GT-02287, A CLINICAL STAGE GLUCOCEREBROSIDASE REGULATOR FOR THE TREATMENT OF PD, EASES ER STRESS AND ENHANCES LYSOSOMAL ENZYME ACTIVITY

POSTERS: C02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Natalia Perez-Carmona[1], Ilaria Fregno[2], Tatiana Solda[2], Mikhail Rudinskiy[2], Sara Cano-Crespo[1], Ana Ruano[1], Manolo Bellotto[3], Ana Garcia-Collazo[1], Maurizio Molinari[2,4]
[1]Gain Therapeutics, Barcelona, Barcelona, Spain, [2]Institute for Research in Biomedicine, Protein Folding And Quality Control, Bellinzona, Switzerland, [3]Gain Therapeutics, Lugano, Lugano, Switzerland, [4]Ecole Polytechnique Fédérale de Lausanne, School Of Life Sciences, Lausanne, Switzerland

Aims: Glucocerebrosidase (GCase) deficiency is linked to pathophysiological features in Parkinson's disease (PD), including heightened endoplasmic reticulum (ER) stress. This dysregulation contributes to the accumulation of misfolded alpha-synuclein, leading to dopaminergic neuron degeneration. This study aims to uncover the mechanism by which GT-02287, Gain Therapeutics' PD drug candidate, targets GCase and impacts the disease's underlying biological processes.
Methods: Gain Therapeutics applied its innovative proprietary drug discovery platform, SEE-Tx™, to the development of orally bioavailable and brain penetrant GT-02287. GCase functionality, ER stress and protein quality control were evaluated in patient-derived fibroblasts harbouring mutated GCase. A mutated GCase-HaloTag-HEK293 cell-based model was used to measure GCase transport to the lysosome.
Results: The L444P GCase mutation delays its conformational maturation in the ER, shown by prolonged association with ER-resident lectin chaperone calnexin. GCase retention in the ER triggers an unfolded protein response, shown by overexpression of ER stress markers BiP and GRP94. GCase retained in the ER is eventually degraded by the ubiquitin-proteasome system. GT-02287 treatment accelerated conformational maturation of mutant GCase, thus promoting release from calnexin. Reduced retention of the mutant protein in the ER alleviated cellular stress, as shown by return to physiological BiP and GRP94 levels and enhanced lysosomal transport. Accordingly, GT-02287 increased lysosomal GCase activity which led to a reduction in levels of its substrate, glucosylceramide.
Conclusions: Through interaction with GCase in the ER, GT-02287 aids correct GCase folding and prevents it undergoing protein quality control-mediated ER retention and ER-associated degradation. Enhanced stability of GCase promotes its release from the ER, alleviating cellular stress and allowing trafficking towards lysosomes, where GCase accomplishes its enzymatic activity. The enhanced lysosomal activity ensures that GCase substrate is efficiently processed, further contributing to cell health.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1018 / #2066

Poster Topic: *Theme C: α-Synucleinopathies / C02.i. Therapeutic Targets, Mechanisms for Treatment: Protein aggregation, misfolding, chaperones*

TRANSTHYRETIN HAS CONFORMATION-SELECTIVE PROTEOLYTIC ACTIVITY AGAINST ALPHA-SYNUCLEIN

POSTERS: C02.I. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: PROTEIN AGGREGATION, MISFOLDING, CHAPERONES

Zsuzsa Sárkány[1], Tiago Gião[2], Márcia Liz[3], Antoni Planas[4], Sandra Macedo-Ribeiro[1], Isabel Cardoso[2], Gemma Arsequell[5], Pedro Martins[1]
[1]i3S - Instituto de Investigação e Inovação em Saúde, Biomolecular Structure And Function Group, Ibmc, Porto, Portugal, [2]i3S - Instituto de Investigação e Inovação em Saúde, Molecular Neurobiology Group, Ibmc, Porto, Portugal, [3]i3S - Instituto de Investigação e Inovação em Saúde da Universidade do Porto – Associação, Neurodegeneration Team, Nerve Regeneration Group, Ibmc, Porto, Portugal, [4]Institut Químic de Sarrià, University Ramon Llull, Laboratory Of Biochemistry, Barcelona, Spain, [5]Institute of Advanced Chemistry of Catalonia (IQAC-CSIC), Biological Chemistry, Barcelona, Spain

Aims: Transthyretin (TTR) is a plasma protein known as a transporter of thyroxine and retinol but also can inhibit the formation of amyloid β-peptide (Aβ) fibrils and catalyze the proteolysis of apolipoprotein A-I and Aβ. Here, recombinant TTR is shown to have proteolytic activity against specific conformations of α-synuclein (aSyn), a protein that accumulates in intraneuronal inclusions characteristic of Parkinson's disease (PD). Our discovery stemmed from the observation of a marked decrease in aSyn aggregation in the presence of submicromolar concentrations of TTR.
Methods: We integrate multiple biophysical approaches, including fluorescence spectroscopy, electron microscopy, gel electrophoresis and mass spectrometry to show that the conformation of aSyn must be changed before TTR-mediated proteolysis occurs.
Results: We found that aSyn aggregation is prevented due to the proteolytic cleavage of free aSyn by TTR, in a reaction that is slower for S-glutathionylated TTR and faster for TTR preparations containing vestigial amounts of ~70 kDa TTR oligomers (oTTR). Interestingly, this proteolysis-trigger effect is not unique to oTTR since it can also be induced by Teflon and glass surfaces independently of which TTR preparation is tested.
Conclusions: The link between protein misfolding and the pathogenesis of PD, AD or TTR-related amyloidosis remains poorly defined especially in the non-hereditary forms of such disorders. Our study additionally shows that the proteolytic activity of TTR against aSyn is determined by conformational changes arising from physical interactions of aSyn with solid surfaces. On the side of TTR, S-glutathionylation is shown to influence the proteolytic activity of TTR, probably due to the introduction of steric hindrances to substrate binding. The proteolysis of misfolded aSyn emerges as a possible TTR function with implications for the understanding of different neurodegenerative disorders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1019 / #2803

Poster Topic: *Theme C: α-Synucleinopathies / C02.j. Therapeutic Targets, Mechanisms for Treatment: Gene therapy and gene editing*

DIRECT CELLULAR REPROGRAMMING IN PARKINSON´S DISEASE USING CRISPR/CAS9

POSTERS: C02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

Iolo Balken
Helmholtz Munich, Institute Of Developemental Genetics, Neuherberg, Germany

Aims: Parkinson´s disease is a neurodegenerative disorder, mainly characterized by the specific degeneration of nigrostriatal dopaminergic neurons in the substantia nigra pars compacta. So far no causal treatment option exists and therapy is primarily symptomatic. However, several attempts are realized utilizing in situ direct cellular reprogramming of somatic cells, like fibroblast or astrocytes, to generate dopaminergic neurons as a curative option. The efficiencies of generating functional dopaminergic neurons were not satisfying so far and it was found that one limitation during reprogramming is induced cell death via apoptosis and ferroptosis. So this work focuses on reducing cell death via apoptosis and ferroptosis in combination with multiplexed *in vitro* and *in vivo* activation of transcription factors to reprogram astrocytes into dopaminergic neurons.
Methods: This is achieved by using a CRISPR/Cas9 activator system to upregulate the transcription factors Ascl1, Lmx1a, Nr4a2 or Ascl1, miR124, miR9, Pitx3, Foxa2 to facilitate the reprogramming and additionally the transcription factors Mcl1 and Bcl2 as well as Gpx4 and Fsp1 to inhibit apoptosis and ferroptosis respectively.
Results: In this ongoing project an improved upregulation of transcription factors used for reprogramming was achieved. Using CRISPRa a sufficient upregulation of transcription factors inhibiting apoptosis and ferroptosis could be established on RNA as well as on protein level. It could be shown that Gpx4 and Fsp1 increase cell viability upon Ferroptosis induction. The beneficial effect of the increased cell viability on direct reprogramming is being analyzed.
Conclusions: Inhibiting Apoptosis and Ferroptosis during direct cellular reprogramming is a suitable method to increase the reprogramming efficiency of astrocytes to dopaminergic neurons. Ongoing *in vivo* experiments are investigating the effect of this reprogramming in a Parkinson´s Disease mouse model.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1020 / #2147

Poster Topic: *Theme C: α-Synucleinopathies / C02.j. Therapeutic Targets, Mechanisms for Treatment: Gene therapy and gene editing*

INTRONIC ENHANCERS OF HUMAN SNCA GENE PREDOMINANTLY REGULATE ITS EXPRESSION PROVIDING NEW TREATMENT TARGET

POSTERS: C02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

Fubo Cheng, Wenxu Zheng, Thomas Ott, Kathrin Grundmann, Olaf Riess
Univesity of Tuebingen, Institute Of Medical Genetics And Applied Genomics, Tuebingen, Germany

Aims: Alpha-synuclein (SNCA) is a key gene in the pathogenesis of Parkinson's disease (PD). Evidences from both human PD patients and SNCA overexpressing transgenic animal models supported that increased human α-synuclein levels contribute to PD pathogenesis. However, little is known about the transcription control of the human SNCA gene in brain. Our previous report showed decreased SNCA expression in both THAP1 patients' iPSCs derived middle brain dopaminergic (mDA) neurons and THAP1 heterozygous knock-out SH-SY5Y cells, but the detailed mechanisms are still unclear.
Methods: In this study, multi-omics approaches combined with multiple cellular and animal models were used to characterize the transcriptional regulation of *SNCA* gene in vitro and in vivo.
Results: We found that THAP1 regulates expression of SNCA through controlling the activities of its promoter and enhancers via both direct and indirect pathways. Chromatin conformation capture analysis proved the physical interaction between the enhancers in intron 4 of the *SNCA* gene and the promoter region. Further luciferase report assay confirmed the role of SNCA intronic enhancer in controlling its expression. Furthermore, knocking-out one enhancer fragment of the *SNCA* intronic enhancer regions in both dopaminergic SH-SY5Y cells repress the expression of SNCA. In our human SNCA transgenic rat models, deletion of the large intronic region drastically reduced the expression of SNCA in the whole brain.
Conclusions: Taking together, our study revealed how DYT6 gene product THAP1 regulates the expression of SNCA, which potentially links two dopaminergic pathway associated diseases. Both in vitro and in vivo data supported the critical role of SNCA enhancers in regulating its own expression, which may provide new gene therapy approaches for SNCA aggregated neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1021 / #1113

Poster Topic: *Theme C: α-Synucleinopathies / C02.j. Therapeutic Targets, Mechanisms for Treatment: Gene therapy and gene editing*

SYNTHETIC SENSOR-ACTUATOR CIRCUIT FOR UNTANGLING THE COMPLEXITY OF ENVIRONMENTAL ORIGIN OF SPORADIC NEURODEGENERATIVE DISORDERS

POSTERS: C02.J. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: GENE THERAPY AND GENE EDITING

Mychal Grames, Xinli Tian, Madison Elsaadi, Kelsea Keys, Xiao-Hong Lu
LSU Health, Pharmacology, Toxicology, And Neuroscience, Shreveport, United States of America

Aims: PD is the second-most prevalent neurodegenerative disease, where the majority of incidences have no identifiable inheritance and occur in a sporadic form. Environmental risk factors (e.g., pesticide/herbicides, exposure to metals, solvents, PCBs, virus infection, and head trauma) have been speculated as a trigger to sporadic PD.
Methods: To explore the causal and pathogenic evidence of environmental triggers, we exploited long-standing observations that genotoxic DNA damage can significantly increase permissivity to AAV transduction, and host cell DNA damage response (DDR) is an innate antiviral defense mechanism and is thus inhibitory to viral life cycles. We harnessed the recombinant adeno-associated virus (rAAV) genome-processing machinery and the instability of a hypermutable repeat sequence to detect neuronal genomic instability and visualize neurodegeneration in post-mitotic differentiated neurons. Viral genetic probe sensitively detected genotoxic stressed neurons exposed to environmental toxicant Paraquat. Targeted next-generation sequencing validated genetic variation in poly-G repeat on the rAAV genomic region.
Results: Moving beyond traditional genetic perturbation in all cells, we developed a synthetic sensor-actuator circuit as a "Cellular Robot," which enables precise genetic engineering in cells damaged by exposure to environmental toxicants. A genetic actuator was implemented via a Cre-dependable conditional shRNA to knockdown ATM, a major orchestrator of the DDR for slowing down the progression of neurodegeneration. Conditional knockdown of ATM in DNA-damaged burdened cells ameliorated the progression of paraquat-aggravated synucleinopathy, motor decline, and cognitive deficits.
Conclusions: These studies can pave the way for new paradigms to determine the causal and pathogenic roles of environment-driven genotoxic stress in the progression of neurodegenerative disease and highlight potential therapeutic avenues.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1022 / #591

Poster Topic: *Theme C: α-Synucleinopathies / C02.k. Therapeutic Targets, Mechanisms for Treatment: ASO and RNAi*

NANOPARTICLE-BASED NOSE-TO-BRAIN DELIVERY OF SMALL RNA MEDIATES DOWNREGULATION OF ALPHA-SYNUCLEIN IN A PARKINSON´S DISEASE MOUSE MODEL

POSTERS: C02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ASO AND RNAI

Isabell Drath[1,2], Malte Feja[1,2], Birthe Gericke[1,2], Sandra Weiß[1], Alexander Ewe[3], Achim Aigner[3], Franziska Richter[1,2]
[1]University of Veterinary Medicine Hannover, Department Of Pharmacology, Toxicology, And Pharmacy, Hannover, Germany, [2]University of Veterinary Medicine Hannover, Center For Systems Neuroscience (zsn) Hannover, Hannover, Germany, [3]University of Leipzig, Rudolf-boehm-institute For Pharmacology And Toxicology, Clinical Pharmacology, Faculty Of Medicine, Leipzig, Germany

Aims: Potential strategies to develop new treatments for Parkinson`s disease (PD) target specific, disease-associated proteins like alpha-Synuclein (aSyn). A promising new approach to lower aSyn protein levels is the therapeutic use of small RNAs. Efficient delivery of small RNA is challenging due to their instability and the need to bypass the blood-brain barrier. Therefore, we developed a nanoparticle-based approach for intranasal delivery of small RNAs, opening this gene therapy strategy to broad clinical application.
Methods: In this project, seven different polymeric nanoparticles (NPs) were tested *in vitro* for their ability to penetrate neuronal cells. Differentiated SH-SY5Y neuroblastoma cells were incubated with NPs loaded with fluorescent-labeled control RNA and evaluated by confocal microscopy. Furthermore, we administered different control RNA-NPs intranasally to aSyn overexpressing (Thy1-aSyn) mice once daily on four consecutive days. For functional experiments, Thy1-aSyn mice received either nanoparticles loaded with small RNA targeting human *SNCA* mRNA (SNCA-NPs) or with control RNA intranasally. Mice were sacrificed and brains collected for immunohistochemical, western blot and qPCR analysis.
Results: All tested NPs were able to penetrate SH-SY5Y neuroblastoma cells. Furthermore, all labeled NPs reached the brain after intranasal application. They distributed extensively across the brain and were detectable in different regions including the olfactory bulb, substantia nigra and prefrontal cortex. Quantitative evaluation revealed that cationic polymers reached the brain in the highest amount. Mice showed no overt adverse behavioral effects nor increased reactivated microglia. After only four days of intranasal administration, SNCA-NPs significantly reduced brain aSyn levels with a polymer-dependent efficacy.
Conclusions: Non-invasive NP-mediated intranasal application of small RNA to aSyn overexpressing mice is able to reduce aSyn levels in the brain and could be a novel therapeutic approach to treat PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1023 / #487

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

NX210C PEPTIDE: A PROMISING DRUG CANDIDATE FOR BLOOD-BRAIN BARRIER REPAIR IN PARKINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Nicolas Rebergue[1], Chris Greene[2], Matthew Campbell[2], Gwen Fewell[3], Supriya Mahajan[4], Damir Janigro[4], Juliette Le Douce[1], Sébastien Marie[1], Annette Janus[1], Yann Godfrin[1,5], Sigihld Lemarchant[1]
[1]Axoltis Pharma, -, Lyon, France, [2]Smurfit Institute of Genetics, Lincoln Place Gate, Trinity College Dublin, Dublin, Ireland, [3]Synvivo, -, Huntsville, United States of America, [4]Flocel, -, Cleveland, United States of America, [5]Godfrin Life-Sciences, -, Caluire-et-Cuire, France

Aims: Recent works show that blood-brain barrier (BBB) leakage represents a disease-driving feature of PD, as shown by the reduction of tight junction proteins and the increased BBB paracellular permeability in animal models. Accordingly, BBB disruption was also shown in the substantia nigra of PD patients. Here, we screened the effect of a subcommissural organ-spondin-derived peptide (NX210c) known to be beneficial in PD models, on BBB integrity *in vitro* and *in vivo*.
Methods: Mouse endothelial cell (EC) monolayers (bEnd.3) and human BBBs (EC, astrocytes, pericytes) in static or microfluidic conditions, were treated with NX210c (1-100µM), or its vehicle (water). 3- and 21-month-old mice were treated intraperitoneally with NX210c at 10mg/kg or its vehicle for 5 days once a day and brains collected at day6.
Results: In mouse EC, NX210c induced a transient increase in occludin levels after 24h treatment (+37%, 100µM; western-blot). Claudin-5 levels were also increased after 24h (+43%, 100µM) and 72h (immunocytochemistry). Accordingly, NX210c decreased by half the permeability to a 40 kDa-FITC-Dextran and increased transendothelial electrical resistance (TEER). In the human static BBB model, NX210c increased by 30% the TEER at 100µM after 3 and 5 days. NX210c also increased TEER in the human 3D dynamic BBB model at 100µM after 4h, and reduced the permeability to a 4 kDa-FITC-dextran. NX210c restored aging-induced reduction of claudin-5 and occludin levels in the cortex and/or hippocampus. This is in alignment with positive signals of BBB repair after repeated intravenous injections of NX210c in elderly healthy volunteers in a phase 1b clinical trial.
Conclusions: NX210c is a promising drug candidate for modifying PD course, notably by reducing BBB leakage. Therefore, we are now evaluating if NX210c promotes BBB repair in a PD mouse model.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1024 / #2272

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

MULTI-TARGETED STRATEGIES TO ARREST PARKINSON'S DISEASE: THE UTILITY OF REPURPOSING DRUGS FOR NEUROPROTECTIVE APPROACHES

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Rita Silva[1,2], Bruna Araújo[1,2,3], Richard Wade-Martins[4], Hugo Fernandes[4], Fábio Teixeira[1,2]
[1]Institute for Research and Innovation in Health (i3S), Neurobiology & Neurologic Disorders, Porto, Portugal, [2]Center for Translational Health and Medical Biotechnology Research, Translational Health And Medical Biotechnology Research, Porto, Portugal, [3]PT Government Associated Lab, Icvs/3b's Associate Lab, Braga, Portugal, [4]University of Oxford, Department Of Physiology, Anatomy & Genetics, Oxford Parkinson's Disease Centre, Oxford, United Kingdom

Aims: Repositioning disease-modifying approaches is imperative to achieve meaningful translational gains in Parkinson's Disease (PD) research. Under this concept, two drugs have demonstrated promising effects in dopaminergic system preservation and PD mechanistic modulation, namely N-acetylcysteine (NAC) and Felodipine (FEL). Therefore, this study aimed to target PD major hallmarks using a multimodal approach combining NAC and FEL's potential neuroprotective/disease-modifying abilities, rather than establishing an isolated approach to modulate PD brain parenchyma and compromised DAn in affected brain regions.
Methods: To better understand the impact of NAC and FEL on DAn functional recovery, a specific cell model of PD (Lund Human Mesencephalic (LUHMES)-derived dopaminergic neurons) was characterized. For recovery studies, cells were treated with 10μM of NAC, 100nM of Felodipine and the combination. As readouts, we evaluated the main mechanisms associated with PD pathology and how our drugs could modulate them. Following this step, we analyzed the most effective therapeutic approach for PD. An in-house PD rat model was used, mimicking PD symptoms and pathology. NAC (1200mg/kg) and FEL (20mg/day) were administered individually or conjugated to study their effect on multiple PD dimensions.
Results: Preliminary in vitro and in vivo studies revealed promising findings. Notably, the treated group appeared to modulate specific mechanisms associated with PD degeneration compared to controls. Indeed, modifications in DAn networks/signaling pathways, functional outcomes, and histological and molecular-cellular features were observed.
Conclusions: In retrospect, with the pilot results acquired in this study, we provided an important proof-of-concept milestone regarding therapeutical combinatorial applications. Following such research approach will allow the development of a targeted-based strategy that can generate clinical benefits, including a novel treatment opportunity for individuals in prodromal stages, potentially delaying clinical manifestation in high-risk patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1025 / #2265

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

IMPACT OF ABROGATION OF ADULT HIPPOCAMPAL CYTOGENESIS ON PARKINSON'S DISEASE PRE-CLINICAL MODEL

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Bruna Araújo[1,2,3,4], Rita Silva[2,4], Per Svenningsson[5,6], Luísa Pinto[1,3], Fábio Teixeira[2,4]
[1]Life and Health Sciences Research Institute (ICVS), ¬School of Medicine, Neuroscience Domain, Braga, Portugal, [2]Center for Translational Health and Medical Biotechnology Research, School of Health, Porto Polytechnic Institute, School of Health, Porto Polytechnic Institute, Translational Health And Medical Biotechnology Research (tbio), Porto, Portugal, [3]PT Government Associated Lab, Icvs/3b's Associate Lab, Braga, Portugal, [4]Institute for Research and Innovation in Health (i3S), Neurobiology & Neurologic Disorders, Porto, Portugal, Portugal, [5]Karolinska Institutet, Clinical Neuroscience, Stockholm, Sweden, [6]Karolinska Institutet, Department Of Clinical Neuroscience, Stockholm, Sweden

Aims: Deficits in adult hippocampal neurogenesis (AHN) is a common feature of depression and Parkinson's Disease (PD). Indeed, depressive disturbances occur in 40–50% of patients with PD, influencing many clinical aspects of the disease. Adult-born hippocampal cells showed abnormal morphological development and altered differentiation markers' expression, exhibiting singular AHN signatures in PD patients. Additionally, the number of proliferating cells in the subventricular zone and dentate gyrus (DG) was reduced in PD patients and mice models. Since both regions comprise dopaminergic innervation and inputs from the nigrostriatal areas, it has been hypothesized that dopaminergic system may exert some control over or under cytogenic brain regions, representing a promising therapeutic target for depression in PD patients.
Methods: Firstly, we used a transgenic rat (glial fibrillary acidic protein (GFAP)-thymidine kinase (TK)) to induce a PD model. Then, to determine the effect of cytogenic abrogation on a PD pre-clinical model, the antiviral drug ganciclovir was administrated for 18 days. Due to its interaction with TK and its impact on cell replication blockage, the TK-GFAP-TK animals exhibit reduced newborn cells in DG, oppositely to WT-GFAP-TK rats. Since non-motor symptoms play a key role in leading to severe disability, we characterized the anxiety/depressive-like behavior of the animals.
Results: Analysis demonstrated that cytogenesis abrogation may potentiate the anxiety/depressive-like phenotype of PD rats, indicating that the modulation of neurogenesis may have a role in the functional performance of PD.
Conclusions: Understanding the impact of the modulation of AHN and the role of non-motor symptomatology in PD may allow us to study early cellular/molecular and functional alterations promoted by age-related events. By following this, novel perspectives about new potential mechanisms and therapeutic targets could be opened for PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1026 / #1912

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

INVESTIGATION OF THE MECHANISM OF ACTION OF AN ANTIPARKINSONIAN NEUROPROTECTIVE PEPTIDE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Gabriel Campos, Diogo Vieira Tibery, Márcia Renata Mortari
University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil

Aims: Parkinson's Disease (PD) is a relentless and progressively debilitating neurodegenerative disorder that brings economic, social, and psychological burden to its patients. Neurodegeneration in PD involves multiple cell death pathways, representing a great challenge in pharmacological treatment aiming for neuroprotection. In this work we studied a synthetic peptide bioinspired by a toxin isolated from the venom of the social wasp *Polybia occidentalis*. This peptide, called Neurovespina, has been studied previously, exhibiting a neuroprotective effect in an animal model of parkinsonism induced by 6-OHDA. To investigate the mechanism of action responsible for Neurovespina's neuroprotective effect, we performed binding and reuptake assays, as well as patch clamp assays, targeting two potentially neuroprotective mechanisms.
Methods: We used radioactive glutamate and cortical synaptosomes in receptor binding and reuptake assays to evaluate the effect of multiple concentrations of Neurovespina on glutamate neurotransmission. Neurovespina at a concentration of 50 µM was also studied using the patch clamp whole-cell technique to evaluate inhibition or modulation of voltage-gated calcium channels (Cav 1.2, Cav 1.3, Cav 2.1, Cav 2.2, and Cav 2.3).
Results: We observed no competition between Neurovespina and glutamate on mice cortical receptors, nor modulation of glutamate reuptake on synaptosomes. However, at 50 µM, Neurovespina inhibited calcium current amplitude between 14-18% in all channels tested, and this current inhibition was reversible after washing. Current inhibition occurred without changing the probability of channel opening, as demonstrated by the absence of modulation in the conductance curves.
Conclusions: Our results reveal that Neurovespina inhibits voltage-gated calcium channels. This mechanism is consistent with neuroprotection, as observed with other channel blockers, such as those from the dihydropyridine class. Yet, it is possible that the antiparkinsonian effect this peptide showed is associated with more than one target.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1027 / #201

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

AMANTADINE DIFFERENTIALLY EFFECTS STRIATAL DIRECT AND INDIRECT SPINY PROJECTION NEURONS IN BRADYKINETIC AND DYSKINETIC STATES IN PARKINSONIAN MICE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Gaurav Chattree[1], Radosław Chrapkiewicz[2], Jane Li[2], Yanping Zhang[2,3], Mark Schnitzer[2,3]
[1]Stanford University, Neurology & Neurological Sciences, Stanford, United States of America, [2]Stanford University, Cnc Program, Stanford, United States of America, [3]Howard Hughes Medical Institute, Hhmi, Stanford, United States of America

Aims: Amantadine is a unique medication that improves both bradykinetic and dyskinetic movements, but its use is limited by serious side effects and its mechanism of action is unknown. **The aim of this study is** to determine Amantadine's effects on striatal direct and indirect spiny projection neurons (dSPNs and iSPNs) in bradykinetic and dyskinetic states to gain insight into Amantadine's mechanism of action. This may be useful for the development of new, improved treatments for Parkinson's disease.
Methods: We used two-photon calcium imaging to simultaneously record the firing activity of dSPNs and iSPNs in the dorsolateral striatum of mice as they ran on a wheel. We first recorded behavior and neural activity in the pre-lesion baseline state, then injected mice with 6-OHDA in the ipsilateral substantia nigra pars compacta (SNc) to induce unilateral dopamine depletion. We then recorded behavior and neural activity in dopamine depleted mice receiving the following intraperitoneal injections: Saline (vehicle control), Amantadine 60mg/kg, L-DOPA 10mg/kg, and L-DOPA 10mg/kg + Amantadine 60mg/kg.
Results: In dopamine depleted mice, compared to Saline alone, Amantadine increased the maximum achieved running speed and mean dSPN calcium event rate per trial. Additionally, compared to L-DOPA 10mg/kg alone, Amantadine (when given with L-DOPA 10mg/kg) reduced the percentage of time mice spent having dyskinetic movements and increased the mean iSPN calcium event rate per trial.
Conclusions: Amantadine improves bradykinesia and increases dSPN activity in dopamine depleted mice. Amantadine also reduces dyskinesias and increases iSPN activity in dopamine depleted mice given high-dose L-DOPA. This data suggests that increasing iSPN activity may be a useful strategy for treating dyskinesias. This could be used to guide the development of selective, novel treatments for dyskinesias with better side effect profiles than Amantadine.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1028 / #359

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

CHANGES IN QUALITY OF LIFE, DEPRESSION, AND SATISFACTION IN WOMEN WITH PARKINSON'S DISEASE FOLLOWING DEEP BRAIN STIMULATION

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Sun Ju Chung[1], Sungyang Jo[1], Kye Won Park[1], Seung Hyun Lee[2], Yun Su Hwang[3], Mi Sun Kim[1,2]
[1]Asan Medical Center, Neurology, Seoul, Korea, Republic of, [2]Seoul Medical Center, Neurology, Seoul, Korea, Republic of, [3]Jeonbuk National University Hospital, Neurology, Jeonju, Korea, Republic of

Aims: To investigate the changes in quality of life (QoL), depression, and satisfaction of women with Parkinson's disease (PD) following deep brain stimulation (DBS).
Methods: This mixed-method case study involved the analysis and categorization of completed interviews with participants. Data were collected through questionnaires, individual in-depth interviews, and a review of electronic medical records. Patients were recruited between December 2019 and April 2020 to gather qualitative data. Additionally, we analyzed quantitative data using the United Parkinson's Disease Rating Scale (UPDRS), Beck Depression Inventory (BDI), and the 39-item Parkinson's Disease Questionnaire (PDQ-39) both before and after DBS implantation.
Results: Twelve women with PD who underwent DBS implantation participated in this study. The average age was 57.5±8.8 years with an average implantation period of DBS of 5.9±5.0 years. The patient's baseline UPDRS part III significantly improved after the surgery (39.3±10.4 vs 25.0±16.8; p=0.038). The axial symptoms (p=0.003) and off duration (p=0.008), and mean modified Hoehn and Yahr stage (p=0.017) significantly improved after DBS implantation. However, PDQ-39 scores (60.3±24.2 vs 56.9±22.7) and BDI scores (20.3±11.5 vs 17.1±7.7) before and after surgery were not significantly different ($0.45<p<0.70$). The reasons for subjective dissatisfaction included "stress due to external changes seen by others," "pain at the implantation site," "reduction in DBS implantation effect," "economic burden of battery replacement surgery," and "anxiety when DBS goes off."
Conclusions: This study found that female patients with PD did not exhibit significant difference in their self-reported quality of life (QoL) and levels of depression before and after the procedure, although they had improvement in motor symptoms after DBS surgery. These results underscore the importance for medical service providers to recognize and address patients' discomfort and concerns from a therapeutic perspective.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1029 / #464

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

TT-P34: A NOVEL FIRST-IN-CLASS PEPTIDE DRUG FOR TREATMENT OF PARKINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Anders Dalby[1], Nathalie Berge[2], Mathias Ollendorff[1], Simon Jensen[1]
[1]Teitur Trophics, R&d, Aarhus, Denmark, [2]Aarhus University Hospital, Department Of Nuclear Medicine And Pet, Aarhus, Denmark

Aims: TT-P34 is a novel cyclic peptide drug which has been developed by Teitur Trophics, a biotech company based I Aarhus, Denmark. The peptide induces mitochondrial and lysosomal biogenesis through upregulation of master regulators PGC1a and TFEB. It is well established that α-synuclein aggregation and propagation leads to dysfunction of both mitochondria and the lysosomal autophagy system (LAS), resulting in axonal degeneration and neuronal death. Here, we assessed the therapeutic efficacy of TT-P34 as a first-in-class peptide in Parkinson's Disease. The aim was to investigate the potential of TT-P34 to protect against dopaminergic cell loss and reduce pathological α-synuclein inclusions as a result of restoring the affected mitochondrial and lysosomal pathways mitochondrial.
Methods: The peptide was evaluated in two different rodent models; 1) the MPTP mouse model and in 2) a brain-initiated Parkinson's disease rat model using recombinant alpha-synuclein fibrils injected unilaterally into the amygdala of aged (14 months old) rats.
Results: In the MPTP mouse model, once-daily administration of TT-P34 significantly increased locomotor activity in the open field test in a dose-dependent manner as well as completely rescued grip strength. These behavioral improvements were accompanied with significant rescue of TH^+ neurons in substantia nigra pars compacta area (SNc). Once daily treatment with TT-P34 (0.2mg/kg) of the PFF-rat model led to a 75% reduction of α-synuclein inclusions and dramatic increase in TH^+ neurons in SNc.
Conclusions: By driving gene transcription of key regulators, PGC1a and TFEB, in neuronal health TT-P34 offers a unique approach to target multiple affected cellular pathways in Parkinson's. Taken together, this validates the therapeutic efficacy of TT-P34 as a novel and first-in-class drug for Parkinson's Disease and other neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1030 / #2644

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

LONG-TERM EFFECTS OF GLIAL CELL-LINE DERIVED NEUROTROPHIC FACTOR (GDNF) IN HUMANS

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Lotta Granholm[1], John Slevin[2], Anah Gilmore[3], Isaac Colvett[3], Frederick Schmitt[2], Tritia Yamasaki[2], Samuel Guzman[4], Jorge Quintero[5], Craig Van Horne[5], Greg Gerhardt[5]
[1]University of Colorado Denver Anschutz Medical Campus, Neurosurgery, Aurora, United States of America, [2]University of Kentucky, Neurology, Lexington, United States of America, [3]University of Colorado Anschutz Medical Campus, Neurosurgery, aurora, United States of America, [4]University of Colorado Anschutz Medical Campus, Pathology, Aurora, United States of America, [5]University of Kentucky, Neurosurgery, Lexington, United States of America

Aims: Glial cell line-derived neurotrophic factor (GDNF) is a member of the TGF-beta superfamily of growth factors with neurotrophic activity on midbrain dopaminergic neurons and on motoneurons of the brainstem and spinal cord. Our group previously showed that GDNF administration can rescue dopaminergic cell loss in the 6-OHDA lesioned rat and that GDNF knockout mice are born without dopaminergic neurons. Patients with Parkinson's disease (PD) have reduced levels of GDNF and are dependent on GDNF for dopaminergic neuronal survival. This led to the first clinical trials of infusion of GDNF into the putamen of patients with PD. A few years ago, two studies were published, showing modest clinical benefits of GDNF infusion in two different cohorts of patients. We now present data from two *postmortem* brains from patients who received intra-putaminal GDNF infusions over 20 years ago.
Methods: Two patients who received unilateral GDNF infusions died from unrelated causes during the last few years. The brains were extracted, and anatomical regions were dissected and fixed according to the NIA-AA protocol for brain processing. The tissue was paraffin embedded and 5-micron sections were de-paraffinized and processed for immunohistochemistry, using antibodies directed against tyrosine hydroxylase (TH) and alpha-synuclein. The following brain regions were investigated: middle frontal gyrus, the head of the caudate nucleus, putamen/globus pallidus, and substantia nigra.
Results: Preliminary studies support an increase in TH innervation in the putamen of the GDNF-infused hemisphere. In depth bilateral comparisons of innervation densities are currently ongoing.
Conclusions: Preliminary data suggest that a 24-month infusion of GDNF gave rise to a long-lasting increased dopaminergic innervation in the ipsilateral putamen, suggesting that longer term infusions of GDNF may produce more sustained effects on damaged dopamine neurons.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1031 / #2586

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

GOLEXANOLONE, A GABAA RECEPTOR-MODULATING STEROID ANTAGONIST, IMPROVES FATIGUE, ANXIETY, DEPRESSION AND SOME COGNITIVE AND MOTOR ALTERATIONS IN 6-OHDA RATS

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Yaiza María Arenas Ortiz[1,2], Paula Izquierdo-Altarejos[1], Mar Martinez-García[1], Gergana Mincheva[1], Magnus Doverskog[3], Thomas P. Blackburn[3], Marta Llansola[1], Vicente Felipo[1]
[1]Centro de Investigación Príncipe Felipe, Neurobiology, valencia, Spain, [2]INCLIVA, Neurological Impairment, valencia, Spain, [3]Umecrine Cognition AB, Umecrine Cognition Ab, Solna, Sweden

Aims: Enhanced GABAergic neurotransmission contributes to Parkinson's disease (PD) pathogenesis and to some motor and non-motor symptoms. In animal models, GABA levels are increased in substantia nigra pars compacta, leading to reduced expression of tyrosine hydroxylase (TH) in neurons which contributes to the behavioural deficits. The aim was to evaluate whether treatment with golexanolone, a well-tolerated $GABA_A$ receptor-modulating steroid antagonist in clinical development, that reduces $GABA_A$ receptors activation and neuroinflammation, may improve some motor and non-motor deficits in a rat model of PD.
Methods: We used the unilateral 6-OHDA rat model. Rats positive in the apomorphine-induced rotation test were included, together with sham-operated controls. Golexanolone treatment (50 mg/kg, daily, intragastric) started four weeks after surgery. Motor symptoms were assessed by motorater and CatWalk tests. The following non-motor behaviour was evaluated: fatigue (treadmill), anhedonia (sucrose preference test), anxiety (open field) and short-term memory (Y maze). Neuroinflammation and key proteins involved in PD pathogenesis were analyzed by immunohistochemistry and western blot
Results: 6-OHDA rats showed impaired motor coordination and locomotor gait alterations measured by motorater and CatWalk tests. Golexanolone treatment improved motor coordination and reversed some of the locomotor gait alterations. Regarding non-motor deficits, 6-OHDA rats showed increased fatigue in the treadmill test, anxiety in the open field test, anhedonia in the sucrose preference test and impaired short-term memory in the Y maze. These alterations were reversed by golexanolone treatment. Golexanolone also reversed some neuroinflammation parameters.
Conclusions: Golexanolone treatment may be useful to improve different symptoms that affect the patients' quality of life: anxiety, depression, fatigue, some aspects of motor coordination and locomotor gait, and some cognitive alterations. These beneficial effects would be due to a reduction of GABAergic neurotransmission and neuroinflammation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1032 / #1278

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

ASSESSING BIOINSPIRED PEPTIDE FRATERNINE-24 ANTOPARKINSONISM EFFECT IN MICE AND RATS IN 6-OHDA PARKINSON'S DISEASE MODEL

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Caio De Azevedo, Márcia Renata Mortari, Andréia Mayer, Gabriel Campos, Henrique Amaral, Danilo De Oliveira, Solange Rego, Adolfo Carlos De Souza, Raffael De Castro, Anamélia Bocca
University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil

Aims: Develop a peptide bioinspired in the natural form Fraternine, which presented promising effects for treating Parkinson. Fraternine presented neuroprotective effects and improvement in motor coordination, however, it is quickly degraded from blood serum. Consequently Fraternine-24 was developed looking to, improve motor coordination model, reduce the activation of the microglia and proinflammatory cytokines levels and decrease dopaminergic neurons depletion in the *Substantia Nigra* (SN).
Methods: Therapeutic efficacy was evaluated using 6-OHDA toxin model, the peptide was delivered through a guide canula, the doses were 20, 10 and 5 µg/animal. The tests utilized were apomorphine-induced rotational behavior test to assess the lesion and two Rotarod test for motor coordination. Neuronal depletion was assessed through counting TH-reactive cells and comparing the 6-OHDA-lesion side and the non-lesion side. Pro-inflammation rates were measured with capture enzyme-linked immunosorbent assay, accounting for TNF-α, IL-1β and IL-6.
Results: Fraternine-24 did not present significant difference in the Rotarod tests in comparison to the 6-OHDA group. The dose 20µg/animal was the only one to stay less time in the rotarod then the SHAM group suggesting neuromuscular toxicity. All doses had a lower number of rotations when compared to the L-DOPA group in the Apomorphine test. Furthermore, the highest dose showed significantly different from the 6-OHDA group. Dose 10µg/animal and 20µg/animal presented more dopaminergic neurons than 6-OHDA group, having significant difference.
Conclusions: Fraternine-24 exerted a potential neuroprotective and anti-inflammatory effect in the 6-OHDA-induced model of hemiparkinsonism. The dose of 20 µg/animal preserved dopaminergic neurons in the SN and reduced apomorphine-induced rotations. However, it did no effect motor coordination, and the higher dose was toxic possibly causing motor impairment. Toxicity is a challenged that requires further studies. This work was supported by FAPDF, CAPES and CNPq.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1033 / #1710

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

SINEUPS: A NOVEL RNA TOOL FOR THE NEUROPROTECTION OF DOPAMINERGIC NEURONS IN PARKINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Carlotta Bon[1], Bianca Pierattini[1], Stefano Espinoza[2], Sabrina D'Agostino[1], Gloria Ros[1], Omar Peruzzo[1], Piero Carninci[3], Francesca Persichetti[2], Remo Sanges[4], Claudio Santoro[2], Stefano Gustincich[1]
[1]Istituto Italiano di Tecnologia, Rna Lab, Genova, Italy, [2]Universita' del Piemonte Orientale, Department Of Health Sciences And Research Center On Autoimmune And Allergic Diseases (caad), Novara, Italy, [3]Human Technopole, Genomics Research Center, Functional Genomics Programme, Milano, Italy, [4]SISSA, Area Of Neuroscience, Trieste, Italy

Aims: SINEUPs are a functional class of natural and synthetic antisense long non-coding RNAs that enhance the translation of partially overlapping sense mRNAs. Their activity depends on the combination of two domains: the overlapping region that dictates the specificity, and the embedded inverted SINEB2 element that acts as the effector domain controlling the enhancement of mRNA translation (Carrieri *et al.*, Nature 2012). By artificial engineering, synthetic SINEUPs can increase the translation of virtually any target gene of interest. We have previously developed active SINEUPs for the Glial cell-derived neurotrophic factor (GDNF), which is a well-established neurotrophic factor promoting the survival of dopaminergic (DA) neurons and a potential agent to halt neurodegeneration in Parkinson's disease (PD). Upon stereotaxic injection of AAV-SINEUP-GDNF, endogenous GDNF protein levels increased up to 3-fold and ameliorated motor deficits and neurodegeneration of DA neurons in a PD neurochemical mouse model (Espinoza *et al.*, Molecular Therapy 2020). Yet, several pieces of evidence suggest the need for additional SINEUPs targeting genes, which increased expression could be combined to efficiently protect DA neurons *in vivo*.
Methods: We designed SINEUP RNAs for GDNF and RET and multiSINEUPs targeting both transcripts at the same time. SINEUP activity was evaluated by measuring endogenous GDNF and RET protein levels by western blot. Their post-transcriptional control of target gene expression was monitored with qRT-PCR.
Results: Here we show that single and multi-target SINEUP RNAs can increase endogenous protein levels of molecules with therapeutic interest by about 2-fold.
Conclusions: Our study provides first evidence that multiSINEUPs can increase endogenous levels of more than one candidate therapeutic molecule for PD at the same time paving the way for a new RNA therapeutic strategy for multitarget drugs in neurodegenerative diseases.

P1034 / #699

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

THE PREVENTIVE EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS ON THE PNEUMONIA IN PATIENTS WITH PARKINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Aryun Kim[1], Jun Yeon Cho[2]
[1]Chungbuk National University Hospital, Department Of Neurology, Cheongju, Korea, Republic of, [2]Chungbuk National University Hospital, Department Of Internal Medicine, CHEONGJU-SI, Korea, Republic of

Aims: Cough is one of the most common adverse events of angiotensin-converting enzyme (ACE) inhibitors. Previously, there has been controversy on the protective effect of ACE inhibitors on pneumonia in the general population and patients with stroke possibly related to this adverse event. We aimed to elucidate the effects of ACE inhibitors on the pneumonia in patients with Parkinson's disease.
Methods: We analysed National Health Insurance System (NHIS) database in South Korea from January 1, 2004 to December 31, 2019. The inclusion criteria are; (1) Older than 40 years, (2) Newly diagosed Parkinson's disease (PD) with V124 code, (3) Hypertension previous than PD. They were devided into two groups including ACE inibitor users and non-users.
Results: The total number of patients was 1,302,897. The number of each group was 38,919 when matched by sex, age, disease duration, and Charlson Comorbidity Index (CCI). More bacterial pneumonia developed in patients with female gender, older age, history of pneumonia in the previous year, higher CCI score, and longer disease duration. The strongest risk factor was history of pneumonia during the previous year. In addition, use of ACE inhibitors for any duration did not affect the incidence of pneumonia. It decreased the risk of pneumonia only when used for more than 60 days.
Conclusions: According to our nation-wide cohort study, ACE inhibitors can decrease the risk of aspiration pneumonia in patients with PD. However, its preventive effects are significant only during the period of use.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1035 / #1631

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

EXPLORING THE MULTIPLE MECHANISMS UNDERLYING HER-096 NEUROPROTECTION AND REGENERATION

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Natalia Kulesskaya, Kira Holmström, Henri Huttunen
Herantis Pharma, Scientific Department, Espoo, Finland

Aims: HER-096 is a brain-penetrating peptidomimetic derived from the active site of human CDNF protein and is developed as a disease-modifying treatment for Parkinson's disease. The aim of this study is to improve understanding of the multimodal mechanism of action of HER-096.
Methods: In vivo effects of HER-096 were studied in an aged mouse model with intranigral injection of alpha-synuclein oligomers and systemic glucocerebrosidase inhibition. HER-096 was administered subcutaneously three times a week starting one week after alpha-synuclein injection. Neurotransmitter, metabolite and protein levels were analysed from nigrostriatal lysates by mass spectrometry and immunoassays. Transcriptomic changes were analysed from dissected striatum and substantia nigra and spatial transcriptomics focused on substantia nigra. Regenerative mechanisms were studied using hiPSC motor neuron cultures in microfluidic chambers which were subjected to mechanical axotomy. Corresponding changes in protein biomarker levels both in vivo and in vitro will also be studied.
Results: In the aged mouse synucleinopathy model, HER-096 protected dopamine neurons and reduced alpha-synuclein aggregation. This was accompanied by normalized nigrostriatal levels of dopamine and dopamine turnover correlating with improved motor function (bar walking test, grid walking test). Protein levels of tyrosine hydroxylase and dopamine transporter were increased supporting the increased number of dopamine neurons and terminals. In an axotomy model, HER-096 strongly enhanced axonal regeneration of hiPSC motor neurons, without affecting non-axotomized motor neurons. The on-going transcriptomic and protein biomarker analysis is expected to provide further insight into underlying multimodal biological mechanisms.
Conclusions: A multi-omics approach was employed to uncover the multimodal mechanism underlying the effects of HER-096 on functional recovery in chronic and acute degeneration. Our results suggest that HER-096 promotes functional recovery and regeneration of stressed neurons via multiple complementary ways.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1036 / #486

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

NX210C PEPTIDE: A PROMISING DRUG CANDIDATE FOR NEUROPROTECTION IN PARKINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Sigihld Lemarchant[1], Juliette Le Douce[1], Alexandre Henriques[2], Noëlle Callizot[2], Yann Godfrin[1,3]
[1]Axoltis Pharma, -, Lyon, France, [2]Neuro-Sys, -, Gardanne, France, [3]Godfrin Life-Sciences, -, Caluire-et-Cuire, France

Aims: PD is characterized by the accumulation of α-synuclein and blood-brain barrier disruption, thereby contributing to the loss of dopaminergic neurons in the substantia nigra. Here, we have evaluated the effect of a subcommissural organ-spondin-derived peptide (NX210c) on PD progression using *in vitro* and *in vivo* rat models.
Methods: Primary rat dopaminergic neurons were exposed for 48h to human α-synuclein and treated simultaneously with NX210c (100, 250, 500 µg/mL) or its vehicle (water), or to 6-OHDA and then treated for 2h with NX210c or its vehicle. Neuronal survival, neurite growth, microglial activation and/or α-synuclein aggregation were evaluated by immunocytochemistry. Sprague Dawley rats were subjected to an injection of AAV1/2-hA53T-α-synuclein or an empty AAV (control) in the substantia nigra, and treated 2 days later with NX210c at 2.5, 5 or 10 mg/kg and then once a day for 41 days. Rats were sacrificed on D42 to measure dopamine levels (LC-MS/MS), dopamine transporters (autoradiography), and α-synuclein aggregation (ELISA) in the striatum.
Results: NX210c reduced α-synuclein-induced neurite network retraction, neuronal death and microglial activation in dopaminergic neuron cultures, when applied in parallel of α-synuclein regardless of the dose used. Dopaminergic neurons were also protected from 6-OHDA when post-treated for 2h with NX210c at 500 µg/mL, likely due to the decrease in α-synuclein aggregation (-71%, $p=0.004$, $n=4$-5). *In vivo*, daily treatment with NX210c at 5 mg/kg significantly increased dopamine levels and its transporters in the striatum compared with that of untreated PD rats ($n=9$-11, $p<0.05$. No effect was observed at 2.5 and 10 mg/kg. In this model, NX210c did not reduce α-synuclein aggregation ($p>0.05$).
Conclusions: NX210c is a promising drug candidate for reducing neuropathological changes in PD, notably the loss of dopaminergic neurons.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1037 / #2281

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

GAMMA AUDITORY STIMULATION CONTRIBUTES TO NEUROMODULATORY EFFECTS ASSESSED BY EEG IN PARKINSON'S DISEASE RAT MODEL

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Sheng Ke Lin[1,2], Jun-Qi Huang[1,2], Hou-Hsuan Lee[2], Chi-Wei Kuo[2], Tsung-Hsun Hsieh[2]
[1]Chang Gung University, Department Of Biomedical Sciences (master's Program In Clinical Trials Assessment), Taoyuan City, Taiwan, [2]Chang Gung University, School Of Physical Therapy And Graduate Institude Of Rehabilitation Science, Taoyuan City, Taiwan

Aims: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder. Previous studies on PD have suggested that alterations in abnormal electroencephalography (EEG) patterns may reflect the neural communication and underlying neuronal dysfunction. Additionally, studies have demonstrated that gamma-frequency sensory stimulation could improve the cognitive and memory functions in Alzheimer's disease mouse model. However, the effects of gamma-frequency sensory stimulation on PD remain uncertain. Therefore, this current research specifically aims to apply the PD animal model to investigate the neuromodulatory effects following gamma auditory stimulation.
Methods: 6-hydroxydopamine (6-OHDA) was injected into the left medial forebrain bundle to induce a hemiparkinsonian rat model. EEG data were collected using five electrodes implanted in the left/right frontal lobes, parietal lobe, and occipital cortex. The EEG data were then analyzed across multiple frequency bands (delta, theta, alpha, beta, low/high gamma) within a time frame that included pre-, during-, and post-gamma auditory stimulation.
Results: We observed a decrease in EEG power especially in low-gamma frequency (30-48 Hz) in the sham-PD lesion rats after stimulation compared to pre-stimulation period. Additionally, a similar pattern was found in the PD rats, indicating a reduction in low-gamma frequency following gamma auditory stimulation.
Conclusions: This study demonstrated the role of gamma auditory stimulation in neuromodulation, as assessed by EEG, in a PD rat model. Future research could focus on enhancing gamma frequency oscillations with the purpose of improving motor cortex plasticity in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1038 / #1934

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

EFFECT OF EARLY DEEP BRAIN STIMULATION IN THE PARKINSON'S DISEASE RODENT MODEL INDUCED BY INTRACEREBRAL INFUSION OF 6-HYDROXYDOPAMINE.

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Miguel Cesar Merino Ruiz[1], Gabriely Penha[2], Ingrid Araujo[2]
[1]Sarah Network of Reabilitation Hospitals, Neurologic Rehabilitation., Brasília, Brazil, [2]Unb, Neuropharmacology, Brasília, Brazil

Aims: - To test the early brain stimulation model in the rodent model of Parkinson's disease (PD) induced by 6-hidroxidopamine (6-OHDA).
- To develop a deep brain stimulation device to be used in mice after induction of hemiparkinsonism by injection of 6-OHDA.
- Evaluate the motor response in different behavioral tests (rotarod test, apomorphine and cylinder test).
- To evaluate the impact of deep brain stimulation on the animals clinical condition.
Methods: Animals: Swiss mice (20 to 35g) were allocated to 3 experimental groups by simple randomization. Each group consisted of 8 individuals and was structured as follows: Group 1: DBS implants, activated, and left nigrostriatal lesion (6-OHDA + DBS). Group 2: DBS implants, inactive, and left nigrostriatal lesion (6-OHDA). Group 3: No DBS implant and no nigrostriatal lesion (Naive). Parkinsonism was induced by injecting 6-hydroxydopamine (6-OHDA) into the left striatum, and at the same time, a deep brain stimulation electrode was implanted in the ipsilateral subthalamic nucleus. High-frequency deep brain stimulation (DBS) using constant current square waves (130 Hz, 60 μs, 100 μA) were delivered for a period of 3 hours a day, for four days. To quantify DBS impact, we performed the Cylinder test and Rotarod test, as well as corporal mass changings.
Results: We found favorable responses in the animals submitted to DBS when compared to parkinsonian mice without brain stimulation, in terms of recovery of body mass and motor performance recorded by the cylinder and rotarod tests.
Conclusions: Early DBS in the rodent model of Parkinson's Disease shows effectiveness in corporal mass recovery, as well as motor performance improvement.

P1039 / #1943

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

EVALUATION OF THE ANTIPARKINSONIAN EFFECT OF FRATERNINE-10 IN MICE AND RATS IN MODEL OF PARINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Márcia Renata Mortari, Andréia Mayer, Henrique Amaral, Danilo De Oliveira, Gabriel Campos, Solange Rego, Adolfo Carlos De Souza, Raffael De Castro, Anamélia Bocca
University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil

Aims: This study aimed to synthesize the peptide Fraternine-10 based on the natural fraternine, which had demonstrated neuroprotective properties against dopaminergic lesions induced by 6-OHDA. However, the original peptide was quickly degraded in the bloodstream, so improving its properties was crucial. Fraternine-10 was designed to reduce the levels of inflammatory mediators TNF-α, IL-6, and IL-1ß in the cortex, enhance motor coordination, and decrease the loss of dopaminergic neurons through a neuroprotective effect.
Methods: The 6-OHDA-induced Parkinson's disease model was used to assess therapeutic efficacy in vivo, with Fraternine-10 administered intracerebroventricularly at three doses (10, 5 and 1 µg/animal). Motor coordination was evaluated using the Rotarod test. An apomorphine-induced test was conducted to assess the degree of lesion. Immunohistochemistry was employed to evaluate neuronal depletion in the Substantia Nigra, with TH-reactive cells counted on both lesioned and non-lesioned sides. Cytokine levels were measured using a capture enzyme-linked immunosorbent assay. The peptide's interaction with glutamatergic neurotransmission was tested using binding techniques with rat cerebral cortex.
Results: Fraternine-10 had a theoretical molecular mass of 1,456.71 Da and a theoretical isoelectric point of 9.70. Doses of 5 and 10 µg/animal on day 2 showed a difference compared to the Control group. In the six-hour Rotarod test, the group treated exhibited significant differences in time but not between treatments. Treated animals spent less time on the Rotarod than the SHAM group at all three doses, indicating neuromuscular toxicity. Fraternine-10 did not show a significant difference in cytokine levels or in glutamate binding.
Conclusions: Fraternine-10 improved motor coordination in 6-OHDA-lesioned animals. However, it did not reduce inflammatory mediators and exhibited toxic effects. While promising, toxicity and effectiveness remain challenges to be addressed. This work was supported by FAPDF, CNPq e CAPES.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1040 / #2085

Poster Topic: *Theme C: α-Synucleinopathies / C02.k. Therapeutic Targets, Mechanisms for Treatment: ASO and RNAi*

IN VIVO EFFICACY AND TOLERABILITY OF SNP614, A LRRK2 ANTISENSE OLIGONUCLEOTIDE AS POTENTIAL THERAPEUTIC AGENT FOR PARKINSON'S DISEASE

POSTERS: C02.K. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: ASO AND RNAI

Dai-Shi Su[1], Irene Riera Tur[2], Andreas Zembrzycki[1], Yuka Martens[1], Marta Reyes Jiménez[2], Sven Michel[2], Richard Klar[2], Frank Jaschinski[2], Guojun Bu[1], Min Li[1]
[1]SciNeuro Pharmaceuticals, R&d, Rockville, United States of America, [2]Secarna Pharmaceuticals, R&d, Munich, Germany

Aims: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra and a deficiency of dopamine in the striatum. Pathogenic mutations in the Leucine-Rich Repeat Kinase 2 (LRRK2) gene are strong genetic risk factors for PD. The majority of disease-associated LRRK2 mutations lead to increased LRRK2 kinase activity that disrupts multiple aspects of normal cellular physiology. Our objective is to develop therapeutic agents capable of reducing LRRK2 mRNA to broadly lower PD-associated LRRK2 overactivation in the central nervous system (CNS).
Methods: By performing *in silico* design and cellular screening, a series of antisense oligonucleotides (ASOs) against LRRK2 have been isolated. Here, we describe *in vivo* activities and safety assessments of SNP614, one of the leading candidates.
Results: The candidate ASOs targeting different regions of *LRRK2* effectively knocked down the LRRK2 expression, reduced LRRK2 protein levels, and attenuated its downstream signaling, as demonstrated by reduced phosphorylation of a LRRK2 substrate, RAB10, in human cells. In both rodent and non-human primate (NHP), SNP614 substantially decreased LRRK2 mRNA and protein levels in broad CNS regions of therapeutic interest. Furthermore, the selected ASOs including SNP614 were well-tolerated in the tested animals.
Conclusions: We report the discovery of ASOs that reduce LRRK2 mRNA levels to broadly lower PD-associated LRRK2 overactivation in CNS. These ASOs are potent, efficacious, and well-tolerated, and have excellent potentials to be developed as therapeutic agents for PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1041 / #545

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

EFFECTS OF COMBINED EXCITATORY THETA BURST STIMULATION AND VIDEO GAME-BASED TRAINING ON DEXTERITY IN PARKINSON'S DISEASE: A RANDOMIZED TRIAL

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Manuela Pastore-Wapp[1], Brigitte Kaufmann[1], Thomas Nyffeler[1], Cornelia Cox[1], Tobias Nef[2], Stephan Bohlhalter[1], Tim Vanbellingen[2]
[1]Luzerner Kantonsspital, Klinik Für Neurologie Und Neurorehabilitation (knn), Luzern, Switzerland, [2]University Bern, Artorg Center For Biomedical Engineering Research, Gerontechnology And Rehabilitation Group, Bern, Switzerland

Aims: Persons with Parkinson's disease (PD) are often faced with difficulties performing dexterity-related activities of daily living (ADL) (such as buttoning, writing). The present study aimed to investigate the efficacy of combined excitatory intermittent theta burst stimulation (iTBS) over supplementary motor area (SMA) with video game-based dexterity training (VBT) to improve dexterity-related ADL in PD.
Methods: This single-blinded, stratified (Hoehn & Yahr), randomized, sham-controlled trial included 30 persons with PD (mean age: 67.2 years, duration of PD: 5.4 years, range: 0.3-18.25 years). They received either iTBS (n=15) or sham (n=15) stimulation over SMA (contra-lateral to most affected hand) followed by a 45-min VBT, three times a week for three weeks. The dexterity questionnaire 24 (DextQ-24: dexterity related ADL, primary outcome), the Parkinson's Disease Questionnaire 39 (PDQ-39: quality of life), coin rotation task (CRT) and the nine-hole peg test as secondary outcomes were assessed before and immediately after the intervention.
Results: There were no drop-outs, and +-90% of the patients adhered to the training protocol. The analysis revealed some effects für dexterity-related outcome. Significant effects for quality of life were found, overall ($p = .044$).
Conclusions: This is the first randomized sham-controlled combined iTBS video game-based intervention which evaluated the effects of a short three-week training program to improve dexterity-related ADL in PD. Further larger well-powered RCT's are needed, including more severely affected persons with PD, to further explore the impact of such combined approaches.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1042 / #1766

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

BIOINSPIRED PEPTIDE FRATERNINE-14 EFFECTS ON 6-OHDA-INDUCED MOUSE AND RAT MODELS OF PARKINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Maria Clara Resende[1], Andréia Mayer[2], Henrique Amaral[2], Danilo De Oliveira[2], Adolfo Carlos De Souza[2], Gabriel Campos[2], Solange Rego[2], Raffael De Castro[2], Anamélia Bocca[2], Márcia Renata Mortari[2,3]
[1]Institute of biological sciences/ University of Brasilia, Department Of Physiological Sciences, Brasília, Brazil, [2]University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil, [3]Institute of Biological Science, Department Of Physiology, Brasília, Brazil

Aims: The peptide fraternine, present in the venom of the wasp *Parachatergus fraternus*, has shown neuroprotective capacities against 6-OHDA dopaminergic lesions. However, such peptide has a very low bioavailability. In light of these findings, the aim of this work is to synthesize the peptide Fraternine-14 inspired by the natural fraternine, analyzing its effects over motor coordination, levels of TH+ neurons in the substantia nigra pars compacta (SN), and inflammation mediators TNF-α, IL-6, and IL-1ß in the cortex.
Methods: Maldi TOF/TOF mass spectrometry (MS/MS) was used to determine Fraternine-14's sequence and molecular mass. The 6-OHDA Parkinsonism model was employed for *in vivo* experiments with male Swiss mice (Mus musculus) and Wistar rats in order to investigate the therapeutic efficacy of the peptide. A guide canula was used for its administration, with doses of 10, 5 and 1 µg/animal. Rotarod and apomorphine-induced rotational behavior tests were used to analyze the lesion and motor coordination. TH-reactive cells were counted comparing the 6-OHDA lesion side and non-lesion side to quantify neuronal depletion.
Results: Fraternine-14 reduced the intensity of the lesion caused by 6-OHDA. In the apomorphine rotation test, animals treated with Fraternine-14 at a dose of 5 µg/animal showed a longer stay in the equipment, which may be linked to the reduction of the severity of motor incoordination of the animals.
Conclusions: Motor coordination in 6-OHDA lesioned animals was improved by Fraternine-14. However, the peptide did not reduce inflammatory mediators. It also exhibited toxic effects when in higher doses. These results show that Fraternine-14 is a promising peptide in regards to Parkinson's Disease treatment, but further research is necessary in order to improve its effectiveness and toxicity. This work was supported by FAPDF, CAPES and CNPq.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1043 / #2106

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

AT1 RECEPTOR AUTOANTIBODIES MEDIATE EFFECTS OF METABOLIC SYNDROME ON DOPAMINERGIC VULNERABILITY

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Ana Isabel Rodríguez Pérez[1,2], Maria A. Pedrosa[1], Carmen M. Labandeira[3], Rita Valenzuela[1,2], Jose L Lanciego[2,4], José Luis Labandeira-Garcia[1,2]
[1]Cellular and Molecular Neurobiology of Parkinson´s disease, Research Center for Molecular Medicine and Chronic diseases (CIMUS), Idis, Santiago de Compostela, Spain, [2]CIBERNED, Networking Research Center On Neurodegenerative Diseases, Madrid, Spain, [3]University Hospital of Ourense, Neurology Service, Ourense, Spain, [4]CIMA, University of Navarra, Pamplona, Spain, Neurosciences Division, Pamplona, Spain

Aims: Metabolic syndrome (MetS) is associated with chronic peripheral inflammation and is related to Parkinson's disease (PD). Previous studies have involved the brain renin-angiotensin system (RAS) in PD progression and the angiotensin receptor type 1 (AT1) has been revealed as a major marker of dopaminergic vulnerability in humans. Tissue RAS dysregulation is a key common mechanism for all MetS components. Circulating AT1 agonistic autoantibodies (AT1-AAs) have been observed in several inflammation-related peripheral processes, and activation of AT1 of endothelial cells, dopaminergic neurons, and glial cells has been observed to disrupt blood-brain barrier and induce neurodegeneration, respectively. in this work, we studied if AT1-AAs and ACE2-AAs (antagonist Angiotensin-converting enzyme II autoantibodies) are increased in MetS and if these autoantibodies may mediate an enhancing effect of MetS on dopaminergic death and PD.
Methods: Experiments were carried out in an animal model of MetS and results were confirmed in humans.
Results: MetS causes overactivity of the nigral pro-inflammatory RAS axis, increasing oxidative stress and neuroinflammation and accelerating dopaminergic neurodegeneration. AT1 receptor blockers (ARBs) prevented the dopaminergic neurodegeneration. MetS increased the levels of 27-hydroxycholesterol, LIGHT, and major pro-inflammatory cytokines in rat serum which also showed a significant increase in levels of AT1-AAs and ACE2-AAs. AT1-AAs and ACE2-AAs were also found in CSF. Chronic infusion of AT1-AAs, which disrupted the blood-brain barrier, increased pro-inflammatory RAS activity and dopaminergic neuron death. Observations in rat models were confirmed in a cohort of Parkinsonian and non-parkinsonian patients with or without MetS.
Conclusions: The present results show that peripheral chronic inflammatory processes, such as those observed in the MetS, can induce the production of AT1 and ACE2 autoantibodies in serum and CSF, which may disrupt the blood-brain barrier and increase the progression of neuroinflammation and dopaminergic neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1044 / #616

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

IMMEDIATE EFFECTS OF TRANSCUTANEOUS ELECTRICAL STIMULATION ON DYSPHAGIA IN PD PATIENTS

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Nobutaka Sakae[1], George Umemoto[2], Akihiro Watanabe[1], Hajime Arahata[1], Akifumi Yamamoto[1], Naokazu Sasagasako[1]
[1]National hospital organization Omuta national hospital, Neurology, Omuta City, Japan, [2]Swallowing Disorders center, Fukuoka University Hospital, Fukuoka, Japan

Aims: We aimed to investigate if interferential current stimulation (IFS) through the skin of the neck could immediately improve dysphagia in patients with Parkinson's disease (PD).
Methods: We included patients who had a diagnosis of 14 idiopathic PD with dysphagic complaints in this study. We used a portable device to generate IFS by two different altering currents through both sides of the skin of the neck. To evaluate the effect of IFS on swallowing function, we performed the standardized videofluoroscopic swallowing examination protocol (thin and thick liquid, solid food, and liquid containing the contrast medium) in our hospital, before and immediately after electrical stimuli for 15 min, sequentially. We analyzed the video images including vallecular and pyriform sinus residue, oral transit time, pharyngeal transit time, laryngeal penetration, and aspiration to compare the swallowing function before and after the stimulation in each patient respectively, together with self-evaluation during the study.
Results: Among 14 PD patients with dysphagic complaints, 5 patients did not show swallowing dysfunction before and after IFS in this study. When compared with before IFS, patients revealed significant reduction in oral transit time after IFS. Among 9 patients with abnormal swallowing pattern detected by videofluoroscopic examination, 3 patients shortened the oral transit time for solid food after IFS. Besides, laryngeal penetration disappeared in a patient and aspiration did in another patient after IFS for 15 min.
Conclusions: Although one-third of patients in this study did not show objective swallowing dysfunction, some patients showed immediate improvement in swallowing function in the videofluoroscopic swallowing study after IFS. Our results suggest that IFS through the percutaneous neck could produce an immediate therapeutic effect on dysphagia in some PD patients.

P1045 / #301

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

PARKINSON'S DISEASE: A TALE OF TWO CITIES, THE GENOME AND THE EXPOSOME

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Souvarish Sarkar
University of Rochester Medical Center, Environmental Medicine, Rochester, United States of America

Aims: Epidemiological studies support the role of environmental factors in the pathogenesis of Parkinson's disease (PD). Genetic risk factors, including penetrant single-gene mutations and risk factors identified from genome-wide associated studies (GWAS), also contribute to PD risk and progression, but available model systems are limited in their ability to interrogate gene-environment crosstalk in vivo and at scale.
Methods: We developed a multiplex model in *Drosophila* in which we knocked down GWAS candidate genes in neurons or glia in a new α-synucleinopathy model and exposed the flies to environmental neurotoxicants, rotenone, and Manganese.
Results: We identified multiple interactions among various genes, α-synuclein, and environmental factors and decided to study further the interaction among LRRK2, rotenone, and α-synuclein. Expression of the disease-causing Lrrk-G2019S mutant in the presence of rotenone and α-synuclein-induced behavioral deficits and mitochondrial dysfunction. Further, super-resolution microscopy analysis revealed that the interaction of LRRK2, α-synuclein, and rotenone leads to hyperstabilization of the actin cytoskeleton. Genetic analysis from a patient cohort with previous pesticide exposure revealed that the patient's LRRK2-R1398H mutation reduces the chance of developing PD. Since global actin severing may have unwanted side effects, we used a combination of forward genetic screen and proteomics to identify potential kinases that can be druggable targets. We identified Cdc42 binding protein kinase MRCKα, an actin-binding protein, as a potential target. Genetic and pharmacological inhibition of MRCKα in Drosophila can modify the toxicity induced by the interaction among LRRK2, α-synuclein, and rotenone by inhibiting actin hyperstabilization.
Conclusions: Using our novel multiplex model, we have identified an interaction between LRRK2, α-synuclein, and rotenone, which is modulated by actin stabilization and mitochondrial dysfunction. Our findings have implications for developing a personalized approach to drug discovery and lead identification.

P1046 / #1243

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

FOSGONIMETON PROTECTS AGAINST ALPHA-SYNUCLEIN-MEDIATED PATHOLOGY IN PRECLINICAL MODELS OF PARKINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Sharay Setti, Sherif Reda, Andree-Anne Berthiaume, Wei Wu, Jewel Johnston, Robert Taylor, Kevin Church
Athira Pharma, Inc., Research, Bothell, United States of America

Aims: The aggregation of α-synuclein protofibrils is a major pathological hallmark of Parkinson's disease (PD), triggering lysosomal dysfunction, oxidative stress, and dopaminergic neuron loss, ultimately resulting in motor dysfunction. Here, we assess the impact of fosgonimeton, a small molecule positive modulator of the neurotrophic and neuroprotective hepatocyte growth factor (HGF) system, on these outcomes in preclinical models of PD.
Methods: Rat primary mesencephalic neurons were challenged with α-synuclein preformed fibrils (α-syn-PFF) in the presence or absence of the active metabolite of fosgonimeton (fosgo-AM). After 96 hours, immunostaining for tyrosine-hydroxylase (TH), mitochondrial ROS, and LAMP2 was performed to interrogate key aspects of PD pathology. In vivo, 18-month-old mice received a single bilateral substantia nigral injection of α-syn-PFF followed by administration of lysosomal disruptor conduritol B epoxide (CBE) 3 times weekly for 6 weeks. The impact of daily treatment with vehicle, L-DOPA, or fosgonimeton on motor function in the ladder test was assessed.
Results: α-syn-PFF injury resulted in lysosomal dysfunction, oxidative stress, and dopaminergic neuron loss in vitro. Treatment with fosgo-AM improved dopaminergic neuron survival and preserved neurite networks, as evaluated via TH staining. Fosgo-AM also significantly decreased lysosomal burden and oxidative stress, as indicated by reduced LAMP2 expression and mitochondrial ROS, respectively. In vivo, fosgonimeton significantly attenuated α-synuclein-mediated motor dysfunction after both 3 and 6 weeks of treatment, as indicated by reduced time to cross and reduced errors in the ladder test.
Conclusions: Our data highlight the ability of fosgonimeton to address cellular dysfunction associated with α-synuclein toxicity in vitro, which was consistent with improved motor function in an α-synuclein-driven preclinical model of PD. Overall, the evidence presented here continues to support the therapeutic potential of fosgonimeton for people with PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1047 / #2959

Poster Topic: *Theme C: α-Synucleinopathies / C02.m. Therapeutic Targets, Mechanisms for Treatment: Other*

PHYLLANTHIN OFFERS NEUROPROTECTION IN AN IN VITRO MODEL OF PARKINSON'S DISEASE

POSTERS: C02.M. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT: OTHER

Joshua Delport[1], Sylvester Omoruyi[2], Okobi Ekpo[3]
[1]University of the Western Cape, Medical Bioscience, Cape Town, South Africa, [2]University of the Witwatersrand, Anatomical Sciences, Johannesburg, South Africa, [3]Khalifa University, Department Of Anatomy And Cellular Biology, Khalifa University, Abu Dhabi, United Arab Emirates

Aims: Parkinson's disease (PD) is among the most common neurodegenerative conditions in the ageing population, affecting about 2% of persons older than 60 years of age. It is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) region of the of the midbrain, often leading to a decline in motor and cognitive functions. Levodopa is the current effective treatment for PD, however, its long-term use often leads to debilitating side effects. Therefore, research into alternative PD treatments is plausible, especially botanical phyto-compounds. The aim of this study is to investigate the potential neuroprotective effects of phyllanthin, a bioactive lignan, in an *in vitro* model of PD
Methods: An MPP^+-induced SH-SY5Y cellular model of PD was used to investigate the cytotoxic effects of phyllanthin while the optimum concentrations of phyllanthin and MPP^+ were determined using the MTT cell viability assay. Experiments to determine nitric oxide (NO), adenosine triphosphate (ATP), intracellular calcium levels, mitochondrial membrane potential (MMP), and caspase 3/7 activity were performed. Molecular docking was performed to determine phyllanthin interaction with the enzymes acetylcholinesterase (AChE), butyrylcholinesterase (BuChE) and monoamine oxidase-B (MAO-B)
Results: Overall, results show that phyllanthin could protect cells against MPP^+-induced toxicity. Specifically, phyllanthin increased cell viability in MPP^+-treated cells, attenuated mitochondrial dysfunction by increasing ATP production and prevented cell death through the inhibition of MPP^+ induced increase in caspase 3/7 activities. Results from the *in-silico* studies and enzymatic assays also showed weak binding of the enzymes AChE, BuChE and MAO-B to phyllanthin, as well as very poor enzyme inhibition.
Conclusions: The results obtained suggest that phyllanthin has neuroprotective effects, thus supporting its potential use as a neuroprotective agent. However, more experiments are needed to elucidate its mechanisms of action.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1048 / #325

Poster Topic: *Theme C: α-Synucleinopathies / C03.b. Drug Development, Clinical Trials: Vitamins, antioxidants, neuroprotective compounds*

VQ-101, A SMALL MOLECULE ALLOSTERIC ACTIVATOR OF GLUCOCEREBROSIDASE, DEMONSTRATES NEUROPROTECTION IN MODELS OF GBA-PARKINSON'S DISEASE AND ROBUST IN-VIVO TARGET ENGAGEMENT

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

Daniel Ysselstein, Maria Nguyen, Jianbin Zhang, Hyunkyung Jeong, Eric Zluhan, Sida Shen, Jennifer Hu, Razaul Karim, Cynthia Martinez, Jeremiah Brittin, Zhiquan Lei, Greg Sheyka, Paola Carrilo, Nikki Huynh, Kori Kirby, Jim Sullivan, Kevin Hunt
Vanqua Bio, Research And Development, Chicago, United States of America

Aims: Heterozygous mutations in the gene *GBA1*, which encodes for glucocerebrosidase (GCase), are a major risk factor for Parkinson's disease (PD) accounting for 7-13% of all PD cases. *GBA1* mutations result in reduced enzymatic activity in the lysosome and have detrimental effects on lysosomal function and neuronal health. Here we evaluate VQ-101, a novel small molecule allosteric activator of GCase, that activates lysosomal GCase in a live cell assay *in vitro*, *ex vivo* and *in vivo*, demonstrates pathway engagement and blocks the accumulation of insoluble alpha synuclein (aSyn).
Methods: VQ-101, a selective, CNS-penetrant small molecule activator of GCase, was evaluated using *in vitro* and *in vivo* models to assess target engagement and downstream effects of GCase activation. *In vitro*, dopaminergic neurons (DaNs) differentiated from GBA-PD patient-derived induced pluripotent stem cells (iPSCs) were used to assess changes in GCase activation, GCase substrates, and accumulation of insoluble aSyn. *In vivo* target engagement was directly assessed by measurement of GCase activation following oral administration of VQ-101 across preclinical species.
Results: GCase activation of 50-100% above baseline was achieved in iPSC-derived DaNs carrying *GBA1* mutations treated with nanomolar concentrations of VQ-101. Treatment at concentrations that activate GCase by 50-100% resulted in a reduction in GCase lipid substrates and significantly blocked the accumulation of insoluble aSyn. *In vivo*, dose- and time-dependent GCase activation was observed in peripheral blood across preclinical species after oral administration of VQ-101.
Conclusions: VQ-101 demonstrates significant GCase activation and neuroprotection in DaNs from GBA-PD subjects. The robust GCase target engagement observed in preclinical species is readily translatable to target engagement of GCase activators in clinical studies. These findings support the continued development of VQ-101 for GBA-PD and other synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1049 / #720

Poster Topic: *Theme C: α-Synucleinopathies / C03.a. Drug Development, Clinical Trials: Immunotherapy*

A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY WITH UB-312, AN ANTI-ALPHA-SYNUCLEIN PEPTIDE VACCINE IN PARKINSON'S DISEASE PATIENTS.

POSTERS: C03.A. DRUG DEVELOPMENT, CLINICAL TRIALS: IMMUNOTHERAPY

Pepijn Eijsvogel[1], Hui Jing Yu[2], Philip Kremer[1], Lauren Fedor[2], Igor Radanovic[1], Dario Mirski[2], Maurits Vissers[1], Marieke De Kam[1], Jean-Cosme Dodart[2], Geert Jan Groeneveld[1]
[1]CHDR, Neurology, Leiden, Netherlands, [2]Vaxxinity, Inc, Neurology, Florida, United States of America

Aims: Alpha-Synuclein (aSyn) plays a central role in Parkinson's disease (PD) and is considered a target for disease modification. UB-312 is a synthetic aSyn peptide conjugated to a T-helper peptide and is expected to induce antibodies specifically against oligomeric and fibrillar aSyn, making UB-312 a potential immunotherapeutic for synucleopathies. The aim of the trial was to investigate the safety, tolerability, and immunogenicity of UB-312 in a two-part Phase 1 clinical trial, in healthy volunteers (HVs) and PD patients.
Methods: Participants were enrolled in a 44-week, randomized, placebo-controlled, double-blind study. A total of 28 HVs and 19 PD patients were randomized to three intramuscular UB-312 or placebo injections at weeks 1, 5, and 13 at varying dose levels. Safety and tolerability were assessed by adverse events (AEs) and standard safety assessments. Immunogenicity was assessed by measuring serum and cerebrospinal fluid (CSF) anti-aSyn antibodies.
Results: In HVs, the antibodies were detectable in 100% of the HVs who received 3 doses of 300µg UB-312 and in 92% of PD patients who completed dosing with UB-312. Anti-aSyn antibodies were also detectable in CSF. Most AEs were mild and transient. UB-312 was generally well tolerated with overall adverse event profile similar across UB-312 and placebo groups. No serious adverse events (SAEs) were reported in HVs. Two patients experienced SAEs. Only one event was deemed possibly related to the trial, and all SAEs were resolved.
Conclusions: The trial met its primary objectives. UB-312 was generally safe, well tolerated, and induced anti-aSyn antibodies in serum and CSF. These data support further development of UB-312 for alpha-synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1050 / #1857

Poster Topic: *Theme C: α-Synucleinopathies / C03.b. Drug Development, Clinical Trials: Vitamins, antioxidants, neuroprotective compounds*

RESULTS FROM SHAPE: A PHASE 2 STUDY OF FOSGONIMETON IN PATIENTS WITH PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

Kevin Church[1], Daniel Burdick[2], Kai-Bin Ooi[3], Michael Hale[3], Sharay Setti[1], Hans Moebius[3]
[1]Athira Pharma, Research, Bothell, United States of America, [2]EvergreenHealth Neuroscience Institute and Eastside Neuroscience Institute, Booth Gardner Parkinson's Center, Kirkland, United States of America, [3]Athira Pharma, Clinical Research And Development, Bothell, United States of America

Aims: Parkinson's disease dementia (PDD) and Dementia with Lewy bodies (DLB) are neurodegenerative diseases characterized by protein aggregation that is linked to synaptic dysfunction and neuronal death, with clinical features that include changes in cognition and behavior. Positive modulation of the neurotrophic hepatocyte growth factor system with fosgonimeton may offer a therapeutic approach for several neurodegenerative diseases. This exploratory phase 2 SHAPE trial sought to evaluate the safety of fosgonimeton and effects of treatment on a variety of outcomes including cognition, activities of daily living, motor function, and behavior in participants with PDD and DLB. Plasma samples were collected for biomarker analysis.
Methods: SHAPE was a 26-week, multicenter, randomized, double-blind, placebo-controlled, phase 2 trial of subcutaneous fosgonimeton (40 mg/day or 70 mg/day) versus placebo in participants with PDD or DLB. The primary end point was the effect of fosgonimeton treatment versus placebo at week 26 per change from baseline (CFB) in a composite score Global Statistical Test [GST] combining the z-scores of ADAS-Cog13 and ERP P300L. Secondary efficacy end points were CFB in validated scales for measuring cognitive function (ADAS-Cog13; MMSE), executive response/function (ERP P300L; COWAT), activities of daily living (ADCS-ADL23), motor function (MDS-UPDRS), and other holistic disease burden measures (NMSS; CGI).
Results: Twenty-eight participants (PDD: fosgonimeton n=14, placebo n=6; DLB: fosgonimeton n=5, placebo n=3) in this first-in-patient exploratory trial were randomly assigned. We will report the effects of fosgonimeton versus placebo per GST score, secondary outcomes including biomarker findings, and safety findings based on adverse events.
Conclusions: The synthesis of these data will inform the hypothesis generation for continued development of fosgonimeton as a potential therapeutic for PDD, PD, and DLB.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1051 / #1671

Poster Topic: *Theme C: α-Synucleinopathies / C03.b. Drug Development, Clinical Trials: Vitamins, antioxidants, neuroprotective compounds*

A PHASE 1A FIRST-IN-HUMAN CLINICAL TRIAL OF HER-096, A SUBCUTANEOUSLY ADMINISTERED CDNF-DERIVED PEPTIDOMIMETIC

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

Kira Holmström[1], Katarina Jääskeläinen[1], Natalia Kulesskaya[1], Jani Koskinen[1], Päivi Vuorio[1], Antti Vuolanto[1], Marica Engström[2], Mika Scheinin[2,3], Charlotte Videbaek[1], Aleksi Tornio[2,3], Henri Huttunen[1]
[1]Herantis Pharma, Scientific Department, Espoo, Finland, [2]University of Turku, Institute Of Biomedicine, Turku, Finland, [3]CRST Oy, Clinical Development, Turku, Finland

Aims: HER-096 is a peptidomimetic compound developed from the active site of human CDNF that in preclinical studies has shown brain penetration and protection of nigrostriatal dopamine neurons. In this study we aimed to (1) assess the safety and tolerability of subcutaneously administered HER-096 in healthy volunteers (HV), and (2) assess its pharmacokinetic properties, including blood-brain barrier penetration in humans.
Methods: A randomised, double-blind, placebo-controlled, safety, tolerability and pharmacokinetic study of single ascending subcutaneous doses of HER-096 was conducted at a single site in Finland. In Part 1 of the study, 48 young (20-45 years) male HV subjects were randomised to receive single doses of HER-096 (10, 30, 60, 120, 200 or 300 mg) or placebo at a 6:2 ratio in six dosing cohorts. In Part 2, 6 older (50-64 years) and 6 elderly (65-75 years) male and female HV subjects were administered a single 200 mg dose of HER-096. The primary endpoint was safety, assessed by incidence, type and severity of treatment-emergent adverse events (AE), including injection-related events, as well as standard clinical and laboratory assessments. Secondary endpoints were pharmacokinetic properties of HER-096 (up to 24 h) in plasma and urine in the young HVs, and in plasma, urine and cerebrospinal fluid in the older and elderly subjects.
Results: All study subjects were recruited and dosed in Q2-Q3 2023. Data analysis is on-going. There were no reports of serious AEs or other dose-limiting AEs affecting progression of the clinical study.
Conclusions: Preliminary assessments suggest a good safety profile for single ascending subcutaneous doses of HER-096. Full data analysis will be completed after database lock by November 2023 and the results will be reported in the AD/PD 2024 conference presentation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1052 / #2728

Poster Topic: *Theme C: α-Synucleinopathies / C03.b. Drug Development, Clinical Trials: Vitamins, antioxidants, neuroprotective compounds*

C9-FUNCTIONALIZED DOXYCYCLINE ANALOGS: A PROMISING APPROACH AGAINST A-SYNUCLEIN AGGREGATION AND LPS-INDUCED NEUROINFLAMMATION

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

Rita Raisman-Vozari[1], Rodrigo Tomas Grau[1,2], Clemence Rose[3], Brenda Zabala[1], Patrick Pierre Michel[1], Jean-Michel Brunel[4], Rosana Chehin[2], Laurent Ferrié[5], Bruno Figadère[5]
[1]Hôpital de la Pitié Salpêtrière, Institut Du Cerveau - Icm, Inserm, Sorbonne Université, Cnrs, Paris, France, [2]Universidad Nacional de Tucumán, Immca, Conicet-unt-siprosa, Tucumán, Argentina, [3]BioCIS, Université Paris-saclay, Orsay, France, [4]UMR_MD1, Membranes Et Cibles Thérapeutiques, Marseille, France, [5]Université Paris-Saclay, Biocis, Cnrs,, Orsay, France

Aims: The objective of this study was to investigate the potential of novel doxycycline (DOX) derivatives as neuroprotective agents for Parkinson's disease (PD). Specifically, we aimed to design non-antibiotic tetracycline (TC) derivatives with improved efficacy against PD-related pathomechanisms while minimizing cytotoxicity.
Methods: To achieve our objectives, we designed 18 novel DOX derivatives. The design involved reducing the dimethyl-amino group at C4 to reduce antimicrobial activity and conducting multiple coupling reactions at position C9 of the aromatic D ring, known for its reactivity in introducing substituents. We assessed the effectiveness of these derivatives using the Thioflavin-T assay to inhibit α-Synuclein (α-Syn) aggregation. Additionally, we evaluated their anti-inflammatory effects in a microglial cell culture system modeling PD-related neuroinflammation. We measured membrane integrity and metabolic activity using LDH and MTT assays to assess potential cytotoxicity.
Results: Our study revealed that seven TC compounds among the derivatives were more effective than the parent compound, DOX, in inhibiting α-Syn aggregation. Notably, two of these derivatives, compounds 6 and RDOX, demonstrated superior anti-inflammatory effects compared to DOX. Furthermore, these compounds exhibited no adverse effects on membrane integrity or metabolic activity, as evidenced by the LDH and MTT assays.
Conclusions: Based on our current findings, we conclude that novel 4-des-N-dimethylaminodoxycycline derivatives functionalized at position C9 show greater efficacy in inhibiting pathological α-Syn aggregation compared to DOX. Compound 6 and RDOX emerge as promising drug candidates for the treatment of Parkinson's disease. Their non-cytotoxic nature and potent anti-inflammatory properties make them attractive candidates for further exploration in PD therapy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1053 / #2853

Poster Topic: *Theme C: α-Synucleinopathies / C03.b. Drug Development, Clinical Trials: Vitamins, antioxidants, neuroprotective compounds*

NOVEL NON-ANTIBIOTIC TETRACYCLINE INHIBITS A-SYN PFF UPAKE, SEEDING AND LYSOSOMAL STRESS

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

Rita Raisman-Vozari[1], Maria Del Milagro Teran[2], Rodrigo Tomas Grau[2,3], Diego Ploper[2], Pierre Besnault[3], Estefania Soliz Santander[2], Clemence Rose[4], Alvaro Luna Mercado[2], Patricia Villace[5], Cesar L Avila[6], Jean-Michel Brunel[7], Laurent Ferrié[8], Clarisa Salado[9], Patrick Pierre Michel[10], Bruno Figadère[8], Rosana Chehin[6]
[1]Paris Brain Institute-ICM, Inserm Cnrs Hôpital De La Pitié Salpêtrière, Sorbonne Université, Paris, France, [2]Universidad Nacional de Tucumán, Immca, Conicet-unt-siprosa, Tucumán, Argentina, [3]Hôpital de la Pitié Salpêtrière, Institut Du Cerveau - Icm, Inserm, Sorbonne Université, Cnrs, Paris, France, [4]BioCIS, Université Paris-saclay, Orsay, France, [5]INNOPROT, Innoprot, Derio, Spain, [6]IMMCA, Conicet-unt-siprosa, Tucumán, Argentina, [7]UMR_MD1, Membranes Et Cibles Thérapeutiques, Marseille, France, [8]Université Paris-Saclay, Biocis, Cnrs,, Orsay, France, [9]INNOPROT, Cellular And Molecular Lab, DERIO, Spain, [10]Institut du Cerveau - ICM, Hôpital De La Salpêtrière, Paris, France

Aims: Alpha-synuclein (α-Syn) aggregation is a hallmark of neurodegenerative diseases like Parkinson's. Doxycycline (DOX), a tetracycline, has shown potential in inhibiting α-Syn aggregation, but its antibiotic properties limit its therapeutic use. To address this, we developed a non-antibiotic tetracycline derivative, DDox, which aimed to mitigate α-Syn aggregation and offer a safe alternative for disease models.
Methods: DDox was synthesized through the removal of the dimethylamino substituent at position 4 on ring A and the reduction of the hydroxyl group at C12a. We assessed DDox's antibiotic activity against Gram(+) and (-) bacterial strains and evaluated its toxicity on the SHSY5Y cell line using MTT assay. The capability of DDox at interfering with α-Syn aggregation was assessed through: fluorescent spectroscopy, TEM and immunofluorescence in SHSY5Y cells. Additionally, we studied DDox effects on α-Syn seeding in SH-SY5Y-aS-RFP cells treated with α-Syn preformed fibrils (α-Syn-PFF), its impact on the uptake of fluorescently-labeled α-Syn-PFF and on α-Syn-PFF-triggered lysosomal stress by confocal microscopy.
Results: The chemical modifications that gave rise to DDox effectively diminished antibiotic activity against both Gram (+) and Gram (-) bacterial strains while reducing its toxicity on the SHSY5Y cell line. It outperformed DOX at inhibiting α-Syn amyloid aggregation. In cellular models, DDox reduced α-Syn aggregate formation induced by α-Syn-PFF. Notably, DDox exhibited previously unreported properties by inhibiting α-Syn-PFF uptake and α-Syn-PFF-triggered lysosomal stress, demonstrating its potential in PD models.
Conclusions: In summary, DDox, a novel tetracycline, is non-toxic and exhibited limited antibiotic activity. It also improved α-Syn associated phenotypes and showed anti-inflammatory abilities. These findings position DDox as a promising candidate for preclinical studies of synucleinopathies like PD, offering a potential solution to the antibiotic hurdle associated with DOX.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1054 / #2553

Poster Topic: *Theme C: α-Synucleinopathies / C03.b. Drug Development, Clinical Trials: Vitamins, antioxidants, neuroprotective compounds*

N-DOSE: A DOSE OPTIMALIZATION TRIAL OF NICOTINAMIDE RIBOSIDE IN PARKINSON'S DISEASE

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

Haakon Berven[1,2,3], Katarina Lundervold[1,2,3], Simon Kverneng[1,2,3], Gard Johanson[1,2,3], Erika Sheard[1,2,3], Mona Søgnen[1,2,3], Solveig Geijerstam[1,2,3], Brage Brakedal[1,2,3], Kristoffer Haugarvoll[1,2,3], Geir-Olve Skeie[1,2,3], Christian Dölle[1,2,3], Charalampos Tzoulis[1,2,3]
[1]Haukeland University Hospital, Neuro-sysmed, Department Of Neurology, Bergen, Norway, [2]University of Bergen, Department Of Clinical Medicine, Bergen, Norway, [3]University of Bergen, K.g. Jebsen Center For Translational Research In Parkinson's Disease, Bergen, Norway

Aims: NAD replenishment therapy with nicotinamide riboside (NR) has shown promising results in preclinical and clinical studies on PD and other neurodegenerative disorders. However, individual neurometabolic responses vary and the optimal dose is yest to be determined. Here, we aim to determine the optimal biological dose of NR for the treatment of Parkinson's disease (PD), defined as the dose required to achieve maximal cerebral NAD increase, increase in the expression of the NR related pattern (NRRP), or proportion of MRS-responders, in the absence of unacceptable toxicity.
Methods: N-DOSE is a single-center, randomized, placebo-controlled, double-blinded trial. Participants will be randomized 1:1:2 into either placebo group (n=20), dose stable group (n=20) or a dose escalation group (n=40) for 3 months. Each participant will attend four visits during the trial. **Inclusion criteria:** clinically established diagnosis of idiopathic PD according to MDS criteria, DAT-SPECT imaging consistent with PD, age ≥ 40 at enrollment, Hoehn and Yahr score < 4, and ability to undergo MRI and lumbar puncture. **Exclusion criteria:** supplementation with high dose vitamin B_3 within 30 days of baseline or co-morbidity with another neurodegenerative disorder, neoplastic or severe and debilitating metabolic, psychiatric or physical disorder. Investigations: At all visits, participants will undergo: 31^{P}-MRS, 1^{H}-MRS, FDG-PET, drawing of blood and scoring of clinical scales; MDS-UPDRS, MDS-NMS, MoCA, GIDS-PD, EQ-5L. At baseline and final visit, participants will undergo CSF collection via lumbar puncture and a fecal sample will be collected.
Results: Currently 15 participants have completed the trial and 26 have been randomized. Three participants have dropped out.
Conclusions: Anticipated trial completion: Q4 2024. **Trial registration:** NCT05589766

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1055 / #854

Poster Topic: *Theme C: α-Synucleinopathies / C03.b. Drug Development, Clinical Trials: Vitamins, antioxidants, neuroprotective compounds*

ANTIPARKINSONIAN AND NEUROPROTECTIVE EFFECTS OF A WASP VENOM PEPTIDE IN A MODEL OF PARKINSON'S DISEASE

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

Larissa Lima, Henrique Amaral, Gabriela Pinheiro, Márcia Renata Mortari
University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil

Aims: The present study aims to evaluate antiparkinsonian and neuroprotective effects of OcTx-1202, a wasp venom peptide, in a mouse model of 6-hydroxydopamine-induced hemiparkinsonism.
Methods: The experimental design consisted of a ten-day evaluation period, in which male *Swiss* mice were subjected to a stereotaxic procedure and two behavioral tests, the rotarod test and the apomorphine-induced rotational test. Then, animals were euthanized and brains were collected for quantification of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Subjects were divided on five experimental groups: SHAM (infusion and treatment with vehicle solution), negative control (infusion of 6-OHDA and treatment with vehicle solution) and three experimental groups (infusion of 6-OHDA and diary treatment with OcTx-1202 in 2, 4 or 8 mg/kg).
Results: In the rotarod test, a progressive improvement of motor performance was observed with 8 mg/kg OcTx-1202 treatment, but these results were not obtained for lower doses. For the apomorphine-induced rotational test, treatment with all three doses of OcTx-1202 did not significantly reduce the number of contralateral rotations. As for the neuroprotection of dopaminergic neurons in SNpc, treatment with OcTx-1202 preserved 73%, 44% and 60,7% of dopaminergic neurons in doses of 2, 4 and 8 mg/kg, respectively. Lastly, an interesting finding was the 100% survival rate of animals treated with OcTx-1202 in 8 mg/kg, equivalent to the SHAM group. For the remaining groups, survival rate was 87,5% (OcTx-1202, 4 mg/kg), 81,8% (OcTx-1202, 2 mg/kg) and 66,7% (negative controls).
Conclusions: These findings suggest that OcTx-1202 has antiparkinsonian and neuroprotective effects, being a potential therapeutic alternative for PD. Future studies should investigate its mechanism of action and propose chemical modifications, such as PEGylation or nanoencapsulation. This work was supported by Fundação de Apoio e Pesquisa do Distrito Federal (FAPDF).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1056 / #2954

Poster Topic: *Theme C: α-Synucleinopathies / C03.b. Drug Development, Clinical Trials: Vitamins, antioxidants, neuroprotective compounds*

INHIBITION OF A-SYNUCLEIN PHOSPHORYLATION, SEEDING AND LYSOSOMAL STRESS BY DCT, A NON-ANTIBIOTIC CHLORINATED TETRACYCLINE.

POSTERS: C03.B. DRUG DEVELOPMENT, CLINICAL TRIALS: VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS

Rita Raisman-Vozari[1], María Guayán[2], Rodrigo Tomas Grau[2], Bruno Figadère[3], Clemence Rose[4], Clarisa Salado[5], Rosana Chehin[2], Diego Ploper[2]
[1]Paris Brain Institute-ICM, Inserm Cnrs Hôpital De La Pitié Salpêtrière, Sorbonne Université, Paris, France, [2]Universidad Nacional de Tucumán, Immca, Conicet-unt-siprosa, Tucumán, Argentina, [3]Université Paris-Saclay, Biocis, Cnrs,, Orsay, France, [4]BioCIS, Université Paris-saclay, Orsay, France, [5]INNOPROT, Cellular And Molecular Lab, DERIO, Spain

Aims: Parkinson's disease (PD) is a chronic neurodegenerative disorder that involves the loss of dopaminergic neurons and is triggered by toxic amyloid aggregates of αS, predominantly phosphorylated at Serine 129 (S129). Several tetracyclines (TCs) have shown neuroprotective effects in preclinical models, but their antibacterial activity limits their use. The study aimed to evaluate the potential of Double Reduce Chlortetracycline (DCT), a novel modified TC without antibiotic activity, at interfering with αS-driven pathological features in transgenic PD cell models.
Methods: The novel TC DCT was synthesized by eliminating the dimethylamino substituent at position 4 in ring A and reducing the hydroxyl group at C12a. Toxicity was tested in SH-SY5Y^{WT} cells by MTT assays and in SH-SY5Y-CytochromeC-GFP cells. Ability of DCT to modify αS aggregation was assessed through fluorescent spectroscopy, transmission electron microscopy, and immunofluorescence in SH-SY5Y-αS-RFP cells. The effects of DCT on αS seeding were studied *in-vitro*, and in SH-SY5Y-αS-RFP cells treated with α-Syn preformed fibrils (αS PFF). The impact of DCT on αS PFF-induced lysosomal stress was studied with Lysotracker. Antioxidant properties were revealed using CellROX. DCT influence on phosphorylation of αS^{S129} was discovered using immunostainings. All studies were performed in SH-SY5Y-αS-RFP and visualized by confocal microscopy.
Results: DCT showed no toxicity and conserved important antioxidant properties present in TCs. In addition, DCT inhibited amyloid aggregation, modified the kinetics, and altered the morphology of αS amyloid fibrils. DCT also diminished the ability of exogenous αS-PFF to seed endogenous αS-RFP. Surprisingly, DCT also inhibited the phosphorylation of αS^{S129} and lysosomal stress induced by αS-PFF.
Conclusions: These results poise DCT as an attractive drug candidate for further *in vivo* tests and uncover hidden properties of TCs that could be harnessed for further drug development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1057 / #2592

Poster Topic: *Theme C: α-Synucleinopathies / C03.c. Drug Development, Clinical Trials: Neurotransmitter- and receptor based modulators*

AN OPTIMIZED NURR1 AGONIST PROVIDES DISEASE-MODIFYING EFFECTS IN PARKINSON'S DISEASE MODELS

POSTERS: C03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROTRANSMITTER- AND RECEPTOR BASED MODULATORS

Woori Kim[1], Mohit Tripathi[2], Chunhyung Kim[1], Satyapavan Vardhineni[2], Young Cha[1], Shamseer Kandi[2], Melissa Feitosa[1], Rohit Kholiya[2], Eric Sah[1], Anuj Thakur[2], Yehan Kim[1], Sanghyeok Ko[1], Sunny Manohar[2], Youngbin Kong[1], Gagandeep Sindhu[2], Yoon-Seong Kim[3], Bruce Cohen[1], Diwan Rawat[2], Kwang-Soo Kim[1]
[1]McLean Hospital, Psychiatry, Belmont, United States of America, [2]University of Delhi, Chemistry, Delhi, India, [3]Rutgers University, Institute For Neurological Therapeutics, Piscataway, United States of America

Aims: This study was performed in order to develop an optimized Nurr1 agonist(s) that may provide beneficial disease modifying treatment of Parkinson's disease (PD).
Methods: Herein we carried out an extensive medicinal chemistry search in which over 570 4-amino-7-chloroquinoline (4A7C)-derivatives were generated and characterized for their ability to activate Nurr1. We performed the highthroughput analyses determining cytotoxicity, Nurr1 transcriptional activity, binding affinity to Nurr1, and brain/plasma ratio, to identify an optimized, brain-penetrant agonist(s). The final candidate, 4A7C-301 was tested in vitro models including MPP^+-treated midbrain dopaminergic (mDA) cell lines (MN9D and N27-A) and MPP+- or LPS-treated mDA neuron-glia co-cultures to validate its effects on neuroprotection and neuroinflammation. In addition, 4A7C-301 was administered in vivo models of PD including MPTP-induced mice and AAV2-mediated human α-synuclein (both wild-type and hA53T mutant)-overexpressing mice to verify the efficacy in PD-like behavioral deficits and pathophysiological symptoms.
Results: The brain-penetrant Nurr1 agonist, 4A7C-301, exhibits robust neuroprotective effects in vitro models (e.g., mDA cell lines and primary mDA neuron-glia co-cultures) with enhanced expression of mDA neuron-specific markers along with suppression of microglial activation against MPP^+- and/or LPS-induced toxicities. In addition, 4A7C-301 protects against the loss of mDA neurons in the MPTP-induced mouse models of PD and improves both motor and non-motor deficits without side effects such as dyskinesia-like behaviors. Furthermore, 4A7C-301 significantly ameliorates neuropathological abnormalities and improves motor and non-motor dysfunctions in AAV2-mediated human α-synuclein (both wild-type and hA53T mutant)-overexpressing mouse models, with reduced α-synuclein accumulation and increased dopamine production.
Conclusions: These disease-modifying properties of 4A7C-301 may warrant clinical evaluation of this or analogous compounds for the treatment of patients with PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1058 / #1558

Poster Topic: *Theme C: α-Synucleinopathies / C03.c. Drug Development, Clinical Trials: Neurotransmitter- and receptor based modulators*

REACT-PD – A RANDOMIZED, PLACEBO-CONTROLLED PHASE IIB TRIAL EVALUATING THE EFFICACY OF PIREPEMAT ON FALLS FREQUENCY IN PATIENTS WITH PARKINSON'S DISEASE

POSTERS: C03.C. DRUG DEVELOPMENT, CLINICAL TRIALS: NEUROTRANSMITTER- AND RECEPTOR BASED MODULATORS

Joakim Tedroff, Olivia Vu Van, Clas Sonesson, Nicholas Waters, Susanna Waters
IRLAB Therapeutics AB, Research & Development, Göteborg, Sweden

Aims: Advanced Parkinsons Disease (PD) is associated with auxiliary symptoms including cognitive decline, apathy, and increased frequency of falls, in great need of improved treatment. Emerging data suggests falls in PD are linked to impairment of noradrenergic pathways impinging on cortical areas involved in postural control. Pirepemat is a small molecule compound, enhancing cortical noradrenergic transmission, in clinical development for advanced PD. A phase IIa trial indicated improvement of balance and reduced falls assessed by MDS-UPDRS. REACT-PD is a Phase IIb study with the primary objective to evaluate the effect of pirepemat on falls frequency in people with PD. Secondary objectives include evaluation of safety, tolerability, and effects on apathy, cognition, and general PD symptoms.
Methods: Patients with PD, HY-stage ≥ 2.5, experiencing recurrent falls, are eligible, aiming for a total of 165 subjects. Participants are assigned randomly to 100 or 200 mg of pirepemat or placebo, administered t.i.d day for 12 weeks. Falls are monitored using a falls diary. Other efficacy assessment include MOCA, MDS-UPDRS part I-IV, Neuropsychiatric Inventory (NPI, Apathy/Indifference part), CGI. The analysis of the primary endpoint, falls frequency, will be performed using negative binomial regression.
Results: The study is currently active at 38 study sites across six European countries. A first DSMB meeting was held in July 2023. Top-line results are expected in H1 2024.
Conclusions: Recruitment is ongoing and the study is making good progress. Details on study procedures and early results, as available, will be presented during the meeting. Pirepemat has the potential to become the first treatment in a new class of drugs designed to improve balance and reduce falls and associated injuries in people with Parkinson's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1059 / #1940

Poster Topic: *Theme C: α-Synucleinopathies / C03.e. Drug Development, Clinical Trials: Enzyme modulators*

OPICAPONE EFFECT ON SLEEP DISORDERS IN FLUCTUATING PARKINSON'S DISEASE PATIENTS: FINDINGS FROM THE OASIS EXPLORATORY TRIAL

POSTERS: C03.E. DRUG DEVELOPMENT, CLINICAL TRIALS: ENZYME MODULATORS

Joaquim Ferreira[1], Miguel Gago[2], Raquel Costa[3], Miguel Fonseca[3], Joana Almeida[3], José Rocha[3], Joerg Holenz[3], Claudia Trenkwalder[4]
[1]University of Lisbon, Laboratory Of Clinical Pharmacology And Therapeutics, Lisbon, Portugal, [2]University of Minho, Life And Health Sciences Research Institute (icvs), Guimarães, Portugal, [3]BIAL - Portela, R&d, Trofa, Portugal, [4]Paracelsus-Elena Klinik, Neurology, Kassel, Germany

Aims: This clinical trial aimed to evaluate the effects of OPC treatment on sleep disorders in fluctuating PD patients.
Methods: Open-label, single-arm pilot trial that recruited 16 fluctuating PD patients. All received OPC-50mg once-daily during a 6-week evaluation period. L-dopa/DDCI daily dose, but not number of intakes, could have been adjusted during first 2 weeks. Primary endpoint was change from baseline in Parkinson's Disease Sleep Scale-2 (PDSS-2). Secondary endpoints included tolerability, functional motor and non-motor assessments [MDS-UPDRS, MDS-NMS, 8-item PD Questionnaire (PDQ-8), 16-item PD Fatigue Scale (PFS-16), ON/OFF home diary], and Global Impression of Change [Clinician (CGI-I) and Patient (PGI-I)].
Results: At week 6, there was a significant reduction from baseline of -7.9 points (95%CI: -13.6,-2.2; P=0.0099) in total PDSS-2 score. Similarly, there were also significant reductions in PFS-16 [-9.6 points (95%CI: -17.5,-1.7; P=0.0211), in MDS-NMS total score [-28.9 (95%CI: -44.7,-13.2; P=0.0052), in MDS-UPDRS III and IV [-6.3 (95%CI: -11.6,-0.9; P=0.0253) and -1.2 (95%CI: -2.0,-0.4; P=0.0044), respectively] and in PDQ-8 [-14.2 (95%CI: -23.2,-5.0; P=0.0051). Absolute OFF-time was also reduced (-142.1 mins), mirrored by an increase in ON-time without dyskinesia (+127.1 mins). Most patients (93.3%) and most clinicians (80.0%) reported any improvement as evaluated by the PGI-I and CGI-I, respectively. OPC-50mg was found to be well tolerated.
Conclusions: In this exploratory open single-arm trial, treatment with OPC-50mg as add-on to L-DOPA/DDCI improved PD-specific sleep disturbances and other relevant and troublesome non-motor symptoms. These results support the potential benefit of using opicapone for the treatment of motor fluctuations in patients with PD associated with sleep problems.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1060 / #1601

Poster Topic: *Theme C: α-Synucleinopathies / C03.f. Drug Development, Clinical Trials: Drug delivery systems*

REDUCTIONS IN OFF TIME WITH ND0612 FOR PATIENTS WITH PARKINSON'S DISEASE EXPERIENCING MOTOR FLUCTUATIONS: RESPONDER-ANALYSIS FROM AN OPEN-LABEL STUDY

POSTERS: C03.F. DRUG DEVELOPMENT, CLINICAL TRIALS: DRUG DELIVERY SYSTEMS

Nelson Lopes[1], Werner Poewe[2], Aaron Ellenbogen[3], Stuart Isaacson[4], Nissim Sasson[1], Tami Yardeni[1], Alberto Espay[5]
[1]NeuroDerm.com, Clinical Development, Rehovot, Israel, [2]Medical University Innsbruck, 2. department Of Neurology, Innsbruck, Austria, [3]Michigan Institute for Neurological Disorders, Neurology, Farmington Hills, United States of America, [4]Parkinson's Disease & Movement Disorders Center of Boca Raton, Neurology, Boca Raton, United States of America, [5]University of Cincinnati, Neurology, Cincinnati, United States of America

Aims: We have previously reported that one year treatment with investigational ND0612 infusion was generally safe and well-tolerated. Adjusted mean daily 'Good ON' time (sum of ON time without dyskinesia + ON time with non-troublesome dyskinesia) increased from baseline by 2.3 hours at Month 3 and was maintained for at least 12 months (Poewe et al. Mov Disord 2021; 36: 2687-2692). Here we evaluate the efficacy of subcutaneous levodopa/carbidopa infusion with ND0612 in reducing OFF time in people with Parkinson's disease (PwP) experiencing motor fluctuations.
Methods: The BeyoND study is an ongoing open-label study (NCT02726386) of ND0612 treatment conducted in PD patients (n=214) with Hoehn & Yahr score of ≤3 during ON experiencing ≥2 hours daily OFF-time. In these analyses of daily OFF time (patient home diaries), a responder was conservatively defined as a patient who achieved ≥50% reduction from baseline in adjusted mean daily OFF time.
Results: Using the last observation carried forward, 44.0% patients were classified as treatment responders, and this level of response was maintained over the 12 months of follow-up. Moreover, 63.5% of patients achieved a >25% reduction in OFF time from baseline and 26.9% of patients achieved a >75% reduction in OFF time. Additionally, 12.8% of patients had their OFF time reduced by 100%. Using only observed cases (i.e., not LOCF), the percentage of ND0612 treatment responders increased from 44.0% at Month 1 (N=150) to 53.3% at Month 6 (N=107), and 56.7% at Month 12 (N=90).
Conclusions: This open-label study provides preliminary support for the 12-month efficacy of treatment with ND0612 in reducing OFF time in PwP experiencing motor fluctuations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1061 / #1944

Poster Topic: *Theme C: α-Synucleinopathies / C03.g. Drug Development, Clinical Trials: Non-pharmacological interventions, neurosurgery*

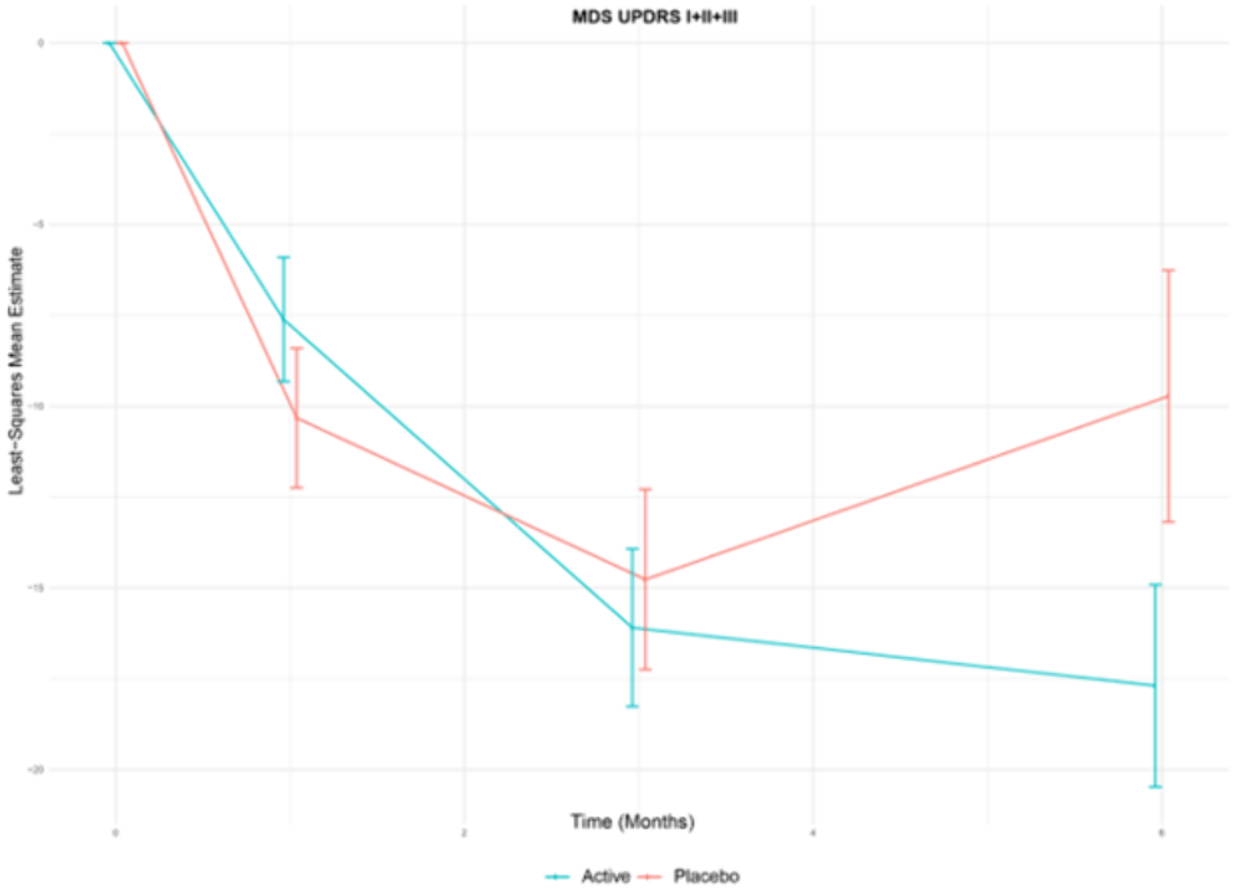
PHASE 2 RESULTS AND PHASE 3 STUDY DESIGN FOR SPECTRAMAX® LIGHT THERAPY FOR MOTOR AND NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE

POSTERS: C03.G. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS, NEUROSURGERY

Suzanne Hendrix[1], Sam Dickson[2], Karl Kieburtz[3], C Olanow[4], Jeffrey Groves[5], Wayne Croft[5], Dan Adams[6], Ray Dorsey[3]
[1]Pentara Corporation, Ceo, Millcreek, United States of America, [2]Pentara Corporation, Statistics, Millcreek, United States of America, [3]University of Rochester, Neurology, Rochester, United States of America, [4]Clintrex Research Organisation, Ceo, Sarasota, United States of America, [5]Aspen Clinical Research, Neurology, Orem, United States of America, [6]PhotoPharmics, Science Officer, Co-founder, American Forl, United States of America

Aims: Presenting safety and efficacy results of a phase 2 study of Spectramax Light Therapy (SLT), a circadian targeted, blue+green light as adjunctive treatment in Parkinson's disease (PD) and describing the design for a currently-enrolling phase 3 trial in a similar population.
Methods: Current treatments do not adequately address many disabling features of PD, including circadian dysfunction. SLT may improve circadian rhythms affecting both motor and non-motor features of PD.[1] A 6-month, phase 2, multi-center, randomized, double-blind, controlled clinical trial of one hour/day of passive exposure to SLT in PD patients on stable dopaminergic therapy demonstrated motor and non-motor benefits. Clinical endpoints included MDS-UPDRS Parts 1-3 (assessed during the On-state), PDQ-39, CGI-I, and ESS. A phase 3 RCT is currently enrolling similar patients and is entirely remote.
Results: 92 subjects (45 active, 47 sham) were randomized. Effects were 8-points for MDS-UPDRS score (p=0.074), 5.7-points for PDQ-39 (p=0.038), 0.37-points for CGI-I (p=0.067), and 1.5-points on ESS (p=0.054) were observed. Non-motor symptoms were significantly affected (MDS-UPDRS Part 1, p=0.006). Spectramax was safe and well
tolerated.

Figure: 6-Month Comparison of Active vs. Control for MDS-UPDRS 1-3



Conclusions: Once-daily Spectramax LT improved PD symptoms, particularly non-motor symptoms and quality of life. SLT was well-tolerated. A phase 3 double-blind study is currently enrolling 300 patients in PD, with the PDQ-39 as the primary and MDS-UPDRS Parts 1-2 as key secondary efficacy outcomes, with ESS, FSS, and MDS-UPDRS Part 3 as additional outcomes. **References** [1] Videnovic A, Rutten S, Croft W, Erickson H, Groves J, Havemann C, Herrington T, Hendrix S, Kieburtz K, Van der Werf Y, Van den Heuvel O. ***Double-blind controlled trial of Spectramax™ light therapy for the treatment of Parkinson's disease patients on stable dopaminergic therapy,*** Mov Disord. 2018 Oct;33 Suppl 2:S429

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1062 / #1597

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

BRAIN MRI VOLUME PERCENTILES ARE ASSOCIATED WITH FUTURE MOTOR AND COGNITIVE SCORES IN PARKINSON'S DISEASE.

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Nuno Pedrosa De Barros[1], Thibo Billiet[1], Thanh Vân Phan[1], Vincenzo Anania[1], Diana Sima[1], Annemie Ribbens[1], Elnaz Ghasemi[2], Marian Shahid[2], Kathleen Poston[2]
[1]icometrix, Clinical Trials, Leuven, Belgium, [2]Stanford University, Neurology And Neurological Sciences, Stanford, United States of America

Aims: In Parkinson's disease (PD), predicting motor and cognitive decline is important for optimal treatment. Previously [1], we identified brain regions-of-interest (ROI) that correlate with future motor and cognitive scores based on voxel-based morphometry (VBM). Here, we aim to validate those findings based on brain volume percentiles calculated for those ROI.
Methods: Brain structures (Tables 1, 2) were segmented with the regulatory cleared ico**brain** software applied on baseline 3D-T1 MRI scans of 726 patients with PD from the Parkinson's Progression Markers Initiative (n=592) and Stanford (n=134) studies. Associations with cognitive and motor scores were assessed with linear mixed effect models. The worst MoCA/MDS-UPDRSIII score in the next 5 years was set as the dependent variable. Brain volume percentile scores (based on an age- and sex-matched healthy reference population) in an ROI, sex, disease duration and age were used as independent variables.
Results: MDS-UPDRSIII was significantly associated with brain volume percentiles of the caudate, putamen, frontal lobe GM, white matter and cerebellar WM. MoCA was significantly associated with the whole brain, gray matter, midbrain, cerebellar WM, temporal lobe, hippocampus and thalamus. Disease duration had a significant effect on MoCA and MDS-UPDRSIII, with longer duration associated with worse clinical scores. Older age was associated with worse MoCA scores and being male with worse MDS-UPDRSIII.

Table 1. Significant results for the model: Future MoCA ~ brain volume percentile + disease duration + age + sex

ROI	ROI vol. prctile		Disease duration		Age		Sex (male)	
	coef.	p-val	coef.	p-val	coef.	p-val	coef.	p-val
GM	0.011	0.006	0.204	<0.001	-0.113	<0.001	-0.495	0.106
WB	0.01	0.009	0.206	<0.001	-0.113	<0.001	-0.48	0.119
midbrain	0.008	0.047	0.199	<0.001	-0.115	<0.001	-0.496	0.108
thalamus	0.008	0.03	0.203	<0.001	-0.115	<0.001	-0.465	0.132
hippocampus	0.015	<0.001	0.206	<0.001	-0.115	<0.001	-0.378	0.217
cerebellar WM	0.008	0.034	0.206	<0.001	-0.117	<0.001	-0.505	0.102
CGM Temporal lobe	0.012	0.001	0.215	<0.001	-0.115	<0.001	-0.467	0.128

Table 2. Significant results for the model: Future MDS-UPDSRIII ~ brain volume percentile + disease duration + age + sex

ROI	ROI vol. prctile		Disease duration		Age		Sex (male)	
	coef.	p-val	coef.	p-val	coef.	p-val	coef.	p-val
WM	**0.038**	**0.006**	**0.449**	**0.001**	0.073	0.189	**2.307**	**0.036**
caudate	**-0.035**	**0.031**	**0.385**	**0.005**	0.069	0.214	**2.409**	**0.028**
putamen	**-0.035**	**0.03**	**0.399**	**0.004**	0.082	0.139	**2.506**	**0.023**
cerebellar WM	**0.045**	**0.004**	**0.459**	**0.001**	0.061	0.274	**2.243**	**0.041**
CGM Frontal lobe	**-0.032**	**0.038**	**0.424**	**0.002**	0.071	0.2	**2.191**	**0.045**

Conclusions: In line with our previous studies [1, 2], results indicate that brain volume percentile scores, compared to a healthy reference population, can have predictive value for future motor and cognitive decline.

Acknowledgments

funded by MJFF-021141

References

[1] Billiet T. et al., Gray matter cortical volumes relate to motor and cognitive disabilities in Parkinson's disease, AD/PD 2023, Gothenburg

[2] Shahid M. et al.,Structural imaging predictors of cognitive severity in Parkinson's disease, AD/PD 2021

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1063 / #2220

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

COMPARISON OF NEUROANATOMICAL CHANGES IN PARKINSON'S DISEASE COHORTS FROM NORTH AMERICAN AND INDIAN POPULATIONS

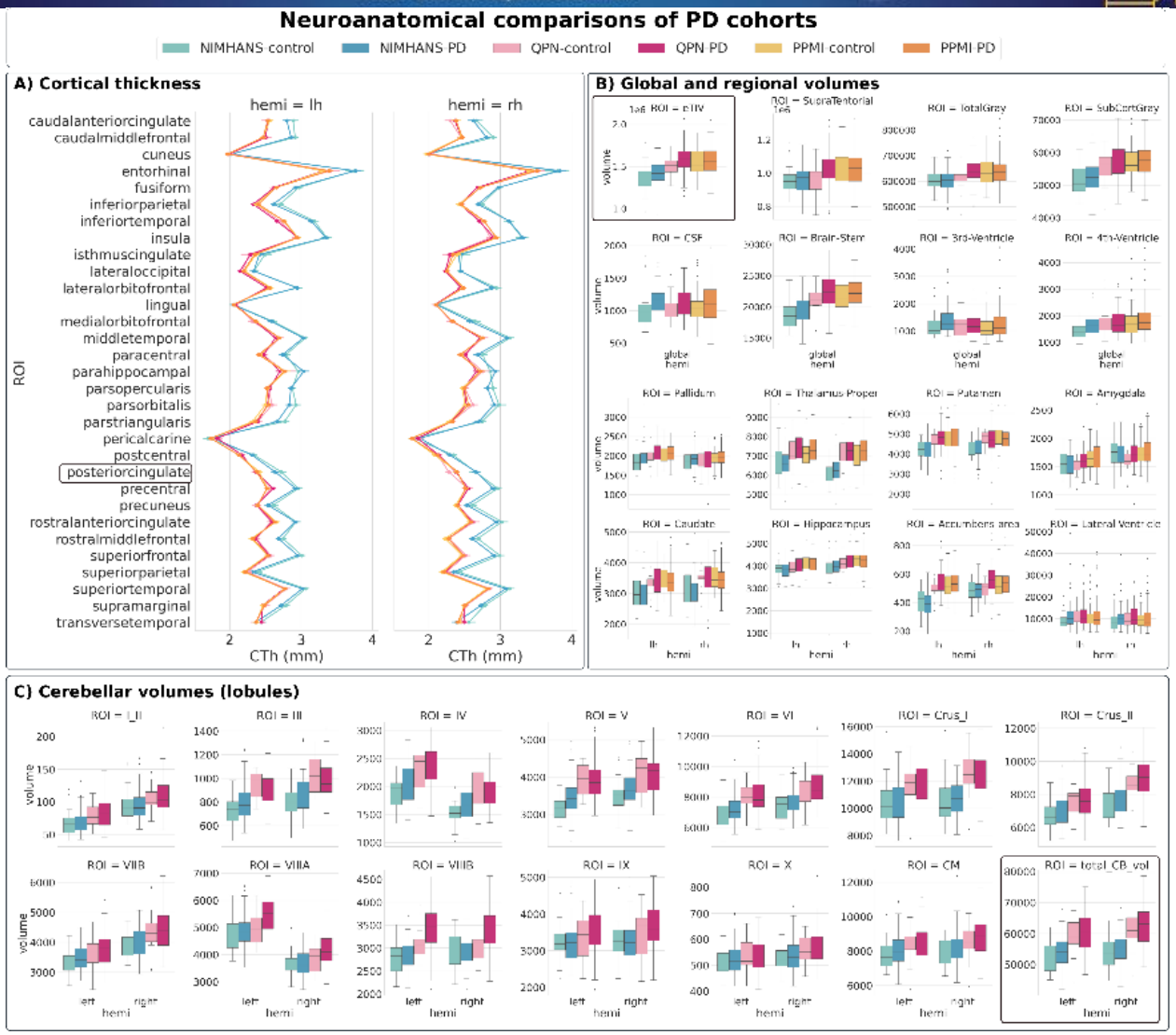
POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Nikhil Bhagwat[1], Shweta Prasad[2], Jitender Saini[2], Pramod Pal[2], Ravi Yadav[2], Edward Fon[1], D Louis Collins[1], Madeleine Sharp[1], Alain Dagher[1], Jean-Baptiste Poline[1]
[1]McGill University, Montreal Neurological Institute And Hospital, Montreal, Canada, [2]National Institute of Mental Health and Neuro Sciences, Neuroimaging & Interventional Radiology, Bengaluru, India

Aims: We compare neuroanatomical signatures associated with Parkinson's disease (PD) from North-American and Indian cohorts quantified using sMRI. We aim to identify commonalities and differences in brain morphometry in PD patients - possibly resultant of genetic, demographic, and lifestyle factors.
Methods: We analyze age-matched samples from PPMI (n=294), QPN (n=162), and NIMHANS (n=138) cohorts. The MRI data are acquired on different scanners but processed with identical pipelines. We quantify cortical thickness (CTh) and subcortical volumes using FreeSurfer-6.0 (DKT parcellation), and cerebellar volumes using the MAGeT Brain pipelines. To control for site effects, we assess CTh and volumetric PD-vs-control differences separately for the three cohorts using GLM. We control for age and sex in all models and additionally for total-intracranial-volume in regional and total-cerebellar-volume in cerebellar volumetric analyses.

Cohort	N (PD|Control)	Age (mean,std)
PPMI	210 84	54.2 (5.7) 51.6 (7.9)
QPN	136 26	55.9 (5.3) 52.5 (7.6)
NIMHANS	108 30	55.4 (7.1) 52.0 (5.9)

Results: NIMHANS consistently shows lower values for total-intracranial, supra-tentorial, and cerebellar volumes, and higher values for regional CTh compared to QPN and PPMI across PD and controls. The PD-vs-control comparisons show significant differences in CTh of posterior-cingulate (right) in both QPN and NIMHANS cohorts. Significant differences in Thalamic (left&right) volume are seen in PPMI, but not in QPN or NIMHANS. In cerebellum, lobules III(right), VIII-A(left), VIII-B (left&right) show differences only in QPN.



Conclusions: The results indicate that cross-cohort differences are affected by both scanner and biological factors. The PD-vs-control comparisons suggest few regional anatomical markers, however only CTh differences in posterior-cingulate are replicated across QPN and NIMHANS. Image harmonization and analysis of clinical phenotypes are needed (ongoing) to address cohort-specific biomarker shifts and isolate reliable PD-specific neurological signatures across datasets.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1064 / #1137

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

EARLY PREDICTION OF NEURODEGENERATION AT BIOBANK-SCALE VIA MACHINE LEARNING AND IMAGING

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Anant Dadu[1,2], Michael Ta[1,2], Nicholas Tustison[3], Ali Daneshmand[4], Andrew Singleton[2], Roy Campbell[5], Michael Nalls[1,2], Hirotaka Iwaki[1,2], Brian Avants[3], Faraz Faghri[1,2]
[1]Data Tecnica LLC, Data Tecnica Llc, Washington, United States of America, [2]National Institutes of Health, Center For Alzheimer's And Related Dementias, Bethesda, United States of America, [3]University of Virginia, Dept Of Radiology And Medical Imaging, Charlottesville, United States of America, [4]Boston University School of Medicine, Department Of Neurology, Boston, United States of America, [5]University of Illinois Urbana Champaign, Department Of Computer Science, Champaign, United States of America

Aims: Alzheimer's disease and related dementias (ADRD) and Parkinson's disease (PD) are the most common neurodegenerative disorders. Patients with ADRD or PD have long asymptomatic phases. Hence, quantitative measures that can provide early disease indicators are necessary to improve patient stratification, clinical care, and clinical trial design. This work uses machine learning techniques to derive such a quantitative marker from T1-weighted (T1w) brain MRI.
Methods: In this retrospective study, we developed a machine learning (ML) based score of T1w brain MRI image utilizing disease-specific Parkinson's Disease Progression Marker Initiative (PPMI) and Alzheimer's Disease Neuroimaging Initiative (ADNI) cohorts. Then, we evaluated the potential of ML-based scores for early diagnosis of ADRD and PD in an independent large-scale population-based cohort, UK Biobank, using longitudinal data. In this analysis, 1,826 dementia (from 731 participants), 3,161 healthy controls images (925 participants) from the ADNI cohort, 684 PD (319 participants), 232 healthy controls (145 participants) from PPMI cohort were used to train machine learning models.
Results: The classification performance is 0.94 [95% CI: 0.93-0.96] area under the ROC Curve (AUC) for ADRD detection and 0.63 [95% CI: 0.57-0.71] for PD detection using 790 extracted structural brain features. The normalized ML model's probabilistic output (ADRD and PD imaging scores) was evaluated on 42,835 participants from UK Biobank using survival analysis. ADRD imaging score is associated with dementia free survival (hazard ratio (HR) 1.76 [95% CI: 1.50-2.05] per standard deviation), and PD imaging score shows association with PD free survival (HR 2.33 [95% CI: 1.55-3.50]) after adjusting for covariates.
Conclusions: Our study demonstrates the use of quantitative markers generated using machine learning techniques and brain structural features are useful for early detection of ADRD and PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1065 / #2118

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

ASSOCIATION BETWEEN GENE EXPRESSION AND BRAIN ATROPHY IN DEMENTIA WITH LEWY BODIES

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Annegret Habich[1], Janna Baumann[1], Christopher Schwarz[2], Scott Przybelski[3], Anna Inguanzo[1], Ketil Oppedal[4], Frederic Blanc[5], Afina Lemstra[6], Jakub Hort[7], Bradley Boeve[8], Dag Aarsland[9], Eric Westman[1], Thomas Dierks[10], Kejal Kantarci[2], Laura Jonkman[11], Daniel Ferreira[1]
[1]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, STOCKHOLM, Sweden, [2]Mayo Clinic, Radiology, Rochester, United States of America, [3]Mayo Clinic, Quantitative Health Sciences, Rochester, United States of America, [4]University of Stavanger, Department Of Electrical Engineering And Computer Science, Stavanger, Norway, [5]Universite de Strasbourg, CHRU de Strasbourg, Cmrr, Strasbourg, France, [6]Amsterdam UMC, Alzheimer Center Amsterdam, Amsterdam, Netherlands, [7]Second Faculty of Medicine, Charles University, Department Of Neurology, Prague, Czech Republic, [8]Mayo Clinic, Department Of Neurology, Rochester, United States of America, [9]Institute of Psychology, Psychiatry & Neuroscience (IoPPN), King's College London, Department Of Old Age Psychiatry, London, United Kingdom, [10]University of Bern, University Hospital Of Psychiatry And Psychotherapy, Bern, Switzerland, [11]Amsterdam UMC location VUmc, Anatomy And Neurosciences, Amsterdam, Netherlands

Aims: Regional atrophy patterns have been observed in dementia with Lewy bodies (DLB). However, determinants of regional vulnerability to atrophy remain largely unexplored. Here, we investigated the association between regional gene expression and grey matter atrophy in probable DLB patients.
Methods: 165 DLB patients along with 165 age- and sex-matched healthy controls from three European centres and the Mayo Clinic (USA) were included. Volumetric atrophy was quantified from MRI using SPM12 in 112 cortical, subcortical, and cerebellar brain regions, and compared between groups, using *w*-scores. Regional expression data of seven genes involved in the formation and degradation of pathological protein aggregates (*APOE*, *APP*, *BIN1*, *GBA*, *MAPT*, *SNCA*, *TMEM175*) was extracted from six healthy donors from the Allen Human Brain Atlas and correlated with regional atrophy *w*-scores. Additionally, we assessed the predictive values of regional gene expression on regional atrophy using Gaussian stepwise backwards linear regression including all seven genes as predictors.
Results: Most brain regions showed atrophy in DLB patients compared to healthy controls, with atrophy being most pronounced in occipital and parietal lobes. Regional expression of *APOE* correlated negatively with regional atrophy in DLB. Conversely, regional expression of *MAPT* correlated positively with regional atrophy. Both APOE and MAPT gene expression were significant predictors of regional atrophy in the regression analysis. None of the other gene expression values was significantly associated with regional atrophy in DLB.
Conclusions: Our findings show that regional expression of genes associated with the abnormal accumulation of amyloid and tau, common co-pathologies in DLB, partially account for the brain atrophy pattern observed in DLB patients. This finding emphasises the relevance of co-pathologies in predicting atrophy progression and identifying potential targets for future disease-modifying treatments.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1066 / #1082

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

EVALUATION OF CHOROID PLEXUS VOLUME AND MICROSTRUCTURE IN PREMANIFEST SYNUCLEINOPATHY: A 7 TESLA MRI STUDY

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Firdaus Fabrice Hannanu[1], Guadalupe Garcia-Gomar[1,2], Kavita Singh[1,3], Stephan Grimaldi[1,4], Subhranil Koley[1], Ambra Stefani[1,5], Aleksandar Videnovic[6,7], Marta Bianciardi[1,6]
[1]Athinoula A. Martinos Center, MGH, Harvard Medical School, Radiology, Charlestown, United States of America, [2]Universidad Nacional Autónoma de México, Escuela Nacional De Estudios Superiores Unidad Juriquilla, Juriquilla, Mexico, [3]National Institute on Aging, NIH, Multiscale Imaging And Integrative Biophysics Unit, Lbn, Baltimore, United States of America, [4]University Hospital La Timone, Neurology And Movement Disorders, Marseille, France, [5]Medical University of Innsbruck, Neurology, Innsbruck, Austria, [6]Harvard University, Division Of Sleep Medicine, Boston, United States of America, [7]MGH, Harvard Medical School, Neurology, Boston, United States of America

Aims: The choroid plexus (ChP) has emerged as a critical player in neurosecretory and neuroimmune mechanisms, with its dysfunction often linked to protein aggregation and neuroinflammation. Changes in ChP volume have been reported in aging, neuroinflammatory disease, and Alzheimer's disease. Our objectives were to investigate if similar change is observed in premanifest-synucleinopathy (e.g. isolated-rapid-eye-movement-sleep-behavior-disorder, iRBD) by evaluating changes in ChP volume and MRI signal-intensity, and to generate a ChP atlas.
Methods: In 12 iRBD patients (11 male, aged 68±5.70 years), and 12 age-sex-matched controls (11-male, aged 65.6±6.2 years), we acquired multi-contrast (0.75mm-isotropic-resolution T_1-weighted-MEMPRAGE; 1.1mm-isotropic resolution T_2*-weighted) MRI at 7 Tesla. ChP in the lateral ventricle was manually segmented on T_2*-weighted images coregistered to T_1-weighted images, using both as reference. Volume (normalized by the total intracranial-volume) and mean T_2*-weighted and T_1-weighted signal intensity of ChP were computed, and compared between cohorts using a two-sample t-test. ChP segmentations were coregistered to stereotactic space and averaged to create a probabilistic ChP atlas.
Results: Compared to controls, in iRBD we observed (Figure 1): (i) a significant decreased volume of the right ChP, with similar trend for the left ChP; (ii) trends towards longer T_2*-weighted values; (iii) no significant changes in mean T_1-weighted values. A probabilistic atlas of left/right ChP in the lateral ventricle in iRBD and controls was created in stereotactic space (Figure

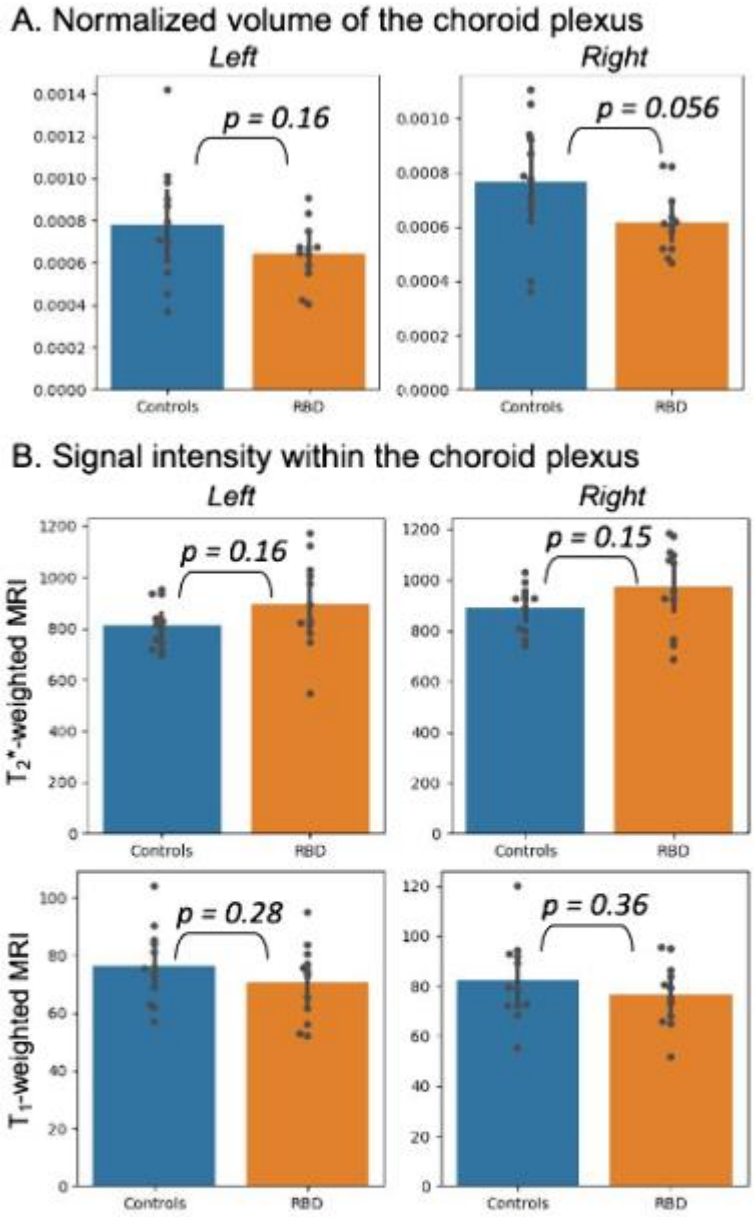


Figure 1. Changes in the volume of the choroid plexus of the lateral ventricles (A.) and in signal intensity (B.) in iRBD compared to elderly controls (n=12) using 7 Tesla multi-contrast MRI. In iRBD we observed decreased volume in right choroid plexus, trends in left choroid plexus volume and longer T_2*-weighted values, and no changes in T_1-weighted values. These results are compatible with atrophy of the choroid plexus in iRBD. We are currently analyzing multi-contrast 7 Tesla data of a larger cohort to further elucidate the choroid plexus role in the pathogenesis and progression of synucleinopathies.

2).

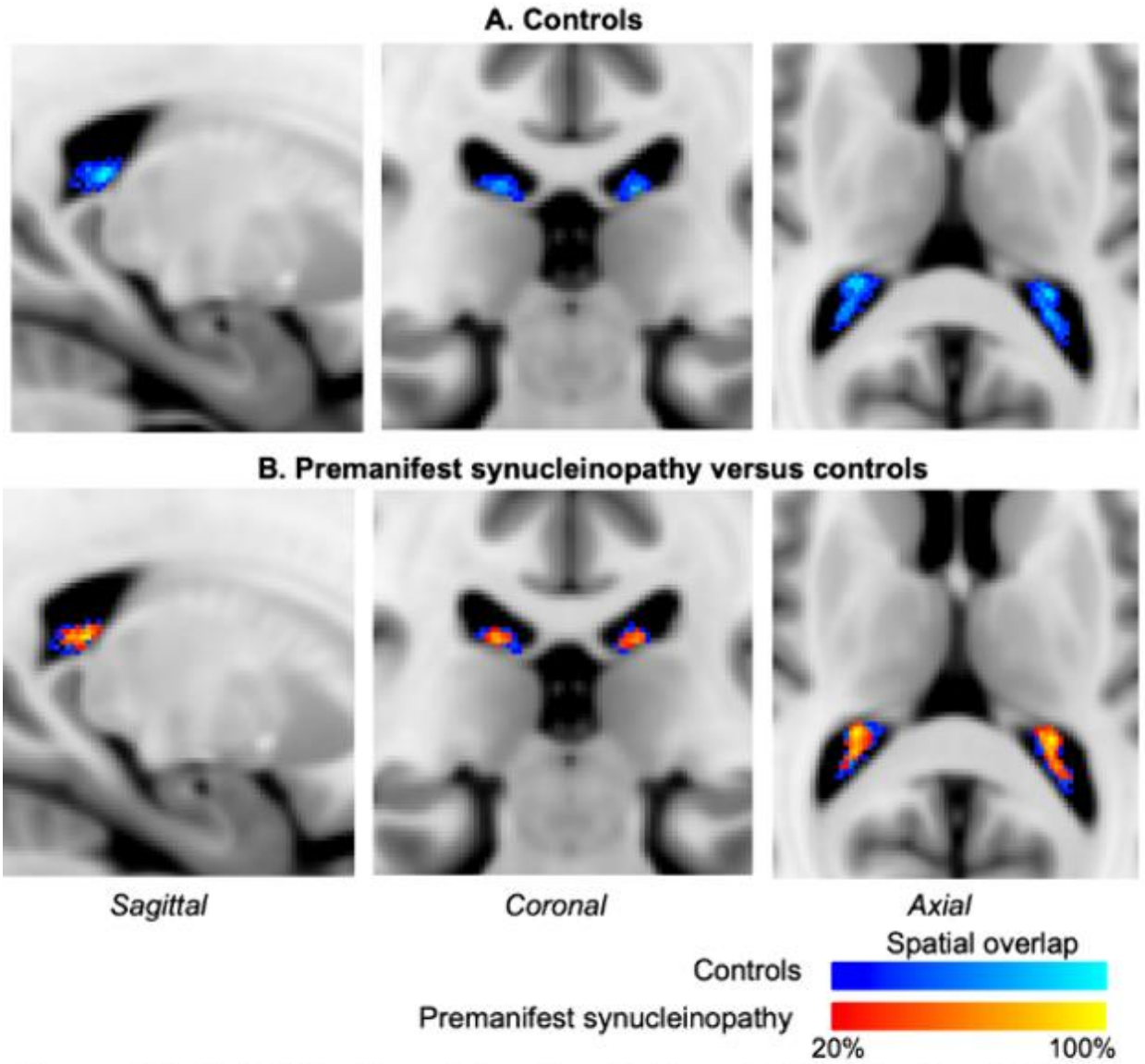


Figure 2. Probabilistic atlas of the choroid plexus in the lateral ventricles in stereotactic (Montreal Neurological Institute, MNI) space in controls (A., blue-light-blue) and in iRBD (B., red-yellow, overlapped with controls), created by computing the spatial overlap across subjects of manual segmentations. Decreased volume of the choroid plexus in iRBD is visible when compared to controls. The creation of a probabilistic atlas of the choroid plexus enhances our understanding of choroid plexus alterations in this premanifest stage, and might provide a valuable tool to automatically segment these structures in future MRI research in neurodegenerative diseases.

Conclusions: These 7 Tesla MRI-based results indicate atrophy of the ChP, which might underlie impaired neuroimmune response and neurofluid production/clearance in premanifest-synucleinopathy. This warrants further investigation to elucidate ChP role in the pathogenesis and progression of

synucleinopathies. The probabilistic atlas of ChP might be a useful tool to the community to automatically identify the location of ChP in conventional/advanced MRI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1067 / #1226

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

STRUCTURAL BRAIN CHANGES IN PRODROMAL PARKINSON'S DISEASE FROM UK BIOBANK

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Mirja Kuhlencord, Andrew Vo, Alain Dagher
The Neuro (Montreal Neurological Institute and Hospital), McGill University, Neurology And Neurosurgery, Montreal, Canada

Aims: Neurodegeneration patterns of diagnosed Parkinson's disease (PD) have been successfully studied with increasingly large datasets but the same does not apply for prodromal stages. In UK Biobank, imaging participants are followed up through a linkage with their electronic health records and those who subsequently develop PD offer a unique opportunity to examine early brain changes. Here, we compared neurodegeneration patterns between unaffected controls (HC), participants with diagnosed PD (dPD) and participants with prodromal PD (pPD) at the time of their brain MRI.
Methods: From the UK Biobank imaging sample, we identified 141 participants with PD and 8,460 matched HCs based on age, sex, BMI, socioeconomic status and ethnicity. Participants with PD were either classified as diagnosed (N = 91, mean time since diagnosis: 6,2 years) if they received the diagnosis prior to the brain MRI or as prodromal (N = 50, mean time to diagnosis: 3,6 years) if they received it afterwards. We performed Kruskal-Wallis tests with FDR-correction comparing subcortical volumes, regional cortical thickness and surface area across the three groups. Significant group effects were examined with post-hoc Dunn tests.
Results: We observed significant differences between HCs and the respective PD groups for cortical thickness and between HCs and pPD patients in right hippocampal volume. Cortical thickness of both dPD and pPD patients was especially reduced in temporoparietal regions. Interestingly, there were no significant differences between the two PD groups. However, dPD patients showed a higher number of significant differences to HCs than did pPD patients. We did not find any significant differences in cortical surface area.
Conclusions: Our results show that pPD patients already display relevant neurodegeneration patterns that are mostly congruent with those observed in dPD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1068 / #1070

Poster Topic: *Theme C: α-Synucleinopathies / C03.g. Drug Development, Clinical Trials: Non-pharmacological interventions, neurosurgery*

WORKING MEMORY MODULATION USING A THETA-TACS OF A FRONTO-PARIETAL NETWORK

POSTERS: C03.G. DRUG DEVELOPMENT, CLINICAL TRIALS: NON-PHARMACOLOGICAL INTERVENTIONS, NEUROSURGERY

Monika Pupíková[1,2], Irena Rektorova[1,2], Adam Šimo[2], Patrik Šimko[2], Martin Lamoš[2], Martin Gajdoš[2], Kristina Mitterová[2]
[1]St. Anne's University Hospital (FNUSA), The International Clinical Research Center (icrc), Brno, Czech Republic, [2]CEITEC MU, Applied Neuroscience Group, Brno, Czech Republic

Aims: Disruption of theta oscillations within the fronto-parietal network (FPN) contributes to working memory deficits in the elderly population. The aim of this study was to test the efficacy of different unifocal and multifocal transcranial alternating current stimulation (tACS) protocols to modulate theta oscillations within the FPCN, which could compensate for working memory loss due to aging.
Methods: In a randomized, placebo-controlled trial, we tested four theta-tACS protocols with simultaneous working-memory task (Twenty seniors aged 60-80): a monofocal frontal, a monofocal parietal, and a bifocal in/out-of-phase fronto-parietal protocol. Electrodes were placed at individualized coordinates of the middle frontal gyrus (MFG) and/or the inferior parietal lobule (IPL) based on functional magnetic resonance imaging (fMRI) activations. The individual theta band stimulation frequency was based on the task-EEG recording. All participants underwent pre-post resting fMRI. Behavioral online data and rs-fmri connectivity data (pre-post stimulation changes) were analyzed using linear mixed models (LMMsfixed factors: stimulation protocol, block number, task difficulty).
Results: LMMs showed a statistically significant interaction between stimulation protocol and task difficulty ($p < 0.0001$) on performance in the N-back task. Subsequent analyses revealed the largest effect of frontal monofocal theta-tACS ($p = 0.004$, effect size $d = 0.30$). Analyses of rs-fMRI data showed a change in connectivity between the right anterior prefrontal cortex (raPFC) and the right dorsolateral prefrontal cortex (rdlPFC) compared to placebo stimulation ($p=0.022$).
Conclusions: Monofocal frontal theta stimulation resulted in small but statistically significant changes in working-memory task performance with a higher degree of difficulty, outperforming other stimulation protocols. The changes produced by tACS frontal monofocal stimulation were accompanied by changes in functional connectivity within the stimulated fronto-parietal network. Our study demonstrated the possibility of modulating working memory by externally influencing the fronto-parietal network using theta-tACS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1069 / #273

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

UPPER SPINAL CORD MORPHOLOGY ACROSS CLINICAL STAGES OF PARKINSON'S DISEASE

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Max Laansma[1], Thiago Rezende[2], Nina Schmitz[1], Conor Owens-Walton[3], Eva Van Heese[1], Emile D'Angremont[1], Fernando Cendes[2], Clarissa Yasuda[2], Ysbrand Van Der Werf[1], Marcondes Franca Jr[2]
[1]Amsterdam UMC, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Anatomy And Neurosciences, Amsterdam, Netherlands, [2]State University of Campinas (UNICAMP), Department Of Neurology And Neuroimaging Laboratory, Campinas, Brazil, [3]Mark and Mary Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Imaging Genetics Centre, Los Angeles, United States of America

Aims: The spinal cord plays a critical role in processing motor and sensory information, connecting the peripheral nervous system with the brain; however, it remains unclear how its structure is affected in Parkinson's disease (PD). We studied upper (cervical) spinal cord morphometry across distinct clinical stages of PD versus controls using a state-of-the-art parcellation technique.
Methods: Spinal cord segments C1-C4 were parcellated from T1-weighted MR images of 189 individuals with PD and 131 controls, derived from two sites, using the Spinal Cord Toolbox (https://spinalcordtoolbox.com/). The PD group was stratified by Hoehn and Yahr (HY) disease stage 1 (n = 26), 2 (n = 102) and 3 and higher (n = 34) (n = 27 no HY-score available), and compared to controls on the surface area and shape of each cervical segment using a linear mixed model, including age, sex and site as covariates.
Results: HY2 and HY3 showed significantly smaller surface area of C1 (d = -0.6, p < 0.001 and d = -0.9 p < 0.001, respectively). Additionally, the surface area of C4 was significantly smaller in HY3 (d = -0.22, p = 0.037). We found no differences in HY1 for surface area and shape.
Conclusions: These results indicate the involvement of specific cervical segments in PD, dependent on disease stage. While HY1 appears normal, smaller C1 and subsequently C4 in following stages may reflect targeted neurodegeneration, in line with disease progression. Follow-up research in a larger sample is needed to confirm the robustness of these patterns and to study the relation with specific symptom domains.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1070 / #1737

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

G2019S-LRRK2 INDUCES NEUROVASCULAR ABNORMALITIES IN A MOUSE MODEL OF PARKINSON DISEASE

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Hannah Fuehrer[1], Bo Ning[1], Khuleshwari Kurrey[1], Lishan Lin[1], Maria Gabriela Mercado Guerra[1], Mali Jiang[1], Peter C.M. Van Zijl[2], Christopher Ross[1], Jun Hua[2], Wanli Smith[1]
[1]School of Medicine, Johns Hopkins University, Psychiatry, Baltimore, United States of America, [2]School of Medicine, Johns Hopkins University, Radiology, Baltimore, United States of America

Aims: Parkinson's disease (PD) is a common neurodegenerative disease characterized by motor impairments resulting from midbrain dopamine (DA) neuron loss. Mutations in LRRK2 cause genetic PD and contribute to sporadic PD. Here, we used LRRK2-G2019S transgenic mouse model to investigate abnormalities in arteriolar cerebral blood volume (CBVa) in various brain regions using the inflow-based vascular-space-occupancy (iVASO) MRI technique.
Methods: CBVa was measured in the substantia nigra (SN), olfactory cortex and prefrontal cortex. Alterations in the blood volume of small arteries and arterioles (CBVa) were detected in the G2019S-LRRK2 mouse model of PD.
Results: Compared to non-transgenic mice, G2019S-LRRK2 mice at clinical stage showed decreased CBVa in the SN, but increased CBVa in olfactory and prefrontal cortex in both male and female groups. On contrast, WT-LRRK2 mice showed no change in CBVa in the SN (male and female), the olfactory (female) and prefrontal (female) cortex, but a slight increase in CBVa in the olfactory and prefrontal cortex in the male group only. These changes in CBVa in the SN and the cortex in G2019S-LRRK2 mice was corresponding with PD pathology.
Conclusions: Our studies suggest the potential value of CBVa as a marker for clinical PD studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1071 / #257

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

ASSOCIATION BETWEEN REGIONAL CEREBRAL PERFUSION AND MOTOR RESERVE IN EARLY PARKINSON'S DISEASE: AN EARLY-PHASE 18F-FP-CIT PET STUDY

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Yeo Jun Yoon[1], Su Hong Kim[2], Phil Hyu Lee[1], Yun Joong Kim[3], Young H. Sohn[1], Yong Jeong[2], Seok Jong Chung[3]
[1]Yonsei University College of Medicine, Neurology, Seoul, Korea, Republic of, [2]Korea Advanced Institute of Science and Technology, Bio And Brain Engineering, Daejeon, Korea, Republic of, [3]Yongin Severance Hospital, Neurology, Yongin, Korea, Republic of

Aims: There are individual differences in motor deficits, despite a similar degree of nigrostriatal dopamine depletion in Parkinson's disease (PD), called motor reserve. This study aimed to investigate the alterations in regional cerebral perfusion associated with motor reserve in patients with PD, using early-phase ^{18}F-FP-CIT PET images.
Methods: We enrolled 397 patients with newly diagnosed PD who underwent dual-phase ^{18}F-FP-CIT PET scans upon initial assessment. Individual motor reserve was estimated based on initial parkinsonian motor deficits and striatal dopamine depletion using a residual model. Then, patients were classified into three groups according to motor reserve estimates: the highest quartile PD group (PD-MR-H, n = 100), the intermediate (i.e., the second and third quartile) PD group (PD-MR-I, n = 197), and the lowest quartile PD group (PD-MR-L, n = 100). We explored the group differences in regional uptake in the early-phase ^{18}F-FP-CIT PET images between the three PD groups.
Results: As expected, patients in the PD-MR-H group exhibited less severe baseline motor deficits than did those in the other PD groups despite having similar levels of dopamine transporter availability in the posterior putamen. There were no significant differences in age and sex between the PD groups, while patients in the PD-MR-H group had a higher level of educational attainment and better cognitive performance in verbal memory function than those in the other groups. Quantitative analyses of early-phase ^{18}F-FP-CIT PET images demonstrated that the PD-MR-L group exhibited decreased uptake in the occipital region, including the lateral occipital, compared to the PD-MR-H group.
Conclusions: The results of the present study suggest that cerebral hypoperfusion in the occipital region on early-phase ^{18}F-FP-CIT PET images are associated with low motor reserve in patients with newly diagnosed PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1072 / #2116

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

DEEP-LEARNING BASED CLASSIFICATION OF DUAL-PHASE 18F-FP-CIT PET IMAGES FOR THE DIAGNOSIS OF PARKINSONISM

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Dongwoo Kim, Daesung Kim, Kyobin Choo, Hyunkyung Han, Jihye Lee, Soomin Kim, Jaekyung Park, Hyunkeong Lim, Mijin Yun
Yonsei University College of Medicine, Department Of Nuclear Medicine, -, Yonsei-Ro, Seodaemun-gu, Seoul , Republic of Korea, Korea, Republic of

Aims: This study aims to develop a deep-learning based framework that helps with the analysis of dual-phase 18F-FP-CIT PET images to detect persons with normal condition (NC), idiopathic Parkinson's disease (IPD), progressive supranuclear palsy (PSP), and multiple system atrophy (MSA).
Methods: This study analyzed 388 cases from 2015 to 2022. Labels were given by the consensus of two experts, one nuclear medicine physician and one clinician. Data was split into train, validation, and test sets by an 8:1:1 ratio to evaluate the effects of model architecture, regularization, and dual-phase imaging. Models were chosen based on F1 score and accuracy, followed by 5-fold cross validation. The top models were compared with their ensemble, and the best ensemble was tested prospectively on 76 cases for a month.
Results: DenseNet, EfficientNet, and a custom CNN were chosen as candidate architectures. The custom CNN had the highest performance (F1 score, accuracy: 0.90, 0.90) individually. Regularization improved its accuracy to 0.92. When trained on delay-phase and early-phase images, its scores dropped to 0.62, 0.77 and 0.83, 0.82. DenseNet showed best performance in 5-fold cross-validation, with an average F1 score of 0.90 (std 0.05) and an average accuracy of 0.92 (std 0.04). In ensemble, the F1 score and the accuracy improved to 0.94 and 0.95. This ensemble model yielded a F1 score of 0.71 and an accuracy of 0.92 during the prospective study.
Conclusions: Convolutional neural network has shown to be capable of classifying 18F-FP-CIT PET images at the level of a skilled nuclear medicine physician. Further research may explore the possibility of performing classification on data from different PET devices.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1073 / #1215

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

A NOVEL ALGORITHM TO PRODUCE POPULATION-BASED INPUT FUNCTION FOR ARTERIAL INPUT FUNCTION

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Daren Ma[1], Sneha Pandya[2], Ashish Raj[1], Ajay Gupta[2]
[1]University of California San Francisco, Radiology And Biomedical Imaging, San Francisco, United States of America, [2]Cornell University, Weill-cornell Medical College, New York, United States of America

Aims: The accuracy of Population-based Input Functions (PBIF) depends on scaling with at least a small number of arterial or late venous blood samples, which defeats its primary non-invasive purpose. We propose to produce the PBIF estimate using machine learning algorithms on limited current data without requiring new blood samples.
Methods: First, we collected the Time Activity Curves (TACs) from 22 subjects, and performed linear interpolation and peak alignments. Next, we divided the processed TACs by their corresponding AUCs for each subject and calculated the average to obtain the PBIF curve. Subsequently, we used demographic data as input for our Gradient Boosting model to generate AUC predictions. Afterwards, we multiplied the PBIF curve by the subject-wise predicted AUCs to form the predicted AIF curves. After obtaining the pAIF, Kinetic modelling was done to extract total V_T , derived from both empirical AIF and pAIF for 86 brain regions in D-K Atlas through the graphical Logan method. Lastly, we implemented a slope-prediction ML algorithm to improve the fit between Logan V_T from AIF and pAIF.
Results: We demonstrate excellent match with arterial blood derived V_T results, comparing favorably to prior naive PBIF techniques. Our PBIF approach doesn't rely on a priori distinguish between healthy and disease subjects. Indeed, it's equally effective on control and Parkinson's patients, and in genetically medium- versus high-affinity binders. Results are shown in Fig 1 and 2.

Fig 1: PBIF Related Curves

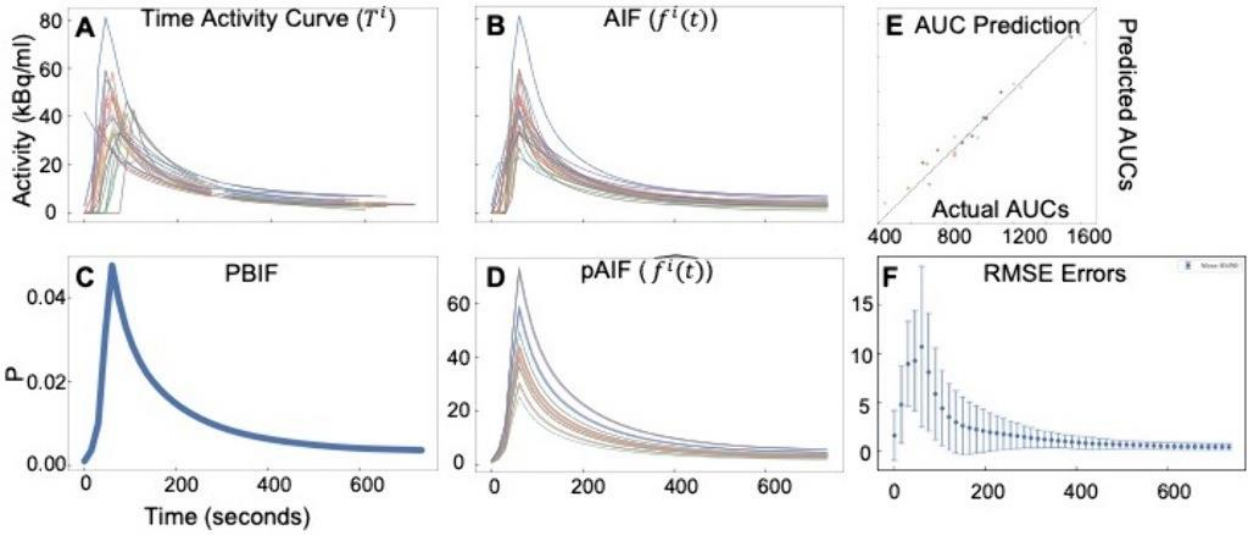
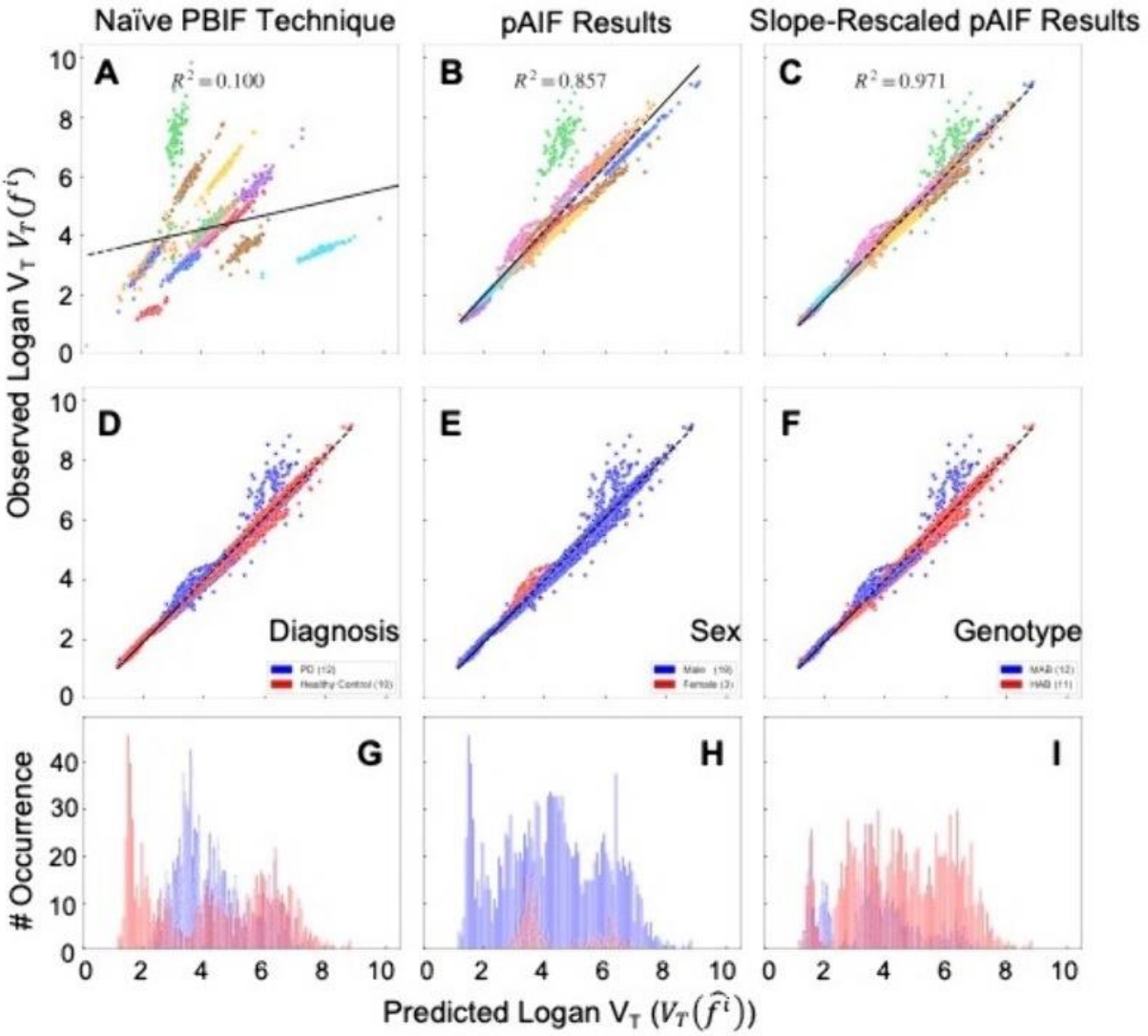


Fig 2: Logan V_T Results



Conclusions: This study shows that [^{11}C] DPA-713 radioligand can be quantified without any arterial blood or venous blood samples, from PBIF based on previously acquired dataset on patients with A-lines, in clinical applications or scientific exploratory analyses where the primary attention is on spatial gradients or heterogeneity of microglial PET signal.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1074 / #2053

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

SPINOCEREBELLAR ATAXIA TYPE 3 (MJD) WITHOUT DISTINCT PARKINSONISM SHOWING PRESYNAPTIC DOPAMINE TRANSPORTER (DAT) UPTAKE LOSS

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Mee Young Park, Jeanseo An, Dong Sung Shin
YEUNGNAM UNIVERSITY MEDICAL CENTER, Neurology, Daegu, Korea, Republic of

Aims: We report a unusual case of SCA3 showing presynaptic DAT uptake loss without initial parkinsonism.
Methods: A 29-year-old female presented with posture imbalance and gait disturbance. Her neurologic examination showed bidirectional gaze evoked nystagmus, dysarthria, ataxia, spasticity but no parkinsonism for 2years. Her family history was usual.
Results: Brain **MRI** demonstrated ponto-cerebellar atrophy and 1**8F FP-CIT PET** imaging demonstrated definite presynaptic dopamine transporter (DAT) uptake loss. Molecular analysis revealed an expanded **SCA3 allele of 15/74 expansion**. Figure 1. Brain MRI of the patient. T2-saggital (A) and T2-FLAIR (B, C) images shows mild ponto-cerebellar atrophy (arrowheads). After 7 months, a follow-up brain MRI (D, E, F) also shows similar findings without significant change. Figure 2. FP-CIT PET of the patients. Diffuse uptake loss of presynaptic dopamine transporter (DAT) binding in Both putamen and caudate nucleus Figure 3. **Cardiac 123I-MIBG** of the patients. Cardiac meta-iodobenzylguanidine (MIBG) uptake is assessed using the heart-to-mediastinum (H/M) activity ratio. This image shows cardiac sympathetic denervation in Cardiac 123I-MIBG scan. (A) early anterior image of the patient (H/M ratio = 1.61). (B) early lateral anterior oblique image of the patient (H/M ratio = 1.86). (C) late anterior planar of the patient (H/M ratio = 1.66). (D) late lateral anterior oblique image of the patient (H/M ratio = 1.93) Table 1. , UPDRS(united PD rating scale) and SARA (Scale for the assessment and rating of ataxia) of the patients for 2 years
Conclusions: In SCA 2 and 3, parkinsonism may rarely presenting as the disease progresses, early diagnosis by DAT scan, L-dopa therapy can improve the patient's QOL. 1. Ludger Scho¨ ls, et al. No parkinsonism in SCA2 and SCA3 despite severe neurodegeneration of the dopaminergic substantia nigra. *BRAIN* 2015:138;3316–26.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1075 / #419

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

EFFICACY OF 18F-DOPA PET AND SNIFFIN' STICKS TEST FOR THE DIAGNOSIS OF PARKINSON'S DISEASE

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Denis Pokhabov[1], Vladislav Abramov[2], Michael Sadovsky[3], Dmitrii Pokhabov[1]
[1]Krasnoyarsk state Medical University, Neurological Diseases, Krasnoyarsk, Russian Federation, [2]Federal Siberian Research Clinical Centre FMBA, Neurological Diseases, Krasnoyarsk, Russian Federation, [3]Siberian Federal University, Computational Technology Process, Krasnoyarsk, Russian Federation

Aims: Parkinson's disease(PD) is among the most common neurodegenerative diseases of the elderly. The etiology of PD is still unknown. Positron emission tomography(PET) is an up-to-date and promising method in diagnosing PD and other diseases. Our aim was to examine patients using PET for the analysis of development and degradation of dophaminergic neurons in PD and also examine their olfactory function.
Methods: 18F-DOPA is the optimal radiopharmaceutical(RP) for studying the dopaminergic system. All patients initially underwent MRI of the brain to exclude structural changes and compare the MRI and PET images. Fifty minutes after the administration of 18F-DOPA, static 3D scanning was performed for 20 minutes on a PET scanner. We analysed the max and mean(ave) values of activity, as well as ratio of the activity of the shell/visual cortex(SOR), caudate/visual cortex(COR), posterior shell/front shell(PAR) and in-shell activity to the activity in the caudate nucleus (SCR). An examination procedure of olfactory function was based on extended olfactory Sniffin' sticks test.
Results: The level of RP uptake in the rear part of the shell is the most diagnostically significant indicator among all relative indices. SOR is the most diagnostically valuable indicator. It is associated with the most significant difference in RP accumulation in the shell and the visual cortex. The diagnostic value of SCR and COR is slightly lower because of the minor difference between the accumulation in the shell and them. Two separate clusters appear in constructing elastic maps using eight selected relative. We also got a three clusters of patients by olfactory test.
Conclusions: Here we present the reference values of the indices for brain PET investigation. The informative indices are determined from the observed PET data. Also, high efficiency of PET for Parkinson's disease was approved.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1076 / #211

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

EFFECTS OF DE-FACING MRI AND PET SCANS ON FDG BIOMARKERS OF DLB

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Christopher Schwarz[1], Walter Kremers[2], Stephen Weigand[2], Scott Przybelski[2], Timothy Lesnick[2], Bradley Boeve[3], Carl Prakaashana[1], Matthew Senjem[1], Qin Chen[1], Julie Fields[4], Jeffrey Gunter[1], Paul Min[1], Manoj Jain[5], Toji Miyagawa[3], Rodolfo Savica[3], Jonathan Graff-Radford[3], Hugo Botha[3], David Jones[3], Neill Graff-Radford[6], Tanis Ferman[7], Prashanthi Vemuri[1], David Knopman[3], Val Lowe[1], Kejal Kantarci[1], Clifford Jack[1]
[1]Mayo Clinic, Radiology, Rochester, United States of America, [2]Mayo Clinic, Quantitative Health Sciences, Rochester, United States of America, [3]Mayo Clinic, Neurology, Rochester, United States of America, [4]Mayo Clinic, Psychiatry & Psychology, Rochester, United States of America, [5]Mayo Clinic, Radiology, Jacksonville, United States of America, [6]Mayo Clinic, Neurology, Jacksonville, United States of America, [7]Mayo Clinic, Psychiatry & Psychology, Jacksonville, United States of America

Aims: Recent work has shown that de-identified brain research scans can potentially be re-identified using face recognition. Software to automatically "de-face" images (remove the face before data sharing) is increasingly used to protect participant privacy. *mri_reface*, which replaces the face with an average face, was shown to have no significant effects on AD biomarkers from MRI, amyloid PET, and tau PET. However, effects on FDG PET and biomarkers of DLB have not been measured.
Methods: We replicated a previous analysis of FDG metabolic signatures of DLB (Kantarci et al., NeuroImage: Clinical, 2021) both with and without applying *mri_reface* to all T1-weighted 3T MRI and FDG PET images. This included images from patients with MCI at the Mayo Clinic Alzheimer's Disease Research Center who underwent PET at baseline and progressed to either probable DLB (MCI-DLB, n=17) or AD dementia (MCI-AD, n=41) during follow-up, and a comparison cohort of age- and sex-frequency-matched cognitively unimpaired (CU) participants from the Mayo Clinic Study of Aging (n=100). We measured the group-discrimination ability of 3 FDG PET biomarkers (Cingulate Island Sign (CIS) Ratio, Substantia Nigra SUVR, and Medial Temporal SUVR) and voxel-wise FDG group differences. We then directly tested for statistical differences between the unmodified and de-faced image analyses.
Results: All analyses were qualitatively similar between unmodified and de-faced image measurements. Region-based analyses had AUC values that differed by ≤ 0.02, and voxel-based analyses found qualitatively identical voxel masks and statistical power. There were no statistically significant differences between any pairs of analyses with unmodified vs. de-faced images.

model	AUC.Unmodified	AUC.DeFaced	p.Original_vs_DeFaced
Group ~ CISRatio	0.79	0.79	0.777
Group ~ MedialTemporal	0.81	0.81	0.687
Group ~ SubstantiaNigra	0.79	0.80	0.717
Group ~ CISRatio + MedialTemporal	0.86	0.86	>0.999
Group ~ CISRatio + SubstantiaNigra	0.88	0.88	>0.999
Group ~ MedialTemporal + SubstantiaNigra	0.89	0.87	0.316
Group ~ CISRatio + MedialTemporal + SubstantiaNigra	0.91	0.91	0.785

Figure 1: For each logistic regression model using regional FDG PET imaging biomarkers, we measured the ability to discriminate between MCI-DLB and MCI-AD using the Area Under the Receiver Operating Characteristic Curve (AUC), first with the unmodified images, and again with the de-faced images. We directly compared these AUC values from the unmodified vs. de-faced images with roc.test(). In total, there were no significant differences between models with measurements from the original vs. the de-faced images.

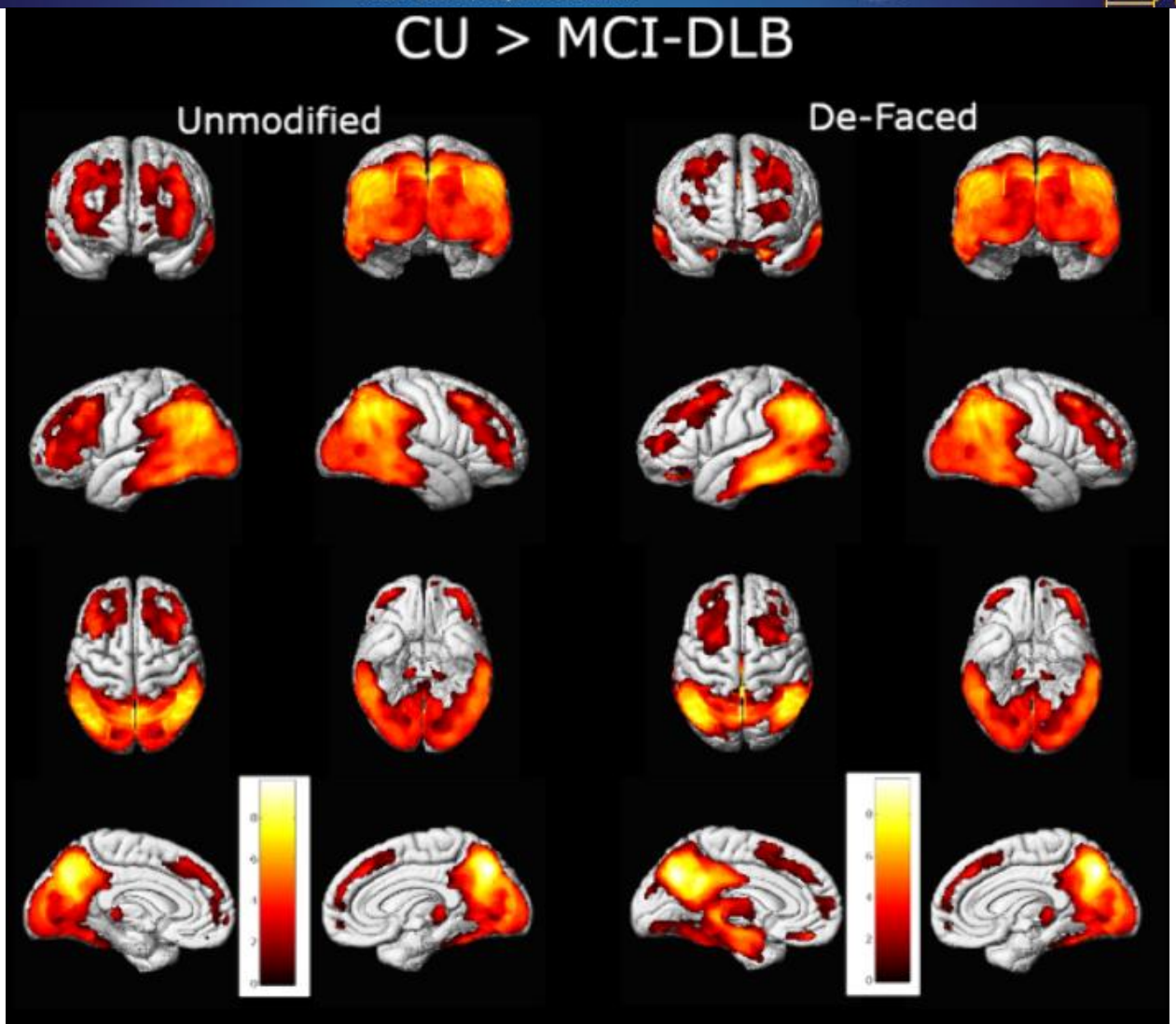


Figure 2: Voxel-based analyses (p<0.05 FWE) with unmodified images (left) vs. de-faced images (right) were qualitatively identical. A second-level analysis comparing these analyses (not shown) had zero significant differences in both directions (p<0.001 uncorrected).

Conclusions: De-facing MRI and FDG PET images with *mri_reface* had no significant effects on analyses of FDG PET biomarkers of DLB.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1077 / #804

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

CHARACTERIZATION OF A PREFORMED FIBRIL SEEDING MODEL OF SYNUCLEINOPATHY WITH A NOVEL ALPHA SYNUCLEIN PET TRACER

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Jonathan Sugam[1], Yuchuan Wang[2], Hyking Haley[2], Mona Purcell[2], Jun Meng[2], Stefan Verhoog[2], Rob Drolet[1], Zhizhen Zeng[2], Patricia Dockery[2], Idriss Bennacef[2], Kerry Riffel[2], Mallory Stenslik[2], Lei Ma[1], Wenping Li[2], Helen Mitchell[3], Jacob Marcus[1], Sean Smith[1], Eric Hostetler[2]
[1]Merck Sharp & Dohme, Discovery Biology, Rahway, United States of America, [2]Merck Sharp & Dohme, Translational Imaging, Rahway, United States of America, [3]Merck Sharp & Dohme, Chemistry, Rahway, United States of America

Aims: The pathological spreading hypothesis of Parkinson's disease (PD) has been modeled preclinically using a preformed fibril (PFF) seeding model. Detection of this synucleinopathy has previously only been possible via post-mortem histological or biochemical evaluations. A PET tracer for alpha synuclein would further validate that the pathology induced by the PFF seeding model is similar to the pathology present in patients and provide a clinically translatable biomarker of efficacy for therapeutic targets of synucleinopathy.
Methods: Young A30P mice (9-10 weeks old) were injected unilaterally into the striatum with varying concentrations of PFF or monomeric synuclein. Animals were imaged with an [^{18}F] labeled synuclein PET tracer 15-16 days following injection. SUVR changes were determined for the striatum using cerebellum as reference, and both bilateral striatal SUVR and right/left striatal uptake ratio were measured.
Results: We observed a dose response related relationship in SUVR in the striatum of animals injected with PFF compared to monomer with higher SUVR for animals injected with higher concentrations of PFF. Further, we also observed elevated SUVR in the right (injected) striatum compared to the left (uninjected) striatum. The ratio of right/left SUVR was greater for higher concentrations of PFF compared to monomer.
Conclusions: As the PFF seeding model is widely used in the field, this data validates that the synucleinopathy induced by PFF is relevant to human PD. This model can also help accelerate the evaluation of novel PET tracers, as PFF seeding induces pathology in young mice in as short as 2 weeks rather than relying on aged transgenic models. As a whole, this platform will be critical for the evaluation of preclinical to clinical translatable biomarkers of disease progression and therapeutic efficacy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1078 / #2086

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

THE POTENTIAL USEFULNESS OF SEMIQUANTITATIVE ANALYSIS OF 10-MINUTES POST-INJECTION F-18-DOPA PET FOR THE DIAGNOSIS OF PARKINSONIAN SYNDROMES

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Tiago Vieira[1], Facundo Diaz[2], Manuel Perez[3], José Oliveira[4]
[1]Atrys, Nuclear Medicine, porto, Portugal, [2]Atrys, Radiology, Barcelona, Spain, [3]Hospital Italiano de Buenos Aires, Radiology, Buenos Aires, Argentina, [4]Atrys, Nuclear Medicine, Porto, Portugal

Aims: F-18-DOPA is a PET agent for presynaptic dopaminergic assessment. PET can be analyzed qualitatively or semiquantitatively using standardized uptake ratio (SUR). SUR of F-18-DOPA PET showed to differentiate subjects with and without parkinsonian syndromes (PS), but 10-minutes post-injection (tenPI) ratios have not been evaluated. We studied the accuracy of semiquantitative analysis of tenPI PET in predicting the visual interpretation of 90-minutes post-injection (ninetyPI) PET in subjects with suspected PS.
Methods: PET was acquired at 2 time-points, 10 minutes and 90 minutes, post-injection of F-18-DOPA; image reconstruction using OSEM. SUVmax was recorded in each basal ganglia and in the occipital cortex, at both time-points. SUR was calculated as SUVmax of basal ganglia/SUVmax of the occipital cortex. The results of the visual analysis of ninetyPI PET, as reported by the nuclear medicine physician, were used for evaluating the accuracy of the semiquantitative analysis in predicting the visual interpretation.
Results: Sixteen subjects include; nine male, 7 female; median age: 63±10 years. As per qualitative analysis, 6 exams were considered to show decreased uptake (DU) in the basal ganglia and 10 exams were interpreted as presenting normal uptake (NU). In tenPI PET, SUR was significantly different between subjects with DU and NU ((p = 0.016); 1.2 (1.1-1.3) and 1.4 (1.3-1.5), in DU and NU, respectively). In ninetyPI PET, SUR was not significantly different between subjects with DU and NU ((p = 0.118); 3.1 (2.5-3.1) and 3.2 (2.9-3.3), in DU and NU, respectively). In tenPI PET, sensitivity, specificity, positive predictive value, and negative predictive value of SUR were 83.3%, 80%, 71.4% and 88.9%, respectively.
Conclusions: For the diagnosis of PS, SUR in tenPI F-18-DOPA PET seems to predict the visual interpretation of ninetyPI F-18-DOPA PET with good accuracy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1079 / #2163

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

THE IMPACT OF AN ADVANCED BAYESIAN PENALIZED-LIKELIHOOD RECONSTRUCTION ALGORITHM ON THE SEMIQUANTITATIVE ANALYSIS OF F-18-DOPA PET FOR THE DIAGNOSIS OF PARKINSONIAN SYNDROMES

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Tiago Vieira[1], Facundo Diaz[2], Manuel Perez[3], José Oliveira[1]
[1]Atrys, Nuclear Medicine, Porto, Portugal, [2]Atrys, Radiology, Barcelona, Spain, [3]Hospital Italiano de Buenos Aires, Radiology, Buenos Aires, Argentina

Aims: F-18-DOPA is a PET agent for presynaptic dopaminergic assessment. PET can be analyzed visually or semiquantitatively using standardized uptake ratio (SUR). SUR showed to differentiate subjects with or without parkinsonian syndromes (PS). We aimed to study the impact of an advanced Bayesian penalized-likelihood reconstruction algorithm (BPLA) - which allows effective convergence, in contrast to ordered subset expectation maximization (OSEM) - on the semiquantitative analysis in predicting the visual interpretation of F-18-DOPA PET from subjects with suspected PS.
Methods: For semiquantitative analysis, SUVmax was recorded in the basal ganglia and in an occipital ROI, using images reconstructed with BPLA and standard OSEM. SUR was calculated as the SUVmax in the basal ganglia/SUVmax in the occipital cortex. The semiquantitative data were compared to the PET visual analysis reported by the nuclear medicine physician.
Results: Sixteen subjects included. Nine were male and 7 were female. Median age: 63±10 years; range: 43-80 years. As per visual analysis, 6 exams were considered to show decreased uptake (DU) in the basal ganglia and 10 exams were interpreted as presenting normal uptake (NU). When using BPLA, the average SUVmax of the two striata was significantly different between subjects with DU and NU ($p = 0.022$; 4.7 (4.5-6) and 6.8 (5.2-7.9), in DU and NU, respectively), and the SUR of the right striatum was significantly different between subjects with DU and NU ($p = 0.042$; 2.9 (2.5-3) and 3.3 (3-3.6), in DU and NU, respectively). When using OSEM, there were no statistically different values of SUVmax or SUR between subjects with DU and NU.
Conclusions: This study suggests that an advanced BPLA reconstruction algorithm positively impacts the ability of semiquantitative analysis to predict the visual interpretation of F-18-DOPA PET for diagnosing parkinsonian syndromes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1080 / #2165

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

INTEROBSERVER VARIABILITY AND ASSERTIVENESS IN THE VISUAL INTERPRETATION OF F-18-DOPA PET FOR THE DIAGNOSIS OF EARLY-STAGE PARKINSONIAN SYNDROMES

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Tiago Vieira[1], Facundo Diaz[2], Adriana Pinto[1], Rui Ferreira[1], Fernando Silva[1], Manuel Perez[3], José Oliveira[1]
[1]Atrys, Nuclear Medicine, Porto, Portugal, [2]Atrys, Radiology, Barcelona, Spain, [3]Hospital Italiano de Buenos Aires, Radiology, Buenos Aires, Argentina

Aims: Interobserver variability affects the overall accuracy of imaging and less assertive interpretation generates diagnostic doubt, increases costs, delays treatment decisions, and causes anxiety to patients. We evaluated the interobserver variability of F-18-DOPA PET visual interpretation in subjects with suspected early-stage parkinsonian syndromes (EPS) and assessed how the assertiveness on imaging interpretation impacts interobserver variability.
Methods: Were included F-18-DOPA PET of subjects with clinical suspicion of EPS. Five nuclear medicine physicians interpreted qualitatively the exams and categorized it in 4 categories of striatal uptake: “definitively normal uptake”, “probably normal uptake”, “probably decreased uptake” and “definitively decreased uptake”; this categorization was considered non-assertive. For assertiveness, interpretation was further catagorized into three types: assertive interpretation balanced for sensitivity and specificity (“definitively normal uptake” and “probably normal uptake” were categorized as “normal uptake”, and “definitively decreased uptake” and “probably decreased uptake” were categorized as “decreased uptake”); assertive interpretation favoring sensitivity (only “definitively normal uptake” were categorized as “normal uptake”); assertive interpretation favoring specificity (only “definitively decreased uptake” were categorized as “decreased uptake”). Interobserver reliability (IR) was analyzed regarding the non-assertive categorization and assertive categorizations.
Results: Sixteen subjects included. Regarding the non-assertive categorization, the IR was very high (average measurements = 0.95 (95% CI 0.89-0.98), p<0.00001). Regarding the assertive categorizations, the IR was perfect when assertiveness pended for increased specificity, very high when assertiveness was balanced for sensitivity and specificity (average measurements = 0.93 (95% CI 0.86-0.97) p<0.00001), and regular when assertiveness pended for increased sensitivity (average measurements = 0.72 (95% CI 0.44-0.89), p<0.00001).
Conclusions: Interobserver variability in the visual interpretation of F-18-DOPA PET for evaluation of EPS is influenced by the type of assertiveness, with higher interobserver variability being associated with assertiveness pending for increased sensitivity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1081 / #2623

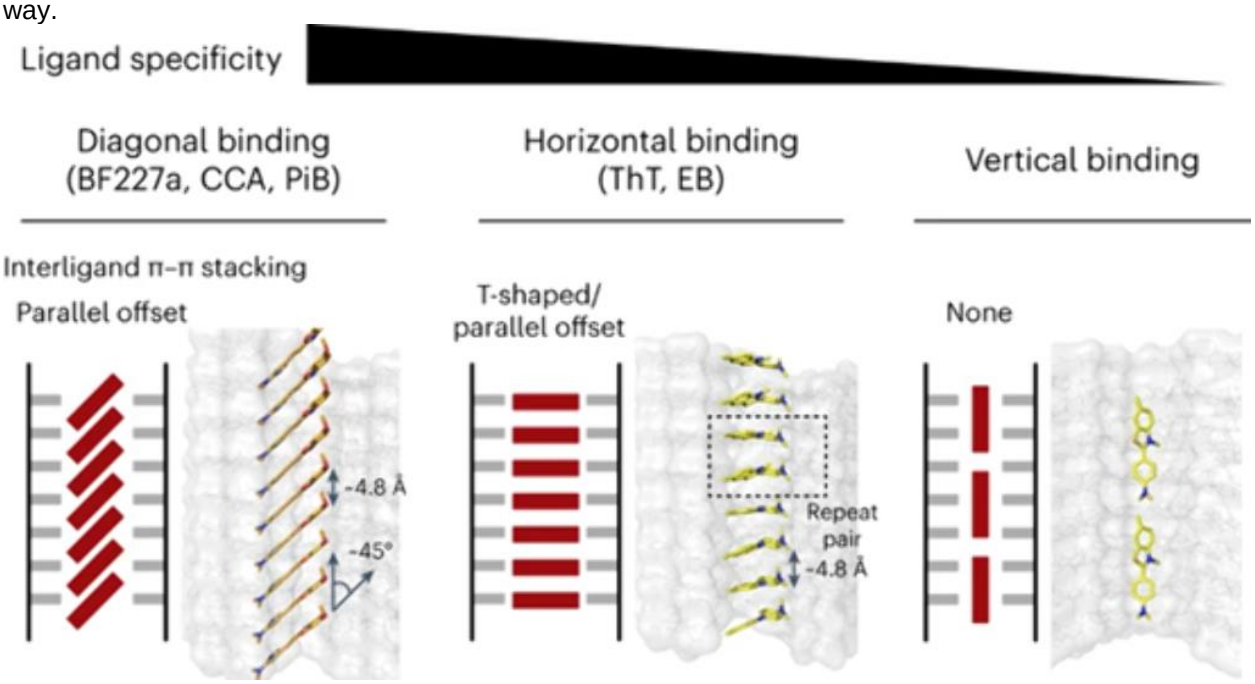
Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

STRUCTURAL MECHANISM FOR SPECIFIC BINDING OF CHEMICAL COMPOUNDS TO AMYLOID FIBRILS

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Shenqing Zhang, Jiang Bian
shanghai jiao tong university, School Of Life Sciences And Biotechnology, shanghai, China

Aims: Amyloid fibril is an important pharmaceutical target for diagnostic and therapeutic treatment of neurodegenerative diseases. However, rational design of chemical compounds that interact with amyloid fibrils is unachievable due to the lack of mechanistic understanding of the ligand–fibril interaction.
Methods: Here we used cryoelectron microscopy to survey the amyloid fibril-binding mechanism of a series of compounds including classic dyes, (pre)clinical imaging tracers and newly identified binders from high-throughput screening.
Results: We obtained clear densities of several compounds in complex with an α-synuclein fibril. These structures unveil the basic mechanism of the ligand–fibril interaction, which exhibits remarkable difference from the canonical ligand–protein interaction. In addition, we discovered a druggable pocket that is also conserved in the ex vivo α-synuclein fibrils from multiple system atrophy.
Conclusions: Collectively, these findings expand our knowledge of protein–ligand interaction in the amyloid fibril state, which will enable rational design of amyloid binders in a medicinally beneficial way.



AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1082 / #1448

Poster Topic: *Theme C: α-Synucleinopathies / C04.a. Imaging, Biomarkers, Diagnostics: Structural MRI, MR spectroscopy*

BRAIN-AGE GAP IN IDIOPATHIC AND GENETIC VARIANTS OF PARKINSON'S DISEASE – ASSOCIATIONS WITH AMYLOID PATHOLOGY AND RATES OF COGNITIVE DECLINE

POSTERS: C04.A. IMAGING, BIOMARKERS, DIAGNOSTICS: STRUCTURAL MRI, MR SPECTROSCOPY

Stefan J. Teipel[1], Hauke Hoffmann[1], Julia Schumacher[1], Alexander Storch[2], Martin Dyrba[1]
[1]Deutsches Zentrum für Neurodegenerative Erkrankungen, Deutsches Zentrum Für Neurodegenerative Erkrankungen, Rostock, Germany, [2]University Medical Center Rostock, Department Of Neurology, Rostock, Germany

Aims: The brain-age gap, i.e. the difference between calendar and estimated brain age, has been proposed as a measure of accelerated brain aging in neurodegenerative brain diseases. Here, we studied brain-age in idiopathic PD and in preclinical and clinical stages of LRRK2 and GBA genetic variants.
Methods: We studied 1,200 cases from the Parkinson's Progression Markers Initiative (PPMI), including 149 asymptomatic GBA and 169 asymptomatic LRRK2 mutation carriers, 112 LRRK2 carriers and 60 GBA carriers with PD, 499 idiopathic PD, and 211 healthy controls. For comparison, we studied brain age in 187 patients with AD dementia and 254 healthy controls from the ADNI cohort. We used Bayesian ANCOVA to determine associations of diagnosis, amyloid and tau pathology, motor impairment, and dopamine function with brain-age gap. Using Bayesian mixed effect models, we determined associations of brain-age gap with rates of cognitive and motor decline.
Results: Brain-age was increased by 0.65 years in idiopathic PD and by 1 year in LRRK2 PD, but was unaltered in preclincial and clinical GBA mutation carriers. Interestingly, brain-age was reduced by 1.1 years in preclinical LRRK2 mutation carriers. Brain-age in AD dementia was increased by almost 6 years. Dopamine function contributed to brain-age gap across all PD diagnoses, but AD pathology contributed to brain-age gap in the idiopathic PD group. A higher brain-age gap was associated with accelerated episodic memory decline.
Conclusions: Brain age was less accelerated in PD than in AD, possibly due to more restricted involvement of cortical brain regions. Dopamine dysfunction contributed to brain-age gap in genetic PD, concomitant AD pathology in idiopathic PD. Decreased brain-age in preclinical LRRK2 mutation carriers may point to developmental changes in brain structure before the manifestation of symptoms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1083 / #365

Poster Topic: *Theme C: α-Synucleinopathies / C04.c. Imaging, Biomarkers, Diagnostics: PET*

IN VIVO IMAGING OF SYNUCLEINOPATHY IN A30P AND PFF-A30P MOUSE MODELS WITH [11C]MK-7337 PET

POSTERS: C04.C. IMAGING, BIOMARKERS, DIAGNOSTICS: PET

Yuchuan Wang[1], Idriss Bennacef[1], Hyking Haley[1], Jonathan Sugam[2], Rob Drolet[2], Jun Meng[1], Wenping Li[1], Helen Mitchell[3], Jacob Marcus[2], Sean Smith[2], Eric Hostetler[1]
[1]Merck Sharp & Dohme, Translational Imaging, Rahway, United States of America, [2]Merck Sharp & Dohme, Discovery Biology, Rahway, United States of America, [3]Merck Sharp & Dohme, Chemistry, Rahway, United States of America

Aims: [^{11}C]MK-7337 is a potent binder for α-synuclein, with first-in-human testing planned. To facilitate translational imaging in PD drug development, we investigate the feasibility of using [^{11}C]MK-7337 PET for imaging the synucleinopathy in both A30P and PFF-A30P mouse models. A30P is a transgenic PD mouse model and PFF-A30P is a seeding model with the pre-formed fibrils (PFF) of recombinant, human α-synuclein administered in A30P mouse brains.
Methods: Longitudinal scans are performed on ten A30P mice, including both homozygous and age-matched wild-type, from 12- to 24-month-old. Standardized uptake value ratio (SUVR) changes were determined for several brain regions-of-interest (ROIs) using cerebellum as reference. Next, four 3-month-old A30P mice are imaged 25-days after intra-striatal administration of both 133 μM α-synuclein PFFs (right-side) and monomers (left-side), with controls injected with only vehicles. Both bilateral striatal SUVR and right/left striatal uptake ratio are measured.
Results: Compared to wild-type, longitudinal imaging of A30P homozygous mice did not reveal elevated SUVR in any brain ROIs until after 16-month-old. Between 16- and 20- months, most homozygous mice showed heterogeneous brain uptake with higher SUVR in midbrain/brainstem which increased aggressively in the following months, concomitant with deteriorating health of the mice. In the young PFF-A30P mice, the PFF-injected (right) striatum, but not the monomer-injected (left) striatum showed significantly higher SUVR (average right/left ratio = 1.5) relative to control mice.
Conclusions: [^{11}C]MK-7337 PET can be used for imaging synucleinopathy in both A30P and PFF-A30P mouse models. The longitudinal changes of synucleinopathy in A30P were typically only detectable in mice aged >16 months. The PFF-induced synucleinopathy were detectable shortly after injections in younger mice, providing a more practical model for translational imaging.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1084 / #2461

Poster Topic: *Theme C: α-Synucleinopathies / C04.d. Imaging, Biomarkers, Diagnostics: SPECT*

DIFFERENTIAL VULNERABILITY IN DOPAMINERGIC PATHWAYS BETWEEN IDIOPATHIC PD AND GBA-PD PATIENTS

POSTERS: C04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: SPECT

Silvia Paola Caminiti[1], Rachele Malito[2], Alice Galli[3], Micol Avenali[4]
[1]University of Pavia, Department Of Brain And Behavioral Sciences, Pavia, Italy, [2]Vita-Salute San Raffaele University, Faculty Of Psychology, Milano, Italy, [3]University of Brescia, Neurology Unit, Department Of Clinical And Experimental Sciences, Brescia, Italy, [4]IRCCS MONDINO FOUNDATION, Uiverisity Of Pavia, PAVIA, Italy

Aims: Parkinson's disease with GBA mutation (GBA-PD) shares common clinical features with idiopathic PD (iPD) without GBA mutation, however, GBA-PD shows more rapid motor and cognitive deterioration, in association with severe autonomic dysfunction and neuropsychiatric symptoms. We already found that GBA-PD patients show more severe striatal dopamine depletion than iPD. Dopaminergic connectivity alterations associated with GBA-mutations have never been investigated.
Methods: We enrolled a total of 87 patients, 44 GBA-PD and 43 iPD patients (matched for age, motor impairment and disease duration) with available brain [123I]FP-CIT-SPECT. We applied molecular connectivity analyses to assess possible alterations in the nigrostriatal and mesolimbic dopaminergic pathways characterizing the two groups, in comparison with a group of healthy controls.
Results: As expected, as the two clinical groups were similar in terms of motor impairment, we observed comparable connectivity alterations within the nigrostriatal motor pathway (GBA-PD: 16%; iPD: 22% altered connections). These changes predominantly affected connections originating from the dorsal putamen and extending to the caudate and premotor cortex. Instead, connectivity within the mesolimbic pathway was more profoundly disrupted in the GBA-PD group (GBA-PD: 13%; iPD: 6% altered connections). In GBA-PD, the connectivity alteration encompasses the ventral striatum, olfactory cortex, parahippocampal gyrus, amygdala, and the anterior cingulate gyrus.
Conclusions: Extensive and severe impairment of mesolimbic pathway connectivity has already been found in the literature in PD, and it was associated with neuropsychiatric symptoms. These new findings in the GBA population represent a further support of the association between mesolimbic dopaminergic connectivity alterations and neuropsychiatric symptoms in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1085 / #561

Poster Topic: *Theme C: α-Synucleinopathies / C04.d. Imaging, Biomarkers, Diagnostics: SPECT*

DATSCAN STRIATAL BINDING RATIO DYNAMICS IN MUTATIONS CARRIERS AT RISK FOR PARKINSON'S DISEASE: A 2-YEAR PROSPECTIVE STUDY

POSTERS: C04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: SPECT

Amgad Droby[1], Daniel Atias[1], Hedva Lerman[2], R. Matthew Hutchison[3], Jesse Cedarbaum[4], Einat Even Sapir[2], Nir Giladi[1], Anat Mirelman[1], Avner Thaler[1]
[1]Tel Aviv Sourasky Medical Center, Neurology, Tel Aviv, Israel, [2]Tel Aviv Sourasky Medical Center, Nuclear Medicine, Tel Aviv, Israel, [3]Biogen Idc, Biomarkers, Cambridge, United States of America, [4]Coeruleus Medical Sciences LLC, Coeruleus Medical Sciences Llc, Woodbridge, United States of America

Aims: ***Background:*** Dopamine transporter spectral positron emission computed tomography (DaTscan) is widely used for establishing PD diagnosis and receives high importance in LR scores estimation. However, the association between DaTscan measures and LR scores over time remains unclear. ***Objectives:*** To investigate the temporal dynamics of striatal binding ratios (SBRs) among individuals with Parkinson's disease (PD)-related mutations and its' association with likelihood ratio (LR) for prodromal PD.
Methods: 52 healthy first-degree relatives (age 52.73±8.72 yrs, 22/30 F/M) were enrolled. All participants were genotyped and underwent DaTscan at baseline and on average after 2.21±0.3 years, and a comprehensive clinical assessment battery. LR scores and striatal binding ratio (SBRs) were calculated for all included participants. The relationship between DaTscan-derived measures and LR scores was investigated using hierarchical regression models accounting for age and sex.
Results: N=14 *GBA* Non-Manifesting Carriers (NMC), N= 14 *LRRK2* NMC, and N=24 age-matched Non-Manifesting Non-Carriers (NMNC) were included in each study group. No significant differences were detected in clinical measures and rates of change (ROC) in striatal SBRs among the study groups. Over time LR difference were associated with right putamen SBR, putamen asymmetry index, right putamen-caudate ratio at baseline (R^2= *0.11* p=0.035*;* R^2= *0.17* p=0.007; R^2= *0.16* p=0.009 respectively), and with SBR ROC in the right caudate (R^2=*0.1* p=0.036).
Conclusions: DaTscan-derived asymmetry metrics might serve as an early marker for LR increase over time, reflecting subclinical changes preceding symptoms onset in the prodromal phase of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1086 / #2370

Poster Topic: *Theme C: α-Synucleinopathies / C04.d. Imaging, Biomarkers, Diagnostics: SPECT*

INSULAR MONOAMINERGIC DEFICITS IN PRODROMAL ALPHA-SYNUCLEINOPATHIES

POSTERS: C04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: SPECT

Alice Galli[1], Andrea Pilotto[1], Cinzia Zatti[1], Fabio Placidi[2], Francesca Izzi[2], Enrico Premi[3], Silvia Paola Caminiti[4], Luca Presotto[5], Andrea Rizzardi[1], Marcello Catania[1], Alessandro Lupini[1], Leandro Purin[1], Maria Pasolini[6], Nicola Mercuri[7], Agostino Chiaravallotti[7], Mariana Fernandes[7], Carmen Calvello[2], Silvia Lucchini[8], Francesco Bertagna[8], Barbara Paghera[8], Daniela Perani[9], Daniela Berg[10], Alessandro Padovani[1], Claudio Liguori[7]
[1]University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy, [2]University of Rome Tor Vergata, Sleep Medicine Centre, Rome, Italy, [3]Spedali Civili Hospital, Stoke Unit, Brescia, Italy, [4]University of Pavia, Department Of Brain And Behavioral Sciences, Pavia, Italy, [5]University of Milan Bicocca, Department Of Applied Physics, Milan, Italy, [6]ASST Spedali Civili, Neurophysiology Unit, Brescia, Italy, [7]University of Rome Tor Vergata, Sleep Medicine Center, Rome, Italy, [8]Spedali Civili Hospital, Nuclear Medicine Unit, Brescia, Italy, [9]University Vita Salute San Raffaele, In Vivo Imaging Unit, Milan, Italy, [10]Christian-Albrechts University, Neurology, Kiel, Germany

Aims: Growing literature is highlighting the presence of monoaminergic alterations in the insula and other extra-nigrostriatal regions in early phases of alpha-synucleinopathies, whereas no large studies on idiopathic REM sleep behaviour disorder (iRBD) are still available. Objective of this multicenter study was to evaluate clinical underpinnings and longitudinal predictive value of extrastriatal monoaminergic deficits in iRBD, contrasting them with controls and overt alpha-synucleinopathies namely Parkinson's disease (PD) and Lewy bodies dementia (DLB).
Methods: Polysomnography (PSG)-confirmed iRBD, age-matched PD, DLB, and controls underwent a standardized neurological examination, and ^{123}I-FP-CIT Brain SPECT imaging. iRBD subjects were classified according to standard visual basal ganglia inspection (DAT+ vs DAT-) and underwent clinical follow-up for phenoconversion. Between-groups differences in ^{123}I-FP-CIT binding were evaluated by voxel-wise analyses adjusted for age, sex and center of recruitment. Longitudinal analyses on iRBD evaluate the value of baseline monoaminergic deficits in predicting phenoconversion using cox-regression analysis adjusted for age, sex, and nigrostriatal deficits at baseline.
Results: One-hundred eighty-four subjects entered the study, namely 45 iRBD, 47 PD, 42 DLB, and 50 age-matched controls. Nigrostriatal standard visual assessment enables the classification of iRBD in RBD-DAT- (n=32), and RBD-DAT+ (n=13). Compared to controls, RBD-DAT- showed an early involvement of the left insula, with an increasing extent in RBD-DAT+, PD, and DLB. Longitudinal cox regression analyses revealed a higher risk of conversion to alpha-synucleinopathies, especially in iRBD subjects only with insular deficits (HR=6.264 [C.I. 95% 0.813-48.247 in RBD-DAT-).
Conclusions: Insular monoaminergic deficits are an early signature of iRBD, associated with higher risk of conversion to alpha-synucleinopathies. Longitudinal ongoing studies with serial imaging and advanced digital and biological prodromal markers are needed to confirm and extend these findings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1087 / #2441

Poster Topic: *Theme C: α-Synucleinopathies / C04.d. Imaging, Biomarkers, Diagnostics: SPECT*

DIABETES IMPACT ON NIGROSTRIATAL VULNERABILITY IN PARKINSON'S DISEASE

POSTERS: C04.D. IMAGING, BIOMARKERS, DIAGNOSTICS: SPECT

Alice Galli[1], Andrea Pilotto[1], Cinzia Zatti[1], Clara Tirloni[2], Alessandro Lupini[1], Barbara Paghera[3], Alessandro Padovani[1]
[1]University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy, [2]ASST Spedali Civili, Neurology Unit, Brescia, Italy, [3]Spedali Civili Hospital, Nuclear Medicine Unit, Brescia, Italy

Aims: Several studies suggested a possible association between diabetes mellitus (DM) and Parkinson's disease (PD). Aim of the study was to investigate in vivo whether diabetes mellitus influences motor function via its impact on nigrostriatal dopaminergic vulnerability in two independent cohorts of drug-naïve patients with early-stage Parkinson's Disease (PD).
Methods: The study included two independent prospective cohorts of drug naïve PD patients who underwent a standardized neurological examination, and ^{123}I-FP-CIT brain SPECT imaging. Each cohort comprised two subgroups of PD patients with diabetes mellitus (PD-DM) or without diabetes mellitus (PD), which were matched 1:1 for age, sex, motor and cognitive impairment at baseline. We tested differences in striatal binding using an ANCOVA test adjusted for age, sex, and handedness. Longitudinal analysis on a subset of PD patients was conducted to evaluate annual difference in striatal binding driven by diabetes mellitus
Results: One-hundred sixty-six drug-naïve PD patients entered the study, namely 54 patients from the single-center DMA-PD cohort, and 112 patients from the PPMI dataset. Compared to PD, PD-DM showed a higher dopamine uptake in left putamen in both the considered cohorts. The longitudinal evaluation revealed that PD-DM had a faster annual decline of left putamen binding than PD (-20% vs. -9%).
Conclusions: Findings showed that diabetes mellitus may impact on compensatory mechanisms of nigrostriatal systems resulting in less dopamine deficits even with comparable degree of motor and non-motor impairment at baseline. This result was further confirmed by the follow-up evaluation showing a greater annual difference in left putamen binding. Results were confirmed in both an Italian monocentric cohort and in the multicentric PPMI cohort.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1088 / #2395

Poster Topic: *Theme C: α-Synucleinopathies / C04.e. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

RECEPTOR DENSITY CHANGES IN MPTP MOUSE MODEL OF PARKINSON'S DISEASE – IN VIVO AND EX VIVO CHARACTERIZATION

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Jussi Rytkönen[1], Kimmo Lehtimäki[1], Pekka Poutiainen[2], Taneli Heikkinen[1], Johanna Uhari-Väänänen[1], Artem Shatillo[1], Susanne Bäck[1]
[1]Charles River, Discovery, Kuopio, Finland, [2]Kuopio University Hospital, Radiopharmacy, Kuopio, Finland

Aims: Loss of dopaminergic neurons in substantia nigra pars compacta is a cardinal feature of Parkinson's disease (PD). The subsequential loss of striatal dopamine (DA) and reduced dopamine transporter (DAT) levels trigger the characteristic movement symptoms for PD, and are important readouts in preclinical PD models. The loss of dopaminergic neurons also triggers changes in receptor density of other neurotransmitters. In this study we used various imaging tools (MRI, PET, autoradiography) to characterize changes in the mouse brain following induction of dopaminergic cell death with systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).
Methods: MPTP was administered intraperitoneally (i.p. 20 mg/kg) two times a day with 3h-interval on two consecutive days. Starting from 2 weeks after the MPTP administration, pathological changes in the brain were evaluated with PET imaging using tracers for DAT (^{18}F-FE-P2I) and glucose consumption (FDG-PET) and with 1H-MRS. Following endpoint sampling, receptor densities were evaluated *ex vivo* with autoradiography.
Results: MPTP administration induced changes in cellular metabolites in striatum when compared to vehicle treated mice. On week 5, a decrease in DAT receptor density was seen in MPTP mice with PET imaging of ^{18}F-FE-P2I. In support of the 1H-MRS findings, we observed that glucose consumption by FDG-PET was significantly decreased at week 6 after the MPTP challenge. *Ex vivo* analysis showed in no change in D2 receptor level in striatum, but upregulation of $GABA_A$ and CB1 in cingulate cortex and reduction in SERT density in substantia nigra. No change in TSPO (translocator protein) receptor density was observed 6 weeks after MPTP challenge.
Conclusions: *In vivo* and *ex vivo* imaging tools can be used to evaluate changes in dopaminergic and non-dopaminergic systems in the brain following MPTP lesioning in mice.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1089 / #2510

Poster Topic: *Theme C: α-Synucleinopathies / C04.e. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

NEUROMELANIN-SENSITIVE MRI CORRELATION WITH I-123 IOFLUPANE SPECT AND MOTOR SYMPTOMS DEPENDS ON COGNITIVE STATUS IN PARKINSON'S DISEASE

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Daniel Huddleston[1], Jason Langley[2], Xiangchuan Chen[3], Kelsey Tucker[3], Amanda Lansdell[3], Xiaoping Hu[4]
[1]Emory University, Neurology - 6th Floor, Atlanta, United States of America, [2]University of California, Riverside, Center For Advanced Neuroimaging, Riverside, United States of America, [3]Emory University, Neurology, Atlanta, United States of America, [4]University of California, Riverside, Bioengineering, Riverside, United States of America

Aims: 1) To study the correlation between neuromelanin-sensitive MRI (NM-MRI) and I-123 ioflupane single photon emission computed tomography (SPECT) measures in the nigrostriatal system in Parkinson's disease (PD) with (CI) and without (NC) cognitive impairment. 2) To assess correlation between substantia nigra pars compacta (SNc) volume measured with NM-MRI and PD motor features in PD-CI and PD-NC.
Methods: PD-NC (n=11) and PD-CI (n=13) patients were recruited at the Emory Movement Disorders Clinic under an IRB approved protocol. Each patient completed a 3 T MRI scan (Siemens Prisma Fit) and an I-123 ioflupane SPECT scan (DaTScan, GE Healthcare). MRI included a magnetization-prepared 2D gradient echo NM-MRI sequence and a T1 structural sequence. Patients were clinically assessed with the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Montreal Cognitive Assessment (MoCA), and a neuropsychological testing battery designed to assess the Lewy body dementias (LBDs).
Results: PD-NC and PD-CI baseline demographics were compared and the groups differed in age (PD-NC=57.7+/-10.5; PD-CI=70.0+/-8.2; p=0.004), but not in sex, race, or education. Analyses were performed controlling for age. Partial correlation between SNc volume (mm3) and putamen binding ratio asymmetry ratio was significant in the combined PD group (r=0.520, p=0.022), driven by a strong correlation in the PD-NC group (r=0.784, p=0.007), while there was no correlation observed in the PD-CI group (r=0.045, p=0.916). Partial correlation between MDS-UPDRS-III and SNc volume was significant in all PD (r=-0.445, p=0.029), with a trend toward significance in the PD-CI group (r=-0.483,p=0.095) and no correlation in the PD-NC group (r=-0.361, p=0.276).
Conclusions: NM-MRI SNc volume is highly correlated with I-123 ioflupane putaminal SPECT in PD-NC, tracks motor symptoms, and has potential as a cost-efficient surrogate outcome measure in PD trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1090 / #184

Poster Topic: *Theme C: α-Synucleinopathies / C04.e. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

RADIOLOGICAL HETEROGENEITY OF TOKYO MEDICAL BIOBANK PARTICIPANTS WITH LEWY BODY DISEASES

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Masanori Kurihara[1,2], Ryosuke Shimasaki[1], Keiko Hatano[1], Kenichiro Taira[1], Ryoko Ihara[1], Mana Higashihara[1], Yasushi Nishina[1], Masashi Kameyama[3,4], Atsushi Iwata[1,2]
[1]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Department Of Neurology, Tokyo, Japan, [2]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Integrated Research Initiative For Living Well With Dementia, Tokyo, Japan, [3]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Department Of Diagnostic Radiology, Tokyo, Japan, [4]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Research Team For Neuroimaging, Tokyo, Japan

Aims: Although biobank samples are useful for validation of recently identified cerebrospinal (CSF) and blood-based biomarkers for Lewy body diseases (LBD), sensitivity may be affected by heterogeneity among participants. The objective of this study was to summarize the radiological heterogeneity of our biobank participants with LBD.
Methods: We recruited all patients receiving lumbar puncture as a part of assessment of neurodegenerative diseases from December 2021 to July 2023 to Tokyo Medical Biobank. Results of dopamine transporter (DAT) SPECT using ^{123}I-ioflupane and ^{123}I-MIBG cardiac scintigraphy were summarized for patients with LBD.
Results: We enrolled 157 participants and 61 were clinically suspected to have LBD. One with negative DAT SPECT finding and one with later diagnosis of progressive supranuclear palsy were excluded. Mean age was 73.3 ± 9.2 years old. Thirty-three were male and 26 were female. Clinical diagnoses were Parkinson's disease (PD) in 50, dementia with Lewy bodies (DLB) in 6, prodromal DLB in 1, pure autonomic failure in 1, and REM-sleep behavior disorder in 1. Results of both DAT SPECT and MIBG scintigraphy were available in 52. Scatter plot showed wide distribution and the correlation between averaged striatal DAT standard binding ratio (SBR) and MIBG delayed heart-to-mediastinum ratio were weak and nonsignificant. Twenty-three (44 %) showed normal MIBG scintigraphy results including 3 of 15 clinically-established and 16 of 30 clinically-probable PD according to the MDS-PD criteria. No significant difference was observed for age, sex, disease duration, and averaged DAT SBR between MIBG-positive versus MIBG-negative group.
Conclusions: We have collected paired blood and CSF samples from participants with LBD with radiological heterogeneity. Whether sensitivities of fluid biomarkers such as seed amplification assays are affected by this heterogeneity will be evaluated soon.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1091 / #2377

Poster Topic: *Theme C: α-Synucleinopathies / C04.e. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

ESYA PD360: A MULTI-PARAMETRIC PLATFORM FOR ESTABLISHING A NOVEL LYSOSOME-BASED BIOMARKER FOR PARKINSON'S DISEASE

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Florence Young, Souvik Modi, Adam Shellard, Hernando M. Vergara
Esya Labs, R&d, London, United Kingdom

Aims: Neuronal homeostasis heavily relies on the lysosomal pathway to remove protein aggregates and damaged organelles. Although altered lysosomal acidification and perturbed autophagy have been linked to both familial and sporadic Parkinson's disease (PD), these features are not currently utilized in diagnostic approaches. Esya's objective is to develop a multiparametric biomarker platform that integrates lysosomal and autophagic function along with transcriptomic changes at the cellular level, ultimately leading to more accurate diagnosis, disease subtyping, and treatment.
Methods: Lysosomal, autophagic and transcriptomic data were acquired from peripheral cell samples across multiple cohorts including healthy and genetic or sporadic PD samples. We assessed: **a)** lysosomal dysfunction using our patented two-ion mapping probes that ratiometrically measure H^+ and Ca^{2+} concentrations with single lysosome resolution; **b)** autophagic alterations by transduction with tandem LC3-autophagy sensors, and **c)** transcriptomic changes through an RNA panel, identified through RNA-seq.
Results: Lysosomal Ca^{2+} and pH are affected in PD patients carrying an LRRK2 mutation, and Ca^{2+} levels are altered in sporadic PD. Defects in the autophagic pathway are identified in PD patients carrying GBA, LRRK2, or Vps35 mutations and sporadic PD, with autophagic dysfunction strongly correlated with lysosomal ionic status. Lastly, we identified differentially expressed gene clusters in PD patients compared to healthy controls, most of which are involved in organellar functions. Finally, integration of these features through principal component analysis allowed us to separate PD from healthy individuals and stratify PD into two distinct populations.

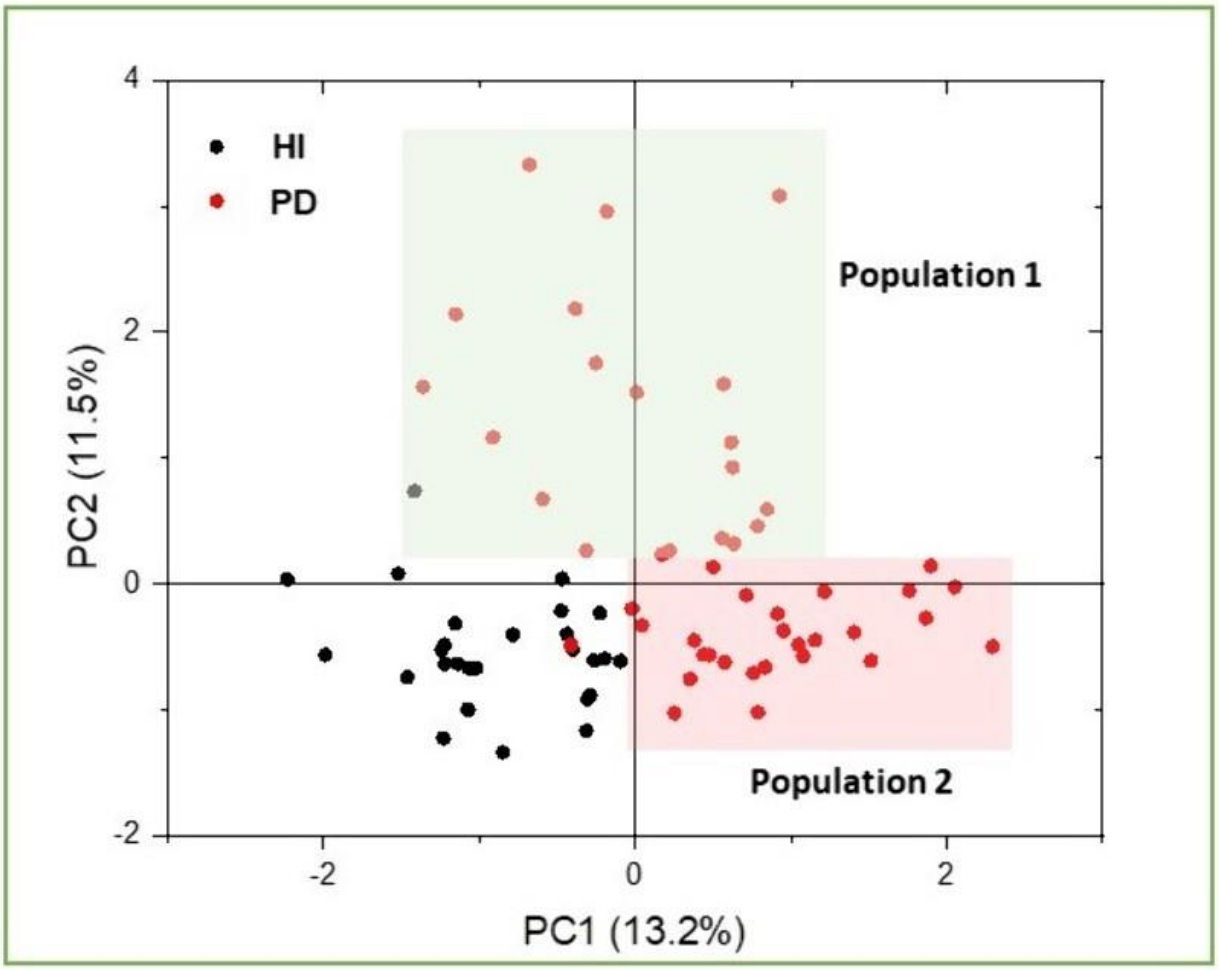


Figure 1. Principal component analysis using 12 lysosomal features and 28 differently expressed RNAs differentiates Parkinson's disease (PD) from healthy individuals (HI) and identifies two PD populations.

Conclusions: We identified disease subclass-specific transcriptomic changes that may be linked to underlying lysosomal and autophagic dysfunction. Moreover, our multiparametric approach accurately distinguishes PD from healthy individuals, and sub-classes PD into distinct populations. This innovative biomarker platform paves the way for improved PD diagnosis and personalized medicine.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1092 / #767

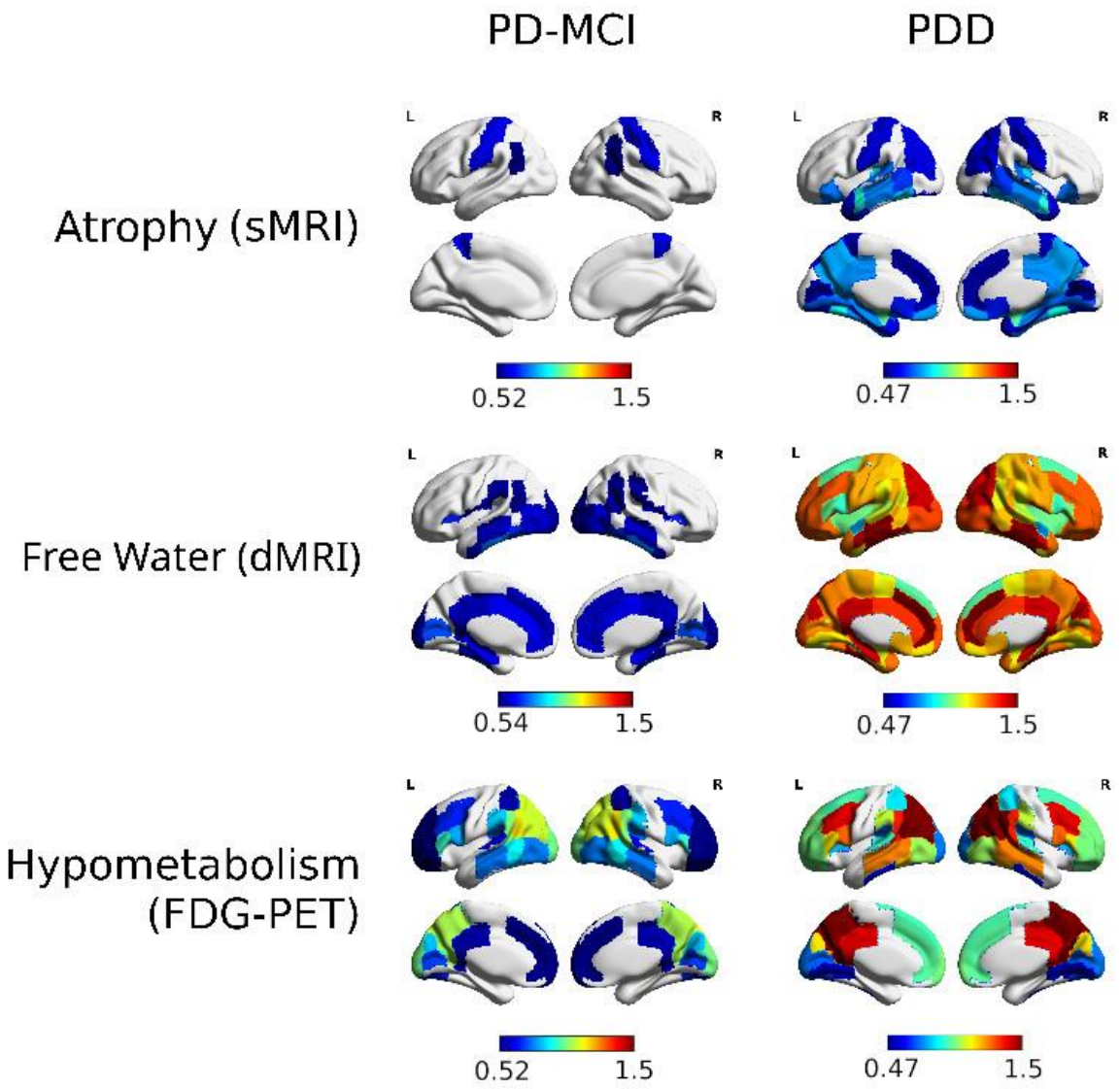
Poster Topic: *Theme C: α-Synucleinopathies / C04.e. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

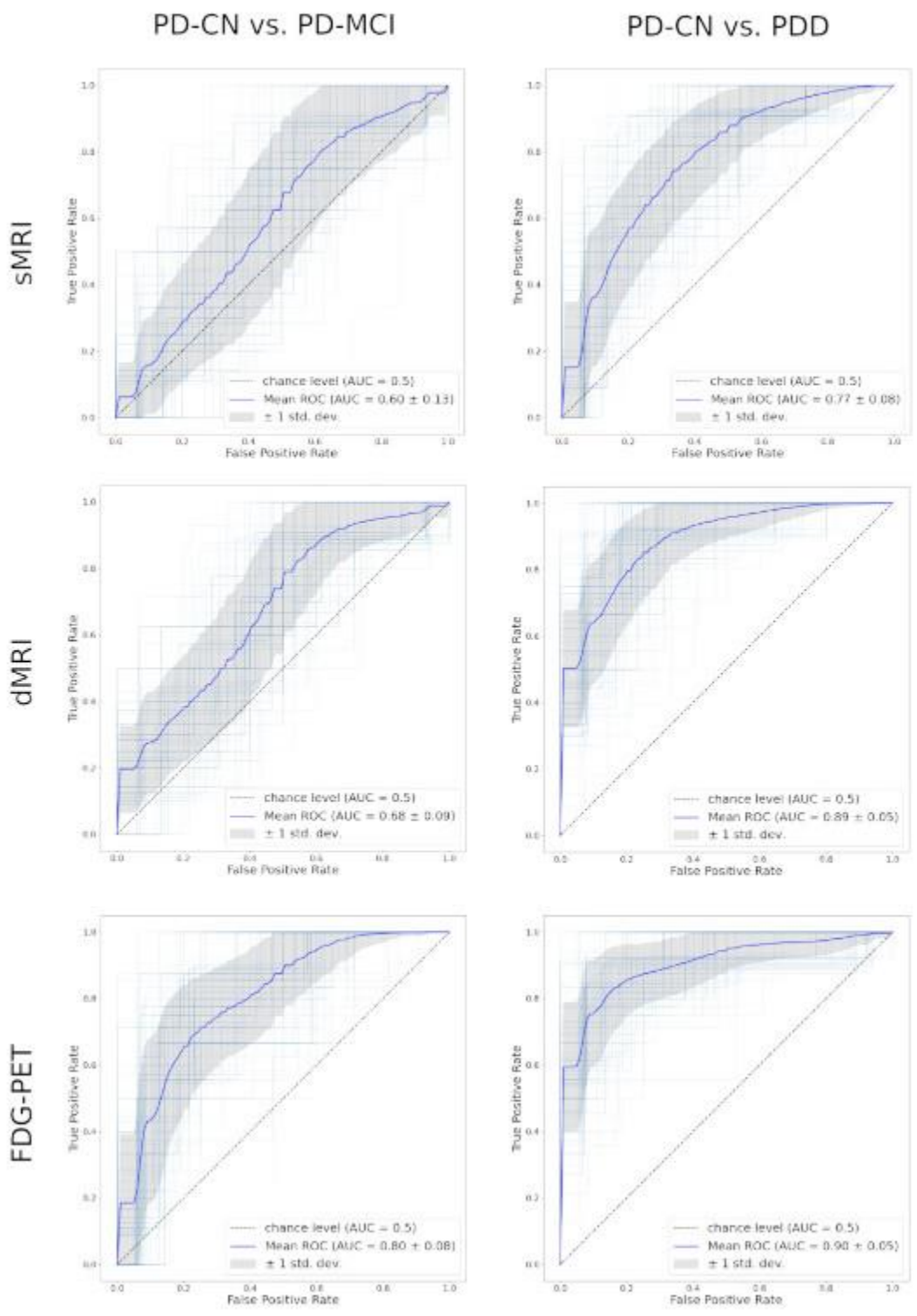
NEUROIMAGING BIOMARKERS FOR DETECTING EARLY CORTICAL CHANGES ASSOCIATED WITH COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE.

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Jesús Silva-Rodríguez[1], Miguel A Labrador-Espinosa[1], Sandra Castro-Labrador[1], María Isabel Reina-Castillo[1], Laura Múñoz-Delgado[1], Pablo Franco-Rosado[1], Ana María Castellano-Guerrero[1], Daniel Macías-García[1], Silvia Jesús[1], Astrid Adarmes-Gómez[1], Fátima Carrillo[1], Juan Francisco Martín-Rodriguez[1], Florinda Roldán-Lora[2], David García-Solís[3]
[1]Institute of Biomedicine of Seville, Movement Disorders Group, Sevilla, Spain, [2]Hospital Virgen del Rocío, Radiology Department, Seville, Spain, [3]Hospital Virgen del Rocío, Nuclear Medicine Department, Seville, Spain

Aims: Imaging biomarkers of cortical neurodegeneration bear great promise for improving diagnosis and prognosis of cognitive impairment in Parkinson's disease (PD). We compared the accuracy of three commonly used neuroimaging modalities for detecting cortical changes associated with mild cognitive impairment (MCI) and dementia in PD.
Methods: 42 cognitively normal PD patients (PD-CN), 23 with MCI (PD-MCI), and 31 with dementia (PDD) underwent structural MRI (sMRI), diffusion-weighted MRI (dMRI) and FDG-PET. Grey matter volumes (GMV, sMRI), mean free water fraction (FW, dMRI), and standardized uptake value ratios (SUVR, FDG-PET) were extracted for all brain regions included in the Harvard-Oxford neuroanatomical atlas. An exhaustive cross-validated feature selection process was used to identify the regions that are most predictive of cognitive status for each modality. Modality-specific diagnostic accuracies for distinguishing PD-MCI and PDD from PD-CN were assessed using bootstrapped receiver operating characteristics (ROC) analyses.
Results: In PDD, sMRI revealed significant atrophy in medial temporal and posterior-parietal areas, while dMRI showed a brain-wide increase in FW (Figure 1). Only subtle effects were observed in PD-MCI for both modalities. FDG-PET revealed significant hypometabolism in posterior cortical regions in both PDD and PD-MCI (Figure 1). FDG-PET SUVR (area under the curve (AUC) =0.90±0.05) and dMRI FW (0.89±0.05) provided significantly higher diagnostic accuracies for distinguishing PDD vs PD-CN compared to sMRI GMV (0.77±0.08, p's<0.001). Only FDG-PET provided notable diagnostic accuracy for detecting PD-MCI (0.80±0.08), which was significantly higher compared to both sMRI (0.61±0.12, p<0.001) and dMRI (0.68±0.09, p=0.028) (Figure
2).


PD-MCI
PDD
Atrophy (sMRI)
Free Water (dMRI)
Hypometabolism (FDG-PET)
L
R
0.52
1.5
0.47
1.5
0.54
1.5
0.47
1.5
0.52
1.5
0.47
1.5



Conclusions: FDG-PET hypometabolism was the most sensitive imaging biomarker for detecting cortical changes associated with cognitive impairment in PD, especially at early stages. In the absence of FDG-PET, dMRI-measured FW represents a promising MRI-based alternative.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1093 / #2372

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

THE SYNUCLEIN ONE STUDY: CUTANEOUS ALPHA-SYNUCLEIN DEPOSITION IN PARKINSON'S DISEASE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Roy Freeman[1], Todd Levine[2], Bailey Bellaire[3], Christopher Gibbons[1]
[1]Harvard Medical School, Beth Israel Deaconess Medical Center, Neurology, Boston, United States of America, [2]HonorHealth, Neurology, Scottsdale, United States of America, [3]CND Life Sciences, Neurology, Scottsdale, United States of America

Aims: The Synuclein-One study is an NIH-funded 30-site trial that included 96 participants with Parkinson's disease (PD), and 120 healthy controls. We report the detection and quantitation of cutaneous phosphorylated alpha-synuclein (P-SYN) in patients with PD in those with and without DaTscan imaging and compare this to the P-SYN detection in the healthy population. Ongoing challenges exist in the search for a simple, reproducible marker of synuclein pathology. Costs and patient convenience limit the use of diagnostic nuclear neuroimaging while lumbar puncture is a complicated outpatient procedure that inadequately reimburses physician time and is not endorsed by patients.
Methods: After signed consent, study participants completed neurologic examinations (MDS-UPDRS), medical history review, cognitive evaluation, orthostatic vital signs and neurodegenerative disease questionnaires. Skin biopsies at the distal leg, distal thigh and posterior cervical sites were performed on all participants with quantitation of P-SYN.
Results: In the 96 PD participants (MDS-UPDRS 49±24; Hoehn and Yahr 2.1±0.5), P-SYN was detected in 89/96 (93%) and in 4/120 (3%) of healthy controls. Cutaneous P-SYN testing performed at 92.7% sensitivity and 96.7% specificity for detection of P-SYN in PD. Seventeen participants with PD completed a DaTscan (16 positive), and 15/16 were P-SYN positive, and the 1 DaTscan negative case was P-SYN positive. There were correlations between P-SYN and UPDRS score ($R=0.43$, $P<0.01$). No serious adverse events were reported, mild bleeding from a skin biopsy site noted in 2 study participants.
Conclusions: Cutaneous P-SYN testing is sensitive and specific for detection of the phosphorylated form of alpha-synuclein in patients with PD. Although only a small proportion completed DaTscan testing, the P-SYN testing was positive in 94%. Quantitative measures of cutaneous P-SYN may offer a novel outcome in disease modifying clinical trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1094 / #2899

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DIAGNOSTIC PERFORMANCE RT-QUIC BASED DETECTION OF ALPHA-SYNUCLEIN SEEDS IN A CLINICAL COHORT WITH COGNITIVE IMPAIRMENT.

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Diana Esteller[1], Jordi Sarto[1], Núria Guillen[1], Neus Falgàs[1], Laura Molina-Porcel[2], Sergi Borrego-Écija[1], Raquel Ruíz-García[3], Laura Naranjo[3], Anna Antonell[2], Albert Lladó[1], Raquel Sánchez-Valle[4], Mircea Balasa[1]
[1]Alzheimer's disease and other cognitive disorders unit, Hospital Clínic, Neurology Service, Idibaps, Barcelona, Spain, [2]Alzheimer's Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic De Barcelona, Idibaps, Barcelona, Spain, [3]Hospital Clínic, Immunology Service, Barcelona, Spain, [4]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Alzheimer's Disease And Other Cognitive Disorders Unit, Neurology Service, Barcelona, Spain

Aims: We aimed to describe the diagnostic performance of the Real-Time Quaking-Induced Conversion assay for detecting alpha-synuclein seeds (RT-QuIC aSyn assay) in cerebrospinal fluid (CSF) to diagnose LBD in a clinical cohort with cognitive impairment.
Methods: A cohort of subjects with cognitive impairment (neurodegenerative and non-neurodegenerative) with available CSF sample at the moment of first evaluation was selected by convenience sample in our database. Subjects had clinical follow-ups ranging from 6 months to 12 years and current clinical diagnosis according to established consensus criteria. The diagnostic performance of RT-QuIC aSyn for the diagnosis of LBD were evaluated.
Results: The test was evaluated in 317 subjects (age 66 years (SD 11), MMSE 25 (SD 4.5), 48% female) with the following clinical diagnoses: LBD (n=71), Alzheimer's disease (AD) (n=134) (all with compatible CSF profile), frontotemporal dementia (FTD) (n=22), non-neurodegenerative mild cognitive impairment (MCI) (n=50), other neurodegenerative diagnoses (n=8) and healthy controls (n=32). aSyn was detected in 62/71 (87%) LBD patients, 18/134 (13%) AD, 2/22 (9%) FTD patients, 0/50 MCI patients, 0/8 patients with other neurodegenerative diseases and 0/32 healthy controls. The sensitivity and specificity of the assay were 87% and 91% respectively for the diagnosis of LBD, with a PPV of 76% and a NPV of 96%.
Conclusions: Detection of αSyn seeds by RT-QuIC has a good performance in identifying patients with LBD in a clinical cohort of cognitively impaired subjects. The test also identifies aSyn co-pathology in a subgroup of subjects diagnosed with AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1095 / #843

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA PTAU181 AS A POTENTIAL PROGNOSTIC BIOMARKER IN LEWY BODY DISEASE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Carla Abdelnour[1], Christina Young[1], Marian Shahid[1], Alena Smith[1], Edward Wilson[1], Hillary Vossler[1], Melanie Plastini[1], Joseph Winer[1], Lu Tian[1], Geoffrey Kerchner[2], Katrin Andreasson[1], Victor Henderson[1], Elizabeth C Mormino[1], Kathleen Poston[1]
[1]Stanford University, Department Of Neurology And Neurological Sciences, Stanford, United States of America, [2]F. Hoffmann-La Roche, Ltd., Pharma Research And Early Development, Basel, Switzerland

Aims: Lewy body disease (LBD) often co-occurs with Alzheimer's disease (AD), influencing disease progression, cognitive decline, and neurodegeneration. This study aims to determine whether plasma phosphorylated-Tau181 (pTau181) is a prognostic biomarker in LBD patients.
Methods: Among 633 Stanford research participants, 565 were selected, including 94 LBD with normal cognition (LBD-nlCog), 83 LBD with abnormal cognition (LBD-abnlCog), 114 AD, and 274 cognitively normal (CN). Plasma pTau181 levels were measured with Lumipulse G fully automated platform by Fujirebio with Lumipulse G Assays. Multiple linear regression models were used to examine the relationship between baseline plasma pTau181 levels and global cognition (MoCA), daily functioning (CDR-SOB), and neuropsychological performance. Linear mixed effects models (LMEM) assessed the impact of baseline and longitudinal changes in plasma pTau181 levels on 4-year declines in clinical outcomes.
Results: In the LBD-abnlCog group, higher baseline plasma pTau181 levels were associated with worse baseline CDR-SOB and MoCA scores. After 4 years, baseline plasma pTau181 levels predicted a more rapid decline in CDR-SOB. Additionally, a rapid increase in plasma pTau181 levels within the first 2 years predicted accelerated declines in MoCA, CDR-SOB, memory, executive function, and attention/working memory. In contrast, no significant associations were found between baseline or longitudinal plasma pTau181 levels and clinical outcomes in the LBD-nlCog group at either baseline or during the 4-year follow-up.
Conclusions: For LBD patients with MCI and dementia, baseline plasma pTau181 levels provide valuable insights into initial and long-term daily functioning. Moreover, a rapid increase in plasma pTau181 within the first 2 years correlates with accelerated declines in cognition, daily function, and neuropsychological performance. This highlights the significant potential of plasma pTau181 as a prognostic biomarker for LBD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1096 / #2531

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CAN BIOMARKERS IN EXTRACELLULAR VESICLES FROM BODILY FLUIDS ACCURATELY DIAGNOSE PARKINSON'S DISEASE OR RELATED DISORDERS? A SYSTEMATIC REVIEW AND DIAGNOSTIC META-ANALYSIS

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Hash Brown Taha[1], Aleksander Bogonwieski[2]
[1]University of Southern California, Leonard Davis School Of Gerontology, Los Angeles, United States of America, [2]University of California Los Angeles, Medical And Molecular Pharmacology, Los Angeles, United States of America

Aims: Parkinsonian disorders, including Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy body (DLB), corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) are often misdiagnosed due to overlapping symptoms and the absence of precise biomarkers. Furthermore, there are no current methods to ascertain the progression and conversion of prodromal conditions such as REM behavior disorder (RBD). Extracellular vesicles (EVs), containing a mixture of biomolecules, have emerged as potential sources for parkinsonian diagnostics. However, inconsistencies in previous studies have left their diagnostic potential unclear. We conducted a meta-analysis, following PRISMA guidelines, to assess the diagnostic accuracy of general EVs isolated from various bodily fluids, including cerebrospinal fluid (CSF), plasma, serum, urine or saliva, in differentiating patients with parkinsonian disorders from healthy controls (HCs).
Methods: The meta-analysis included 21 studies encompassing 1,285 patients with PD, 24 with MSA, 105 with DLB, 99 with PSP, 101 with RBD, and 783 HCs. Analyses were conducted only for patients with PD vs. HCs using bivariate and hierarchial receiver operating characteristics (HSROC) models, given the limited number for other comparisons.
Results: The meta-analysis revealed moderate diagnostic accuracy in distinguishing PD from HCs, with substantial heterogeneity and publication bias. The trim-and-fill method revealed at least two missing studies with null or low diagnostic accuracy. CSF-EVs showed better overall diagnostic accuracy, while plasma-EVs had the lowest performance. General EVs demonstrated higher diagnostic accuracy and less publication bias compared to CNS-originating EVs (estimated 2 out of 21 vs. 5 out of 16 missng studies, respectively), which are more time-consuming, labor- and cost-intensive to isolate.
Conclusions: While holding promise, utilizing biomarkers in general EVs for PD diagnosis remains unfeasible due to existing challenges. Though the diagnostic accuracy of biomarkers in EVs was superior than CNS-originating EVs, both methodologies suffered from substantial heterogeneity and publication bias.The focus should shift toward harmonizing the field through standardization, collaboration, and rigorous validation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1097 / #1095

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EFFECT OF NEFLAMAPIMOD TREATMENT ON PLASMA GLIAL FIBRIALLARY ACIDIC PROTEIN (GFAP) LEVELS IN PATIENTS WITH DEMENTIA WITH LEWY BODIES (DLB)

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

John Alam[1], Marleen Koel-Simmelink[2], Jennifer Conway[1], Amanda Gardner[1], Kelly Blackburn[1], Inge Verberk[2], Charlotte Teunissen[2]
[1]CervoMed, Inc., Clinical Development, Boston, United States of America, [2]Amsterdam UMC location Vrije Universiteit Amsterdam, Department of Laboratory Medicine, Neurochemistry Laboratory, Amsterdam, Netherlands

Aims: In the 16-week phase 2a AscenD-LB study in DLB, the oral drug neflamapimod demonstrated significant positive effects vs. placebo on CDR-SB and Timed Up and Go test, most prominently in patients with pure DLB (i.e., without Alzheimer's disease-related (AD) co-pathology, assessed by plasma ptau181). With a recent report (Hamilton *et.al. Psychological Medicine,* 2023) that plasma GFAP and neurofilament-light-chain (NfL) discriminated MCI-DLB from healthy controls, with GFAP being more discriminant, we evaluated the effects of neflamapimod in AscenD-LB on plasma GFAP and NfL, both overall and in pure DLB patients.
Methods: GFAP and NfL levels (pg/mL) in stored plasma samples from AscenD-LB were determined using the Simoa® platform. Overall design and results (Jiang et.al. Nature Communications, 2022), and analysis after stratification for baseline plasma ptau181 (Alam et.al. Neurology, 2023) are published.
Results: At baseline, GFAP was higher (p=0.02) in DLB with AD co-pathology [282(SD=120, n=29] versus in pure DLB [215(SD=91), n=28]; NfL was not. In the overall population, reduced GFAP levels were seen in neflamapimod-treated participants (n=30, -12.3+/-6.8, baseline-to-week16) and not in placebo-recipients (n=27, +3.7+/-7.8; p=0.13 for neflamapimod-placebo difference). In pure DLB participants, a significant reduction (p=0.04) in GFAP levels with neflamapimod (n=15, -10.6+/-6.4) vs. placebo (n=13, +14.1+/-10.2) was seen. For NfL, no neflamapimod-placebo differences were evident in either population.
Conclusions: Plasma GFAP has potential utility to assess drug effects in DLB, though to lessen masking effects of GFAP production related to AD co-pathology it may be best to make such evaluations in pure DLB patients. To confirm the potential effects of neflamapimod on GFAP levels and evaluate the relation to clinical outcomes, plasma GFAP will be assessed in an ongoing phase 2b clinical study of neflamapimod in early DLB.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1098 / #714

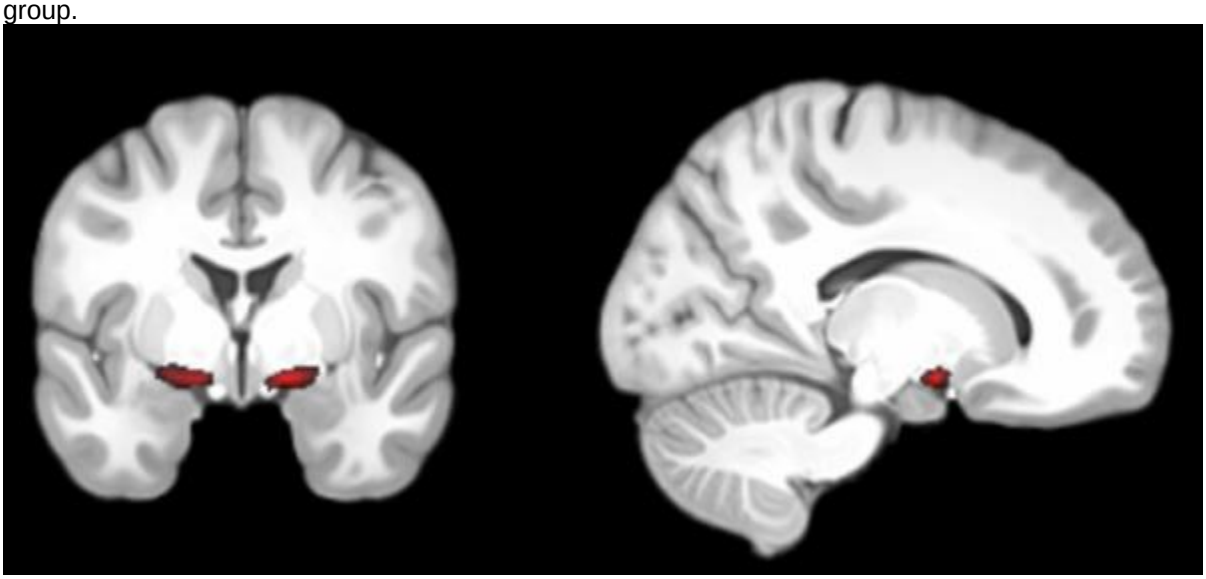
Poster Topic: *Theme C: α-Synucleinopathies / C04.e. Imaging, Biomarkers, Diagnostics: Multimodal imaging*

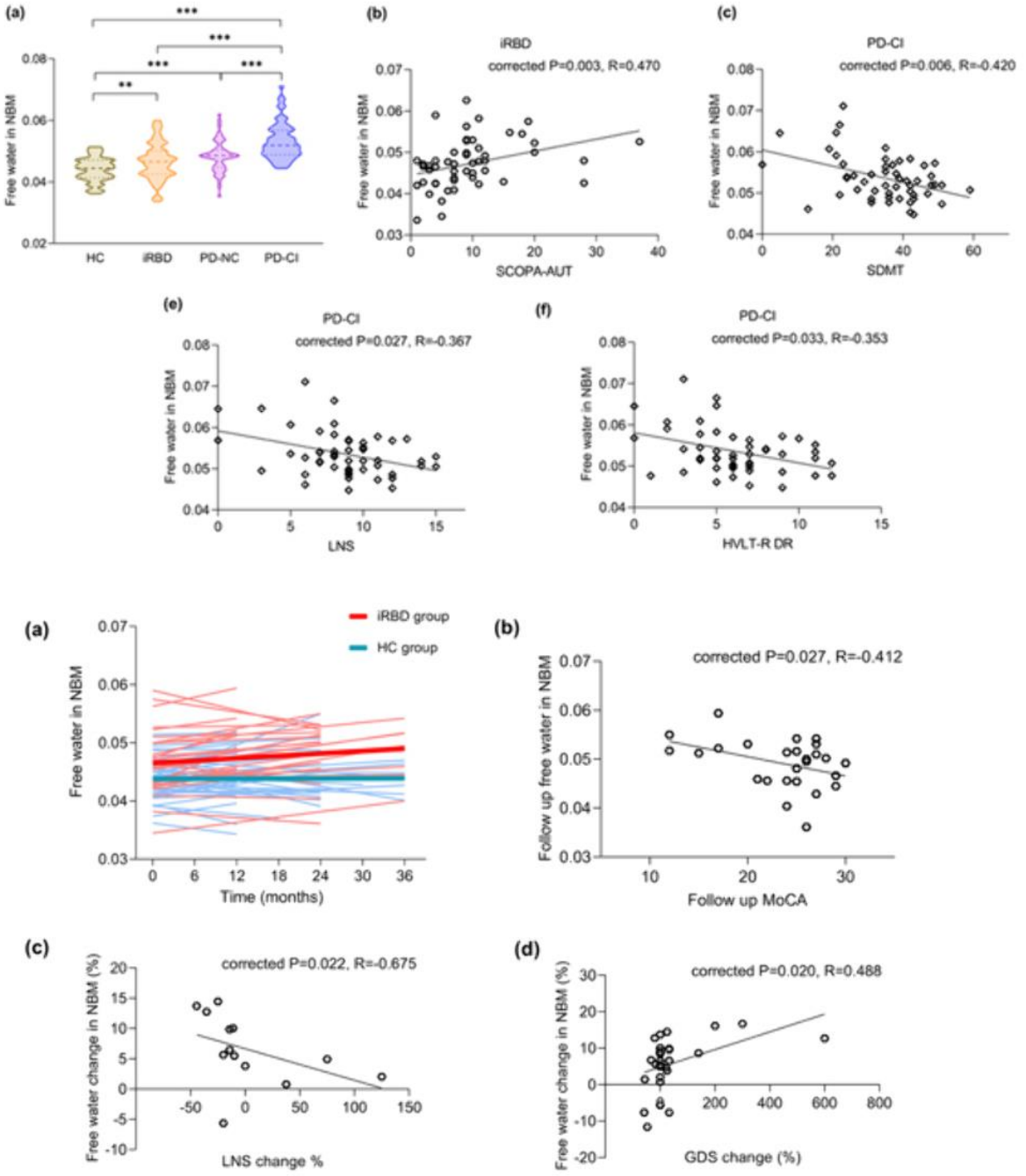
FREE-WATER IMAGING OF THE NUCLEUS BASALIS OF MEYNERT IN IDIOPATHIC REM SLEEP BEHAVIOR DISORDER

POSTERS: C04.E. IMAGING, BIOMARKERS, DIAGNOSTICS: MULTIMODAL IMAGING

Dongling Zhang[1], Liche Zhou[2], Tao Wu[1], Jun Liu[2], Tao Feng[1]
[1]Beijing Tiantan Hospital, Department Of Neurology, Beijing, China, [2]Ruijin Hospital, Department Of Neurology And Institute Of Neurology, Shanghai, China

Aims: Objectives: Cognitive impairments are common in idiopathic REM sleep behavior disorder (iRBD), in which the cholinergic degeneration of nucleus basalis of Meynert (NBM) may play an important role. However, the progressive changes of NBM remain unclear. This study aimed to investigate the cross-sectional and longitudinal microstructural alterations in the NBM of iRBD patients using free-water imaging.
Methods: Methods: We compared the baseline free water values in the NBM between 59 healthy control (HC), 57 iRBD patients, 57 Parkinson's disease (PD) patients with normal cognition (PD-NC), and 64 PD patients with cognitive impairment (PD-CI). 30 iRBD patients and 40 HC had longitudinal data. In iRBD patients, we explored the associations between baseline and longitudinal changes of free water values in the NBM and clinical characteristics and whether baseline free water values in the NBM could predict cognitive decline.
Results: Results: IRBD, PD-NC and PD-CI groups had significantly increased free water values in the NBM compared to HC, while PD-CI had higher free water values compared to iRBD and PD-NC. In iRBD patients, free water values in the NBM were progressively elevated over follow-up and correlated with the progression of cognitive performance and depression. Free water values in the NBM could predict cognitive decline in iRBD
group.





Conclusions: Conclusions: This study proves that free water values in the NBM are elevated cross-sectionally and longitudinally, and are associated with the progression of cognitive impairment and depression in iRBD patients. Moreover, the free water value in the NBM can predict cognitive decline in iRBD patients. Our results suggest that free-water imaging of the NBM has the potential to be a marker for monitoring progressive cognitive impairment and predicting the conversion to dementia in synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1099 / #647

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

CSF NEUROSECRETORY PROTEINS VGF AND NEUROSERPIN IN PATIENTS WITH ALZHEIMER'S AND LEWY BODY DISEASES

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Lorenzo Barba[1], Giovanni Bellomo[2], Patrick Oeckl[3], Davide Chiasserini[4], Lorenzo Gaetani[2], Edoardo Guido Torregiani[2], Federico Paolini Paoletti[2], Petra Steinacker[1], Samir Abu-Rumeileh[1], Lucilla Parnetti[2], Markus Otto[1]
[1]Martin-Luther-University Halle-Wittenberg, Department Of Neurology, Halle (Saale), Germany, [2]University of Perugia, Laboratory Of Clinical Neurochemistry, Section Of Neurology, Department Of Medicine And Surgery, Perugia, Italy, [3]Ulm University, Department Of Neurology, Ulm, Germany, [4]University of Perugia, Section Of Physiology And Biochemistry, Department Of Medicine And Surgery, Perugia, Italy

Aims: VGF (non-acronymic) and neuroserpin are neurosecretory proteins involved in the pathogenesis of neurodegenerative diseases. We aimed to evaluate their cerebrospinal fluid (CSF) concentrations in patients with Alzheimer's disease (AD) and Lewy body disease (LBD).
Methods: We measured VGF [AQEE] peptide and neuroserpin protein levels in 101 patients with LBD (Parkinson's disease, PD n=89; PD with dementia, PDD n=12; dementia with Lewy bodies, DLB n=7), 76 patients with AD and 37 control subjects, and tested associations with clinical scores and AD core biomarkers.
Results: We found increased CSF levels of VGF [AQEE] (p=0.001) and neuroserpin (p=0.009) in patients with AD compared to patients with LBD, especially in cases with dementia. Lower levels of VGF [AQEE] and neuroserpin were significantly associated with lower Mini-Mental State Examination (MMSE) scores, with CSF tau protein levels and with each other in both LBD and AD. After stratification according to the CSF AT(N) profile, VGF [AQEE] and neuroserpin CSF concentrations were significantly increased only in LBD patients with A+T+ profiles and in AD patients compared to controls and other LBD subgroups. Finally, VGF [AQEE] showed a good diagnostic accuracy in the discrimination between AD dementia and PDD/DLB (AUC=0.754) and both biomarkers could well distinguish LBD/A-T- from LBD/A+T+ cases (AUC=0.740 for VGF [AQEE], AUC=0.756 for neuroserpin).
Conclusions: CSF VGF and neuroserpin levels are elevated in patients with AD or LBD with AD copathology, thus, representing markers of AD-related pathogenetic changes of neurosecretory pathways.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1100 / #1850

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

INVESTIGATING ALPHA-SYNUCLEIN CO-PATHOLOGY IN ALZHEIMER'S DISEASE BY MEANS OF CEREBROSPINAL FLUID ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Giovanni Bellomo[1], Andrea Toja[1], Federico Paolini Paoletti[1], Yihua Ma[2], Carly Farris[2], Lorenzo Gaetani[1], Nicola Salvadori[1], Davide Chiasserini[3], Anna Lidia Wojdała[1], Luis Concha-Marambio[2], Lucilla Parnetti[1]
[1]University of Perugia, Laboratory Of Clinical Neurochemistry, Section Of Neurology, Department Of Medicine And Surgery, Perugia, Italy, [2]Amprion, R&d Unit, San Diego, United States of America, [3]University of Perugia, Section Of Physiology And Biochemistry, Department Of Medicine And Surgery, Perugia, Italy

Aims: Neuropathological studies indicate that synucleinopathy represents one of the most common co-pathologies in Alzheimer's disease (AD). We applied α-synuclein seed amplification assay (αS-SAA) in cerebrospinal fluid (CSF) samples of AD patients to estimate the prevalence of αS-SAA positivity, also investigating whether such positivity was associated to clinical and neuropsychological parameters and disease progression.
Methods: A highly reliable αS-SAA protocol was applied on n=430 CSF samples of AD patients encompassing the whole clinical spectrum (n=240), controls (n=85) and individuals with Lewy body disorders (n=105). Association between aS-SAA positivity and cognitive/behavioural changes over time was also evaluated.
Results: As expected, a large majority (87%) of patients affected by Lewy body disorders showed a positive CSF αS-SAA, as opposite to a very low prevalence in controls (9%). In a significant proportion of all clinical AD stages we could see a positive CSF αS-SAA (26-27% in preclinical and prodromal AD; 36% in dementia stage). Of interest, out of 12 cases with posterior presentation, 8 (67%) showed a positive CSF αS-SAA. Moreover, all AD cases with CSF αS-SAA positivity showed a more marked impairment of visuospatial skills at baseline and cognitive decline at followup, as compared to AD cases with negative CSF αS-

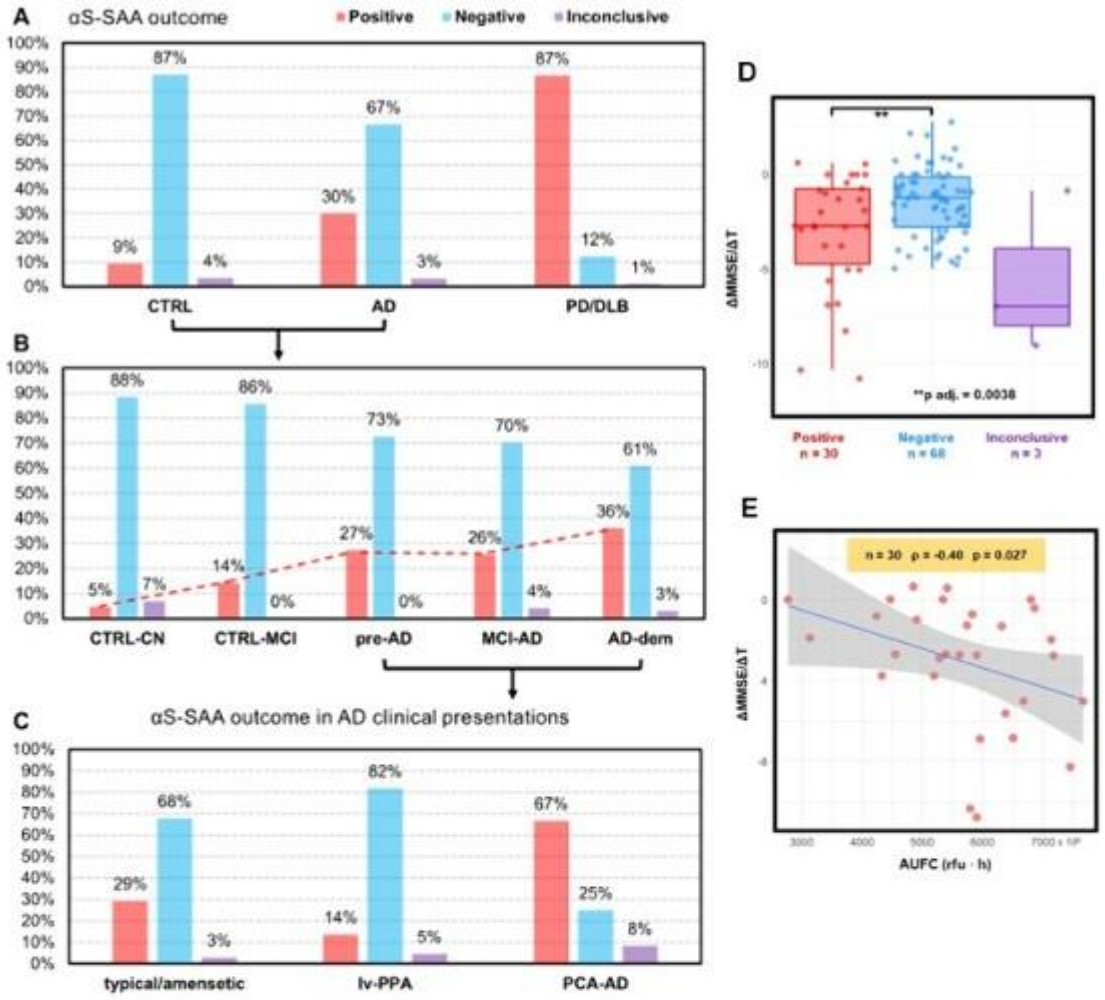


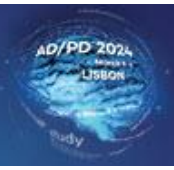
Figure 1. CSF αS-SAA outcome in the clinical groups and subgroups considered. A) Barplot representing the percentages of CSF αS-SAA positive, inconclusive, and negative subjects within CTRL, AD and PD/DLB groups. B) Barplot representing the percentages of CSF αS-SAA positive, inconclusive, and negative subjects within CTRL-CN, CTRL-MCI, pre-AD, MCI-AD, and AD-dem subgroups. C) Barplot representing the percentages of CSF αS-SAA positive, inconclusive, and negative subjects among typical/amnestic AD (n=205) and lv-PAA (n=22) and PCA AD (n=12) clinical variants. D) boxplots representing the rate of change of MMSE score over time (ΔMMSE/Δt) in CSF αS-SAA positive, negative, and inconclusive AD patients in which boxes represent the interquartile range. The horizontal lines within boxes represent the medians and whiskers reflect the first/third quartile -/+ 1.5 times the interquartile range. The p-values reported are calculated by logistic regression for pairwise comparisons and are adjusted for age and sex. E) Linear regression between ΔMMSE/ΔT and AUFC with 95% CI of the linear regression and Spearman's correlation coefficient (ρ) displayed.

SAA.

Conclusions: Our study suggests that α-synuclein-related co-pathology may influence the clinical presentation and prognosis of AD. Accordingly, an update of the A/T/N system including the letter "S" for

"synucleinopathy" should be taken into account in order to better define the molecular profile of AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P1101 / #2932

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PRESYMPTOMATIC DETECTION AND QUANTIFICATION OF ALPHA-SYNUCLEIN USING NOVEL SEEDING AMPLIFICATION IMMUNOASSAY (SAIA)

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ilham Abdi[1], Indulekha Sudhakaran[1], Simona Ghanem[1], Nishant Vaikath[1], Nour Majbour[1], Eldbjørg Hustad[2], Vasilios C. Constantinides[3], Elisabeth Kapaki[3], George Paraskevas[3], Wilma Van De Berg[4], Daniel Erskine[5], Kostas Vekrellis[6], Brit Mollenhauer[7], Michael Schlossmacher[8], Omar El-Agnaf[1]
[1]Qatar Biomedical Research Institute, Qatar Foundation, Neurological Disorder Research Center, Doha, Qatar, [2]Norwegian University of Science and Technology, Department Of Neuroscience, Trondheim, Norway, [3]School of Medicine, National and Kapodistrian University of Athens, Eginition Hospital, First Department Of Neurology, Athens, Greece, [4]Vrije Universiteit Amsterdam, Amsterdam UMC, Section Clinical Neuroanatomy And Biobanking, Department Of Anatomy And Neurosciences,, Amsterdam, Netherlands, [5]Newcastle University, Ageing Research Laboratories, Newcastle upon Tyne, United Kingdom, [6]Biomedical Research Foundation, Academy of Athens (BRFAA), Center Of Basic Research, Athens, Greece, [7]University Medical Center Göttingen, Department Of Neurology, Göttingen, Germany, [8]University of Ottawa, Brain And Mind Research Institute, Ottawa, Canada

Aims: The objective of this study is to validate the Seeding Amplification ImmunoAssay (SAIA) as a sensitive and specific method for the early detection of alpha-synucleinopathies, with an emphasis on its diagnostic capabilities in prodromal stages of the disease. By focusing on prodromal rapid eye movement sleep behavior disorder (RBD) and LRRK2 mutation carriers, this research seeks to establish SAIA as a pivotal tool for identifying individuals at risk of developing Parkinson's disease (PD) before clinical symptoms manifest.
Methods: This extended validation study engaged a broad cohort of CSF samples, including individuals diagnosed with synucleinopathies, tauopathies, and amyloidoses. The assay's clinical applicability was further explored in prodromal RBD cases and asymptomatic LRRK2 mutation carriers, groups at risk for developing PD.
Results: In this comprehensive analysis, SAIA achieved exceptional diagnostic accuracy, with sensitivities and specificities in the range of 80-100% and area under the curve (AUC) values consistently exceeding 0.9. Remarkably, SAIA positively identified 100% of prodromal RBD cases within the study cohort, with 94% sensitivity and 82% specificity. Unprecedently, the assay successfully detected α-synuclein seeds in 78% of LRRK2 mutation carriers who had not yet exhibited clinical symptoms of PD, demonstrating its potential in pre-symptomatic disease detection.
Conclusions: The findings confirm the potential of SAIA in the early detection of synucleinopathies during their prodromal phase, which could revolutionize the diagnostic approach for at-risk populations. The assay's high specificity and sensitivity highlight its value as a diagnostic tool and its role in future clinical trials. Further investigation is warranted to solidify SAIA's role in neurodegenerative disease management and its predictive power in prodromal synucleinopathies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1102 / #1525

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

IMMUNOASSAY DEVELOPMENT FOR FCER2 – A NOVEL BIOMARKER CANDIDATE FOR DLB

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Katharina Bolsewig[1], Imane Al Idrissi[1], Afina Lemstra[2], Eline Willemse[1,3], Charlotte Teunissen[1]
[1]Amsterdam UMC, Department Of Laboratory Medicine, Neurochemistry Laboratory, Amsterdam, Netherlands, [2]Amsterdam UMC, Alzheimer Center Amsterdam, Amsterdam, Netherlands, [3]University Hospital Basel and University of Basel, Department Of Neurology, Multiple Sclerosis Center And Research Center For Clinical Neuroimmunology And Neuroscience Basel, Departments Of Biomedicine And Clinical Research, Basel, Switzerland

Aims: Diagnosing dementia with Lewy bodies (DLB) is still challenging, but could be facilitated by a DLB-specific, easily accessible biomarker. In an antibody-based proteomics study we identified Fc Epsilon Receptor 2 (FCER2) as a novel biomarker candidate, showing reduced levels in DLB compared with controls (CN), Alzheimer's disease (AD) and frontotemporal dementia (FTD). Here, we aimed to develop and validate an immunoassay for the detection of FCER2 in cerebrospinal fluid (CSF).
Methods: We developed an automated immunoassay on the Simpleplex Ella platform. The assay was optimized for antibody combination and concentration, as well as buffer conditions. Assay performance was validated by assessing sensitivity, precision, parallelism, dilution linearity, recovery and sample stability. FCER2 was measured in a pilot cohort (controls: n=29, DLB: n=28, AD: n=31, FTD: n=29) and group differences were assessed by analysis of covariance corrected for age and sex.
Results: The in-house developed FCER2 assay had a lower limit of detection of 14.13 pg/mL. Precision parameters were below a coefficient of variation of 20% (repeatability=12.2%; intermediate precision=19.8%). Mean parallelism was 114%, dilution linearity ranged from 57% to 179%, but was acceptable (85%-99%) within the working range of the assay. Recovery ranged from 93% (high spike) to 145% (low spike). Two out of three samples were stable across 7 freeze-thaw cycles. Lowest FCER2 concentrations were observed in DLB (193 pg/mL vs CN: 238 pg/mL; AD: 202 pg/mL; FTD: 243 pg/mL), but differences across groups did not reach significance ($F(3, 109)=1.411$, $p=.244$).
Conclusions: We successfully developed and analytically validated an immunoassay for the detection of FCER2 in CSF. Next, clinical utility of FCER2 for DLB to differentiate DLB from other diagnostic groups will be evaluated in a larger clinical cohort.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1103 / #2950

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

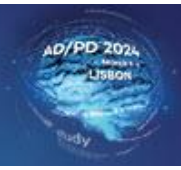
STRATIFICATION OF SUBJECTS WITH PARKINSON'S AND MULTIPLE SYSTEM ATROPHY BY SEMI-QUANTITATIVE ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY.

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Luis Concha-Marambio[1], Carly Farris[1], Yihua Ma[1], John Middleton[2], Hieu Nguyen[1], Sandra Rosete-Gonzalez[1]
[1]Amprion, R&d Unit, San Diego, United States of America, [2]Amprion Inc., Amprion Inc., San Francisco, United States of America

Aims: To determine if alpha-synuclein semi-quantitative seed amplification assay (αSyn SQ-SAA) can stratify patients with synucleinopathies such as Parkinson's disease (PD) and multiple system atrophy (MSA) based on levels of seeding activity present in cerebrospinal fluid (CSF).
Methods: PD and MSA CSF samples were serially diluted in a synthetic diluent developed by Amprion that mimics human control CSF. Each of the dilutions were evaluated using Amprion R&D αSyn-SAA in triplicate. The dilution factor needed to reach 50% of the replicates positive (SD50-DF) for each of the titrated CSF samples was estimated using the Spearman-Karber method. The calculation included adjustment to account for self-aggregation and trimming when needed.
Results: SD50-DF values were different for PD and MSA, with the PD group presenting amplification at much higher dilutions than the MSA group. Seeding activity in CSF from MSA and PD subjects was diluted out (no seeds detected) at 1:17 and 1:729 dilutions, respectively. Thus, two different dilution schemes were used to analyze additional PD and MSA CSF samples. MSA subjects presented a bimodal distribution, effectively dividing the group between "low seeders" and "high seeders". The distribution for PD subjects was more complex and a larger number of samples is needed to determine if subgroups with different levels of seeding activity will emerge.
Conclusions: Our results show that semi-quantitation based on dilutions can identify two subgroups of MSA subjects. Identification of these subjects may enable better selection criteria for clinical trials as SD50-DF may correlate with sub-strain features and/or levels of αSyn-seeds. SD50-DFs for PD CSF are much lower than reported levels for brain, skin, and other tissues, suggesting that normal CSF turnover, or unknown clearance mechanisms, oppose unlimited accumulation of αSyn-seeds in CSF.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P1104 / #2874

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

NUTRITIONAL DECLINE PREDICTS SHORT SURVIVAL IN MULTIPLE SYSTEM ATROPHY

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Yuri Asano, Toshio Shimizu, Kota Bokuda, Shinsuke Tobisawa, Kazushi Takahashi
Tokyo Metropolitan Neurological Hospital, Neurology, Fuchu, Tokyo, Japan

Aims: Multiple system atrophy (MSA) is a neurodegenerative disease that often leads to weight reduction and nutritional problems throughout its course. However, there is limited evidence regarding the relationships between nutritional issues and other clinical features of MSA, including survival length. This study aims to investigate the prognostic significance of nutritional problems in MSA through a retrospective cohort study at a single tertiary hospital.
Methods: A total of 218 patients with MSA who met the 2022 MDS-Ccriteria were enrolled in this study. We assessed onset age, motor subtype, the presence of orthostatic hypotension (OH), Unified MSA Rrating Sscale (UMSARS) Part Ⅳ, serum albumin, blood lymphocyte count, prognostic nutritional index (PNI), and body mass index (BMI) at the time of diagnosis. Additionally, we calculated the post-diagnostic decline rate of BMI per year (ΔBMI). Survival length was defined as the duration between the time of diagnosis and the time of death or tracheostomy. The relationship between each clinical marker and survival was explored using a log-rank test and a Cox proportional hazards model.
Results: The post-diagnostic survival was 2.5 years (mean, SD 2.0). Log-rank tests revealed a significant association between serum albumin, PNI, ΔBMI, and the presence of OH at diagnosis with post-diagnostic survival. Multivariate analysis using the Cox model demonstrated that PNI at diagnosis (HR 2.01; 95% CI 1.00–4.01) and ΔBMI (HR 2.51; 95% CI 1.32–4.76) were independent prognostic factors for survival ($p < 0.05$ and $p < 0.01$, respectively).
Conclusions: Nutritional decline predicts a shorter survival in MSA. Nutritional intervention may be required from the time of diagnosis to improve the survival prognosis in patients with MSA.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1105 / #1211

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DEVELOPMENT OF A HIGH-THROUGHPUT AUTOMATED PROTOCOL FOR SINGLE MOLECULE PULL DOWN AND SUPER RESOLUTION MICROSCOPY FOR PARKINSON'S DISEASE PROTEIN AGGREGATES.

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Asher Dworkin[1], Yu Zhang[1], Evgeniia Lobanova[1], Lakmini Kahanawita[2], Caroline Williams-Gray[2], David Klenerman[1]
[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]University of Cambridge, Department Of Clinical Neurosciences, Cambridge, United Kingdom

Aims: Objectives: Parkinson's disease is characterised by accumulation (aggregation) of not just alpha-synuclein but also other neurodegenerative proteins in the brain which are filtered into the cerebrospinal fluid and blood for removal. A combination of different protein aggregate biomarkers in serum is suggested to work as a sensitive discriminator between early-stage Parkinson's patients and healthy controls [1]. If optimised this may provide an early screening test for a high-risk population for the disease and provide the opportunity for early-stage intervention and treatment. The screening protocols are lengthy and highly labour intensive. Here we present a high throughput platform using a robotic liquid handling system to increase the speed of testing from around 50 samples to hundreds of samples per day.
Methods: Methods: The robotic liquid handling system (CyBio FeliX Robot by Analytik Jena) is used to prepare a sandwich single-molecule pulldown (SiMPull) immunoassay, using commercially available antibodies. Direct Stochastic Optical Reconstruction Microscopy (dSTORM) provides specific morphological data of the aggregates. Analysing the relative prevalence of different protein aggregates (primarily alpha-synuclein and tau) combined with the information on their size and shape gives a combination of metrics for distinguishing the patients from controls.
Results: Results: Preliminary testing indicates that this technique can be used to distinguish Parkinson's patients from controls, as well as patients who have high risk of developing early dementia.
Conclusions: Conclusions: This platform represents the first step towards large scale population screening for early diagnosis and prognosis of Parkinson's disease and provides the basis for similar deployment with other neurodegenerative diseases. **References** [1] Lobanova E. et al. Brain 145, 632–643 (2021)

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1106 / #942

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DIAGNOSIS OF DEMENTIA WITH LEWY BODIES BASED ON A NGS ANALYSIS OF BLOOD MITOCHONDRIAL METHYLCYTOSINES: A MACHINE LEARNING APPROACH

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Marta Blanch[1], Paula Ferrer-Raventós[1], Beatriz Fontal[1], Pau Martí[2], Carla Trapero[3], Jaume Campdelacreu[4], Jordi Gascón[4], Raquel Sánchez-Valle[5], Pablo Martinez-Lage[6], Christopher Fowler[7], Simon Laws[8], Jose Luis Mosquera[2], Marta Barrachina[9]
[1]ADmit Therapeutics S.L., R&d Department, Esplugues de Llobregat, Spain, [2]ADmit Therapeutics S.L., Bioinformatics And Data Science Department, Esplugues de Llobregat, Spain, [3]ADmit Therapeutics S.L., Project Management, Esplugues de Llobregat, Spain, [4]Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), Functional Unit Of Dementia, Service Of Neurology, L'Hospitalet de Llobregat, Spain, [5]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Alzheimer's Disease And Other Cognitive Disorders Unit, Neurology Service, Barcelona, Spain, [6]CITA-Alzheimer Foundation, Area Of Neurology, Donostia-San Sebastian, Spain, [7]The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Clinical Research Group, Melbourne, Australia, [8]Centre for Precision Health, School of Medical and Health Sciences, Edith Cowan University, Collaborative Genomics And Translation Group, Joondalup, Australia, [9]ADmit Therapeutics S.L., Ceo, Esplugues de Llobregat, Spain

Aims: Dementia with Lewy Bodies (DLB), the second most common cause of degenerative dementia, is characterized by non-motor cognitive alterations preceding parkinsonism. Currently, DLB is diagnosed using a combination of medical and neuropsychological tests. However, these methods are sometimes insufficient for a solid and sharp diagnosis. ADmit has developed a cutting-edge technology based on next-generation sequencing (NGS) that identifies differential mitochondrial DNA methylation patterns in blood samples from DLB patients against control subjects. The aim is to develop a classification model to diagnose DLB patients from blood samples.
Methods: Eighty-four subjects were recruited from Bellvitge University Hospital, AIBL Consortium, CITA-Alzheimer Foundation, and Hospital Clínic de Barcelona. The methylation levels of ND1 and D-loop loci were measured by NGS in DLB (n=42) and control (n=42, CDR=0) subjects. Ten different supervised learning methods were considered to build a prototype model. All methods were run using a 3 repeated 10-fold Cross-Validation.
Results: Significant differences in the methylation profile distribution were found when comparing control *vs* DLB blood samples in both loci (FDR < 0.05). Random Forest (RF) method yielded the best performance of the classification model with accuracy=0.83 and Kappa=0.65. The RF model exhibited an accuracy of 0.81 on the testing data, with a 95% Confidence Interval ranging from 0.54 to 0.96, and a Kappa value of 0.63. The Sensitivity and Specificity were 0.75 and 0.875, respectively. The precision of the model was 0.86, and the F1-score 0.8. The ROC curve showed an AUC of 0.891.
Conclusions: These results support the existence of a specific mitoepigenetic signature in blood samples from DLB patients. The present model performs a good classification of DLB patients, representing a promising minimal-invasive diagnostic tool to improve DLB diagnosis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1107 / #1402

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

OPTIMIZED SEED AMPLIFICATION ASSAY (SAA) METHOD AS A DIAGNOSTIC TOOL FOR PARKINSONIAN DISORDERS

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Bárbara Fernandes Gomes[1], Carly Farris[2], Yihua Ma[2], Luis Concha-Marambio[2], Russ Lebovitz[2], David Bäckström[3], Ulf Andreasson[1,4], Henrik Zetterberg[1,4,5,6,7,8], Kaj Blennow[1,4]
[1]Institute of Neuroscience & Physiology, Department Of Psychiatry & Neurochemistry, Mölndal, Sweden, [2]Amprion, R&d Unit, San Diego, United States of America, [3]Umeå University, Department Of Clinical Science, Umeå, Sweden, [4]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [5]Department of Neurodegenerative Disease, Ucl Institute Of Neurology, London, United Kingdom, [6]UK Dementia Research Institute, Ucl Institute Of Neurology, London, United Kingdom, [7]Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China, [8]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America

Aims: To evaluate the ability of a novel optimized alpha-synuclein seed amplification assay (aSyn-SAA) to detect alpha-synuclein (aSyn) aggregates in cerebrospinal fluid (CSF) samples and distinguishing between various movement disorders, including different synucleinopathies.
Methods: This study was performed with CSF samples from a cohort comprised of healthy controls (n=30), and patients with Parkinson's disease (PD) (n=101), corticobasal degeneration (CBD) (n=3), progressive supranuclear palsy (PSP) (n=22), or multiple system atrophy (MSA) (n=26). The detection of aSyn aggregates was evaluated using an optimized aSyn-SAA approach, which rapidly amplifies minimal aSyn aggregate amounts, making them easily detectable by thioflavin-T within just 24 hours.
Results: The optimized aSyn-SAA effectively identified aSyn aggregates in CSF samples, with most of the PD samples testing positive. Samples from MSA patients were mostly positive as well, although to a lesser extent than PD patients. In contrast, tauopathy-related movement disorders, such as PSP and CBD, had predominantly negative results. Furthermore, the majority of samples from healthy controls also tested negative. The small number of negative cases within the PD and MSA groups could indicate false negatives, misdiagnosis or, in case of the PD group, the presence of genetic variants that are not associated with Lewy body pathology, and would therefore test negative on this assay.
Conclusions: These results indicate that this optimized aSyn-SAA exhibits high sensitivity and specificity, and can accurately detect aSyn seeds in individuals with PD and MSA. Furthermore, we show that it can be a valuable tool for distinguishing PD and MSA from other movement disorders like CBD and PSP.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1108 / #338

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PREDICTION OF MOTOR AND NON-MOTOR PARKINSON'S DISEASE SYMPTOMS USING SERUM LIPIDOMICS: A TWO-YEAR STUDY

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Jasmin Galper[1], Gordon Mcdonald[2], Giorgia Mori[2], Diba Rastegar[1], Russell Pickford[3], Simon Lewis[4], Glenda Halliday[1], Woojin Kim[1], Nicolas Dzamko[1]
[1]The University of Sydney, Faculty Of Medicine And Health, Sydney, Australia, [2]University of Sydney, Sydney Informatics Hub, Sydney, Australia, [3]University of New South Wales, Bioanalytical Mass Spectrometry Facility, Sydney, Australia, [4]University of Sydney, Faculty Of Medicine And Health, Sydney, Australia

Aims: To investigate the potential for >900 serum lipids measured at baseline to predict motor and non-motor clinical scores of Parkinson's disease subjects after a two year follow up.
Methods: Untargeted high-performance liquid chromatography–tandem mass spectrometry was used to measure > 900 lipids in serum from Parkinson's disease subjects (*n* = 122). The potential for baseline lipids to predict motor and non-motor clinical scores (UPDRS III, UPSIT, Geriatric Depression Scale and The Schwab and England ADL) after a two year follow up (*n* = 67) was assessed by machine learning. The ability of baseline serum lipids to predict clinical scores was compared to 27 serum cytokines.
Results: Species of lysophosphatidylethanolamine, phosphatidylcholine, platelet-activating factor, sphingomyelin, diacylglycerol and triacylglycerol were top predictors of both motor and non-motor scores. Serum lipids were overall more important predictors of clinical outcomes than subject sex, age and mutation status of the Parkinson's disease risk gene *LRRK2*. Furthermore, lipids were found to better predict clinical scales than a panel of 27 serum cytokines previously measured in this cohort.
Conclusions: These results provide a platform for further targeted investigations into the involvement of lipids in Parkinson's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1109 / #1309

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

FRAMEWORK FOR ISOLATING EVS FROM NEURONS AND MEASURING THEIR CARGO

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Tal Gilboa, Dima Ter-Ovanesyan, Sara Whiteman, David Walt
Harvard Medical School, Wyss Institute, Brookline, United States of America

Aims: This study aims to address two key challenges in isolating neuron-specific extracellular vesicles (EVs) from human biofluids, such as plasma. First, we aimed to identify a neuron-specific marker for immuno-isolation while ensuring its presence on EVs rather than as a soluble protein. Second, we sought to develop methods to confirm the presence of neurodegenerative disease biomarkers within EVs isolated from plasma and quantify the ratio of this cargo in EVs to the total plasma.
Methods: We developed an unbiased pipeline that combined gene expression and EV proteomics data to identify potential cell-type specific EV markers for neuron EV isolation. We also devised a methodology involving a high-yield size exclusion chromatography (SEC) protocol, an optimized protease protection assay, and Single Molecule Array (Simoa) assays for quantifying EV protein cargo. These methods allowed us to achieve ultrasensitive measurements of proteins within EVs
Results: We identified potential novel handles for isolating neuron EVs using our computational-experimental framework. We applied our EV protein cargo quantification method to analyze prominent proteins associated with neurodegenerative diseases, including α-synuclein, Tau, Aβ40, and Aβ42. We found that α-synuclein and Tau are present in plasma EVs at a fraction of the levels in total plasma, whereas Aβ40 and Aβ42 are undetectable in plasma EVs
Conclusions: Our study presents a valuable foundation for determining protein levels in both total plasma EVs and neuron-derived EVs. These findings hold promise for utilizing EVs as potential biomarkers for neurological diseases, offering an exciting avenue for understanding neuronal states and diagnosing neurological disorders non-invasively.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1110 / #140

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DYSREGULATION OF LYSOSOMAL AND AUTOPHAGIC-ASSOCIATED PROTEINS IN PBMCS AND PLASMA FROM PARKINSON'S DISEASE PATIENTS

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Marisa Goo[1], Eric Liang[1], Ritesh Ravi[1], Buyankhishig Tsogtbaatar[1], Yuxi Tian[1], Alexander Haimovich[2], Julian Agin-Liebes[2], Roy Alcalay[2,3], Sarah Huntwork-Rodriguez[1]
[1]Denali Therapeutics, Development-clinical Biomarkers, South San Francisco, United States of America, [2]Columbia University, Department Of Neurology, New York, United States of America, [3]Laboratory of biomarkers and genomic of neurodegeneration, Tel-aviv Medical Center, Tel Aviv, Israel

Aims: To evaluate lysosomal biomarkers in PBMCs and plasma from Parkinson's disease (PD) patients with and without *GBA1* or *LRRK2* mutations compared to healthy controls.
Methods: We analyzed PBMC samples (96 non-carrier PD, 51 non-carrier controls, 33 *LRRK2* PD, 18 *LRRK2* non-PD, 21 *GBA1* PD, 8 *GBA1* non-PD, 5 *LRRK2/GBA1* PD, 1 *LRRK2/GBA1* non-PD) and plasma samples (62 non-PD and 67 PD) for biomarker analysis. Immunoassays on the Meso Scale Discovery (MSD) platform to measure the lysosomal-related proteins LAMP1, Cathepsin B (CatB), glucocerebrosidase (GCase), pS935 LRRK2 and total LRRK2. GCase enzyme activity was measured using the plate-based 4-methylumebelliferone assay and its substrate glucosylsphingosine (GlcSph) by targeted LC-MS/MS based approach.
Results: We observed decreased GCase enzymatic activity and elevated GlcSph levels in PBMCs from *GBA1* mutation carriers versus non-carriers, as well as significantly lower GBA protein levels. *LRRK2* carriers had increased GCase enzymatic activity and reduced GlcSph levels with no change in overall GBA protein levels in PBMCs. LAMP1 levels were significantly, albeit slightly reduced, in PD compared to control in both PBMCs and plasma. CatB was elevated in PD plasma.
Conclusions: Reduced LAMP1 levels in PD patient supports the hypothesis that lysosomes are reduced in PD patients. Additionally, elevated CatB levels in plasma suggests dysregulation in the normal lysosomal pathway in PD patients. We confirmed prior reports of elevated GCase activity in LRRK2 carriers, which may be biologically meaningful considering reduction of GlcSph. Our findings further support loss of function in GBA1 shown by decreased PBMC GCase protein level and enzymatic activity along with elevation in GlcSph. This study provides novel biomarker data on Parkinson's disease and *LRRK2 /GBA1* genetic associations with readouts of lysosomal perturbations in plasma and PBMCs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1111 / #667

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

AGE-RELATED TRENDS IN AMYLOID POSITIVITY IN PARKINSON'S DISEASE WITHOUT DEMENTIA

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Keiko Hatano[1], Masashi Kameyama[2], Masanori Kurihara[1], Kensuke Ohse[3], Ryoji Goto[4], Ryoko Ihara[1], Mana Higashihara[1], Renpei Sengoku[5], Yasushi Nishina[1], Kazutomi Kanemaru[1], Yuko Saito[6], Shigeo Murayama[7], Atsushi Iwata[1]
[1]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Department Of Neurology, Tokyo, Japan, [2]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Department Of Diagnostic Radiology, Tokyo, Japan, [3]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Integrated Research Initiative For Living Well With Dementia, Tokyo, Japan, [4]The University of Tokyo hospital, Department Of Neurology, Tokyo, Japan, [5]The Jikei University School of Medicine, Department Of Neurology, Tokyo, Japan, [6]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Department Of Neuropathology (the Brain Bank For Aging Research), Tokyo, Japan, [7]Osaka University, Brain Bank For Neurodevelopmental, Neurological And Psychiatric Disorders, United Graduate School Of Child Development, Osaka, Japan

Aims: Amyloid-beta plays a pivotal role in cognitive decline in Parkinson's disease (PD). The prevalence of amyloid positivity evaluated by cerebrospinal fluid (CSF) of PD without dementia in their sixties is lower than that in the subjects with normal cognition without a diagnosis of PD (subjects with normal cognition) in the same age range. However, it is unclear whether this is also the case in patients with PD without dementia in their eighties. We aimed to identify the prevalence of amyloid positivity in patients with PD without dementia in their eighties using CSF amyloid-beta 42 levels.
Methods: PD patients (UKPDSBB) without dementia who had been diagnosed between 2013 and 2022, and whose duration of parkinsonism was < 5 years were retrospectively evaluated. CSF was obtained at diagnosis. Patients were divided into two groups based on the age at diagnosis (≥73 or <73); a high group and a low group, because its mean age at diagnosis was 80.2 (± 4.4) and 64.9 (± 7.3), respectively.
Results: Forty-nine and 40 patients were included in the high group and the low group, respectively. The prevalence of amyloid positivity was significantly higher in the high group (30.6%) compared to the low group (10.0%) ($p = 0.02$).
Conclusions: The prevalence of amyloid positivity in both groups was lower than that in the subjects with normal cognition in the same age range, because the prevalence of amyloid positivity has been reported to be in the 40% range and 20% range in the subjects with normal cognition in the eighties and sixties, respectively. Our findings suggested that the inhibitory effects on amyloid positivity by α- synuclein may persist regardless of aging.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1112 / #1963

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

QUANTITATIVE DETECTION OF ALPHA-SYNUCLEIN PATHOLOGY IN PARKINSON'S DISEASE SKIN

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

David Holzinger, Bryan Frey, Simone Giaisi, Michael O'Neill, Stefan Barghorn, Roland Heym
AbbVie Deutschland GmbH & Co. K, Neuroscience Discovery, Ludwigshafen, Germany

Aims: Biomarkers to assess progression of α-synuclein pathology and potential treatment effects in Parkinson's disease (PD) patients are currently lacking. Established α-synuclein seed amplification assays (SAA) for cerebrospinal fluid (CSF) have a binary readout and direct detection of α-synuclein pathology in CSF by ligand-binding assays (LBAs) has not been successful. The skin emerges as an attractive alternative to CSF due to presence of α-synuclein aggregates in peripheral nerves and low invasiveness of collection.
Methods: We developed a new LBA for quantification of phosphorylated (pS129) α-synuclein aggregates in skin homogenate and adapted our in-house SAA method for detection of α-synuclein seeding in skin. Using these assays, we characterized a set of 20 postmortem skin samples from control and PD cases with documented Lewy-body pathology in the brain.
Results: pS129 α-synuclein aggregates were significantly increased in PD skin and undetectable in most controls highlighting the specificity for PD. These LBA results were in concordance with the detection of α-synuclein seeding by SAA in the same samples. We observed a strong correlation between LBA and SAA readouts suggesting a relationship between pS129 α-synuclein aggregates and seeding activity in PD skin. Interestingly, the dynamic range of LBA was at least 30-fold higher than SAA highlighting the advantage of LBA for accurate quantification.
Conclusions: Here, we report the successful development of LBA and SAA for detection of pathological α-synuclein in PD skin. Due to its superior quantification LBA for PD skin offers potential for the assessment of pathology progression and treatment effects. We are currently extending our data set to a larger cohort including early Lewy-body stages to further investigate the relationship between α-synuclein pathology in skin and brain.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1113 / #1749

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

LONGITUDINAL MIXED MODEL ANALYSIS REVEALS ALTERATIONS IN THE TRANSCRIPTOME ASSOCIATED TO PARKINSON'S DISEASE L RESULTS FROM THE PDBP STUDY

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Santiago Sanchez, Aleksandra Beric, Laura Ibanez, Yichen Sun, Charissa Martin
Washington University School of Medicine, Psychiatry, Saint Louis, United States of America

Aims: Objectives: Our primary aim was to identify longitudinal changes in linear RNAs associated with Parkinson's Disease (PD) by leveraging one of the largest available datasets.
Methods: We utilized the Parkinson's Disease Biomarkers Program (PDBP) cohort, that includes 2,939 blood samples from individuals of European origin collected at five distinct time points, all with available transcriptomic data. Our analysis involved employing STAR for sequence mapping to the GRCh38 reference genome and Salmon for transcript quantification. We conducted mixed model differential expression analyses to account for data's longitudinal nature. Additionally, pathway and enrichment analyses were conducted, with all significance levels adjusted for multiple testing using the FDR correction.
Results: We identified 290 transcripts associated with PD progression over time: TET2 (p=4.89x10-4, effect size=0.048), B4GALT1 (p=7.51x10-4, effect size=0.045), and NCL (p=1.08x10-4, effect size=-0.050). In PD patients' substantia nigra, B4GALT1 and TET2 have been shown to exhibit increased expression, while NCL shows decreased expression. We also detected upregulated transcripts previously detected in blood samples from PD participants, including MDM4 (p=7.28x10-4, effect size=0.031) and BCL2L11 (p=4.05x10-5, effect size=0.056). Additionally, we found other PD-related transcripts, such as PARP1, OGA, OGT, NDFIP1 and NOTCH2NLC. Enrichment analyses revealed dysregulation in processes related to lysosomal membranes (p=1.90x10-2), protein folding (p=1.00x10-2), Tauopathies (p=1.30x10-2), cerebral degeneration (p=5.00x10-3), and glycosyl transferase activity (p=3.00x10-2), among other glycosylation-related pathways.
Conclusions: Conclusion: Our findings unveil several known PD-related changes in blood that have already been described in the central nervous system. These results suggest the potential of using blood-derived transcriptomic data as PD biomarkers and adds evidence to the holistic nature of central nervous system diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1114 / #2262

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

SERUM LEUCINE-RICH A2 GLYCOPROTEIN AS A POTENTIAL BIOMARKER FOR SYSTEMIC INFLAMMATION IN PARKINSON'S DISEASE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Takashi Kasai, Takuma Ohmichi, Fukiko Kitani-Morii, Yuzo Fujino, Makiko Shinomoto, Toshiki Mizuno
Kyoto Prefectural University of Medicine, Neurology, Kyoto, Japan

Aims: There is ample epidemiological and animal-model evidence suggesting that intestinal inflammation is associated with the development of Parkinson's disease (PD). Leucine-rich α2 glycoprotein (LRG) is a serum inflammatory biomarker used to monitor the activity of autoimmune diseases, including inflammatory bowel diseases. In this study, we aimed to investigate whether serum LRG could be used a biomarker of systemic inflammation in PD and to help distinguish disease states.
Methods: Serum LRG and C-reactive protein (CRP) levels were measured in 66 patients with PD and 31 age-matched controls.
Results: We found that serum LRG levels were statistically significantly higher in the PD group than in the control group (PD: 13.9 ± 4.2 ng/mL, control: 12.1 ± 2.7 ng/mL, $p = 0.036$). LRG levels were also correlated with Charlson comorbidity index (CCI) and CRP levels. LRG levels in the PD group were correlated with Hoehn and Yahr stages (Spearman's $r = 0.40$, $p = 0.008$). LRG levels were statistically significantly elevated in PD patients with dementia as compared to those without dementia ($p = 0.0078$). Multivariate analysis revealed a statistically significant correlation between PD and serum LRG levels after adjusting for serum CRP levels, and CCI ($p = 0.019$).
Conclusions: We conclude that serum LRG levels could be considered a potential biomarker for systemic inflammation in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1115 / #1637

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

OVERCOMING CHALLENGES OF MEASURING SMALL EXTRACELLULAR VESICLE (SEV) BIOMARKERS IN A CLINICAL SETTING

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Christoph Kleinert[1], Hubert Aviolat[2], Michael Schulz[1], Mario Richter[1]
[1]AbbVie Deutschland GmbH & Co. KG, Qtas (dmpk), Ludwigshafen, Germany, [2]AbbVie Deutschland GmbH & Co. KG, Discovery, Ludwigshafen, Germany

Aims: The objectives of analyzing small extracellular vesicles are to simplify diagnosing or monitoring diseases by shifting from biopsy or CSF sampling to blood-based analysis. Some isolation methods lack the clinical requirements of exosomal yield, purity, reproducibility, and throughput. However, these features are essential in biomarker analysis.
Methods: We compared twelve isolation methods, including size exclusion chromatography (SEC), differential centrifugation (DC), bead-based immunoprecipitation (BBIP), polymer-based precipitation (PolyP), and membrane affinity isolation (MAI). The isolated vesicles were characterized by several methods, including: 1.) Appearance of common EV markers. 2.) Depletion of plasma contaminants. 3.) Amount and size distribution of particles. Throughput and technical requirements of each method of isolation and characterization were estimated, which allows judging the feasibility of application in a clinical setting. Further, we evaluated the reproducibility of selected EV purification methods. For the preferred method, we tested the interindividual variability.
Results: Residual protein corresponds largely to protein contaminations like albumin and IgG. SEC sEVs show an excellent depletion of high-density lipoprotein but a copurification of low-density lipoprotein, while the other isolation methods showed contrary results. We used several methods to quantify tetraspanins, like western blot, ELISA, and NanoView analysis. SEC (SmartSEC, qEVsingle35T) and DC samples showed high exosomal yield. Various particle-sizing methods allowed to represent an EV typical distribution, but the validity seems doubtful.
Conclusions: In conclusion, an adapted SEC protocol gave the highest purity with simultaneously high EV marker yield. The reproducibility matched our acceptance criteria, and it revealed the interindividual variability.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1116 / #1777

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

AN ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY FOR HIGHLY SENSITIVE AND SPECIFIC DETECTION OF LEWY-FOLD ALPHA-SYNUCLEINOPATHIES

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Sebastian Longen[1,2], Alexander Bernhardt[3,4], Svenja Trossbach[2], Günter Höglinger[3,4,5], Armin Giese[2], Johannes Levin[2,3,4,5], Torsten Matthias[1,2]
[1]AESKU.Diagnostics GmbH, N/a, Wendelsheim, Germany, [2]MODAG GmbH, N/a, Wendelsheim, Germany, [3]Ludwig-Maximilians-Universität München, Department Of Neurology, Munich, Germany, [4]German Center for Neurodegenerative Diseases (DZNE), Site Munich, Munich, Germany, [5]Munich Cluster for Systems Neurology (SyNergy), N/a, Munich, Germany

Aims: Misfolded alpha-Synuclein aggregates underlie the pathology of Parkinson's Disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), collectively known as alpha-synucleinopathies. These diseases exhibit distinct misfolded alpha-synuclein strains, with MSA characterized by two unique MSA-fold strains and PD/DLB sharing a Lewy-fold strain. Current alpha-synuclein seed amplification assays (SAAs) lack the necessary specificity to differentiate between these strains, posing a challenge for clinical diagnosis. This study aimed to develop a refined SAA with enhanced strain specificity for precise detection of Lewy-fold alpha-synucleinopathies.
Methods: We designed and implemented an improved SAA and optimized the expression and purification of alpha-Synuclein. 180 cerebrospinal fluid samples of patients with a broad spectrum of clinically diagnosed neurodegenerative diseases from the LMU Munich Department of Neurology were analysed in a blinded fashion, including alpha-Synucleinopathies (MSA, PD, DLB), mixed 3-repeat/4-repeat Tauopathies (Alzheimer disease), 4-repeat Tauopathies (progressive supranuclear palsy), frontotemporal dementia and healthy controls. To further validate strain specificity, brain homogenates from 30 neuropathologically diagnosed cases with Lewy body disease, multiple system atrophy, and progressive supranuclear palsy were employed.
Results: Blinded analysis yielded a high sensitivity and specificity for neuropathologically diagnosed Lewy-fold alpha-Synucleinopathies identifying clinically diagnosed PD and DLB samples correctly but not cases with clinically diagnosed MSA, progressive supranuclear palsy, and frontotemporal dementia. Consistent with previous research, a part of Alzheimer's disease cases showed a copathology.
Conclusions: Our refined SAA is characterized by a unique Lewy-fold specificity. It may assist with the *ante mortem* clinical-biological diagnosis of the Lewy-fold alpha-synucleinopathies PD and DLB and the differential diagnosis from multiple system atrophy as well as other parkinsonian syndromes, such as progressive supranuclear palsy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1117 / #405

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PLASMA SER129 PHOSPHORYLATED ALPHA-SYNUCLEIN/TOTAL ALPHA-SYNUCLEIN RATIO DISCRIMINATES PATIENTS AFFECTED BY PARKINSON'S DISEASE FROM CONTROLS

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Francesca Longhena[1], Vanessa Porrini[1], Andrea Pilotto[2], Cristina Gussago[1], Lucia Paolini[1], Paolo Bergese[1], Emirena Garrafa[1], Fiorella Guadagni[3,4], Alessandro Padovani[2], Marina Pizzi[1], Arianna Bellucci[1]
[1]University of Brescia, Department Of Molecular And Translational Medicine, Brescia, Italy, [2]University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy, [3]IRCCS San Raffaele Roma, Interinstitutional Multidisciplinary Biobank (biobim), Rome, Italy, [4]IRCCS San Raffaele Roma, Department Of Radiology, Rome, Italy

Aims: Parkinson's disease (PD) is the most common neurodegenerative disorder characterized by motor symptoms. The deposition of fibrillary aggregated alpha-synuclein (aSyn) in Lewy bodies (LB) and Lewy neurites (LN) is considered a main neurotoxic event in the brain of patients affected by PD. Of note, several lines of evidence support that mature aSyn aggregates contain elevated levels of Ser129-phosphorylated aSyn (pSer129-aSyn), supporting that this post-translationally modified form of the protein may serve as a biormarker for PD. Recent studies showed that pSer129-aSyn is increased in the serum/plasma of PD patients and suggested that pSer129-aSyn levels correlate with motor severity and progression in patients with PD. Here, we aimed at evaluating the relative amount of pSer129-aSyn in the plasma of PD, dementia with LB (DLB) patients and age-matched healthy controls (HC).
Methods: We developed a novel enzyme-linked immunosorbent assay (ELISA) to evaluate the relative amount of pSer-aSyn in plasma, coupled with a standard ELISA protocol for the detection of total aSyn (taSyn).
Results: We found that the ratio p-Ser129-aSyn/taSyn was significantly higher in PD patients when compared with DLB and age-matched HC. While both PD and DLB patients exhibited lower levels of taSyn, only PD patients showed a significant increase of pSer129-aSyn when compared to HC. Notably, taSyn and pSer129-aSyn levels were found to correlate with UPDRS III scores only in the PD group, while no significant correlation was found in the DLB group.
Conclusions: Taken together, these results support that plasma p-Ser129-aSyn/taSyn ratio may enable to discriminate patients affected by PD and DLB and that combined plasma taSyn and pSer129-aSyn levels may serve as biomarkers of PD severity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1118 / #1427

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

VALIDATION OF PROTEOMICS-DERIVED CSF BIOMARKER CANDIDATES IN PARKINSON'S DISEASE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Fabian Maass, Katharina Obermeier, Peter Lange, Christoph Van Riesen
University Medical Center Göttingen, Germany, Dept. Of Neurology, Göttingen, Germany

Aims: Different studies concerning untargeted proteomics analysis of CSF samples of patients with PD can be found in the literature, yielding different regulated protein candidates. But only few of the reported proteins could be reproduced in other proteomics studies. This might be due to multiple factors (demographical, analytical and statistical differences). Concerning non-CNS specific proteins, simultaneous quantification of paired serum and CSF samples could give further information on the variance of CSF levels dependent on correlating serum levels / correlating individual blood brain barrier dysfunction, but this was not considered in the majority of studies. Therefore, we plan to analyze a selection of promising non-CNS specific protein candidates using paired serum and CSF samples of patients with PD, controls and atypical conditions for comparison.
Methods: Paired samples of 23 PD patients, 23 control patients and 15 atypical Parkinsonian patients (PSP, CBD) will be analyzed concerning the levels of Apolipoprotein A1, Gelsolin, Human Zinc Alpha 2 Glycoprotein and Pigment Epithelium Derived Factor (PEDF) levels, applying commercially available ELISA systems. Additionally, the CSF/serum albumin ratio (QAlb) as a marker for blood brain dysfunction is calculated.
Results: For Apolipoprotein A1, no group difference ($p > 0.05$) but a highly significant correlation ($p < 0.0001$) between CSF levels and the corresponding QAlb values could be detected. Analysis of further candidates is in progress and results will be demonstrated at the AD/PD congress.
Conclusions: The individual blood brain barrier dysfunction - as reflected by QAlb - is an important factor concerning the interpretation of CSF levels of non-CNS specific biomarker candidates and could explain some part of the variance of the results of proteomics studies as reported in the literature.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1119 / #2341

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PREDICTING 10-YEAR DISEASE PROGRESSION: NEUROFILAMENT LIGHT CHAIN SERUM LEVELS AS A BIOMARKER IN NEWLY DIAGNOSED PARKINSON'S DISEASE PATIENTS

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Jodi Maple-Grødem[1], Camilla Pedersen[1], Anastasia Ushakova[2], Ole-Bjørn Tysnes[3], Kaj Blennow[4], Henrik Zetterberg[5], Guido Alves[1], Johannes Lange[1]
[1]Stavanger University Hospital, Stavanger, Norway., The Centre For Movement Disorders,, Stavanger, Norway, [2]Stavanger University Hospital, Department Of Research, Stavanger, Norway, [3]Haukeland University Hospital, Bergen, Norway, Department Of Neurology, Bergen, Norway, [4]Gothenburg University, Psychiatry And Neurochemistry, Göteborg, Sweden, [5]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden

Aims: The role of neurofilament light chain (NFL) as a potential biomarker for Parkinson's disease (PD) severity and progression has yielded varying findings. This study seeks to examine serum NFL levels at the time of PD diagnosis and their correlation with disease progression during the first ten years of disease.
Methods: Serum NFL was measured in up to 172 PD patients and 194 healthy controls from the Norwegian ParkWest cohort at baseline, three years, and five years. Linear mixed-effects regression analysis was employed to assess changes in NFL levels from baseline to year 5 and the association between NFL and repeated measures of MMSE and UDPRS part III scores up to 9.6 years.
Results: PD patients exhibited higher serum NFL levels compared to controls at all time points, and NFL increased more rapidly over five years than in the control group. Elevated baseline NFL in PD correlated with accelerated cognitive and motor decline. Moreover, higher rates of change in serum NFL were linked to faster disease progression.
Conclusions: This study underscores the association of serum NFL with PD and the severity and change of cognitive and motor impairment. The findings suggest that serum NFL holds promise as a biomarker to predict and track disease progression in PD, warranting inclusion in future biomarker panels for the disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1120 / #2007

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EVIDENCE FOR ALPHA-SYNUCLEIN AGGREGATION IN OLDER INDIVIDUALS WITH HYPOSMIA: A BIOMARKER SIGNATURE FOR PARKINSON DISEASE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ken Marek[1], David Russell[1], Luis Concha-Marambio[2], Christopher Coffey[3], Michael Brumm[4], Danna Jennings[1], Seung Ho Choi[4], Ethan Brown[5], Matthew Stern[6], John Seibyl[1], Claudio Soto[7], Andrew Siderowf[6]
[1]Institute for Neurodegenerative Disorders, N/a, New Haven, United States of America, [2]Amprion, R&d Unit, San Diego, United States of America, [3]University of Iowa, Clinical Trials Statisitcal & Data Management Center,, Iowa City, United States of America, [4]The University of Iowa, Neurology, iowa City, United States of America, [5]University of California San Francisco, Neurology, San Francisco, United States of America, [6]University of Pennsylvania, Neurology, Philadelphia, United States of America, [7]University of Texas, Medical School, Houston, United States of America

Aims: Objectives: The Parkinson Associated Risk syndrome (PARS) study is designed to identify a Parkinson disease (PD) biomarker/clinical marker derived cohort enriched to develop typical symptoms of PD. **Background:** PARS participants were enrolled from the community using a sequential clinical marker/biomarker strategy testing olfactory function remotely followed by dopamine transporter (DAT) imaging. About 4800 individuals returned a University of Pennsylvania Smell Identification test (UPSIT), and 203 hyposmic (<15% UPSIT by age and sex) and 100 normosmic participants were evaluated with extensive clinical evaluation and DAT imaging. Individuals with hyposmia were enriched for DAT deficit and were likely to develop symptoms of PD within four years.
Methods: Methods: PARS participants in clinic were followed longitudinally for up to six years with DAT imaging every two years. 99 of the 303 participants (27 normosmic, 72 hyposmic) underwent lumbar puncture during the 6-year follow-up. CSF were blindly analyzed using Amprion's α-synuclein seed amplification assay **(**αS-SAA).
Results: Results: Among the hyposmic participants 34/72 (47.2%) are αS-SAA positive, 36/72 (50%) are αS-SAA negative and 2 are inconclusive. Among normosmic participants 1/25 (4%) are αS-SAA positive. The majority of both α-syn SAA positive (74%) and α-syn SAA negative (92%) hyposmics had no DAT deficit at the baseline visit. During the study, there was a strong trend for α-syn SAA positive hyposmics to be more likely have a DAT deficit compared to α-syn SAA negative hyposmics (12/34 (35%) vs. 4/36 (11%). Among DAT deficit hyposmic SAA positive 8/11 participants developed PD symptoms compared to 0/3 DAT deficit hyposmic SAA negative.
Conclusions: Conclusion: Hyposmics in the PARS cohort demonstrate widespread synuclein pathology that precedes DAT deficit. These data may enable therapeutic PD studies to prevent the onset of clinical PD syndromes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1121 / #2082

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

LIPIDOMIC PROFILE OF CIRCULATING BIOFLUIDS TO DISCOVER BIOMARKERS ASSOCIATED TO DIFFERENT TYPES OF THERAPY IN PARKINSON'S DISEASE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Nicole Piera Palomba[1], Federica Carrillo[2], Giorgio Fortunato[2], Marco Ghirimoldi[3], Marcello Manfredi[3], Sara Pietracupa[1], Nicola Modugno[1], Paola Signorelli[4], Teresa Esposito[1]
[1]IRCCS Neuromed, Neurology, Pozzilli (IS), Italy, [2]Institute of Genetics and Biophysics CNR, Biomedicine, Napoli, Italy, [3]University of Piemonte Orientale, Department Of Translational Medicine, Alessandria, Italy, [4]University of Milan, Aldo Ravelli Center For Neurotechnology And Experimental Brain Therapeutics, Milan, Italy

Aims: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons of substantia nigra pars compacta due to the formation of alpha-synuclein aggregates. Currently, only symptomatic therapies are available, and long-term treatments are associated with adverse effects. It is demonstrated that circulating lipids may mirror the alteration of cellular pathways. In this study, we explored whether long-term treatment of PD patients induced altered lipid metabolism.
Methods: Untargeted lipidomics strategy using ultra performance liquid chromatography was performed to obtain lipidomic signature. We also used multiplex ELISA assay to measure circulating biomarkers such as leptin, ghrelin, FABP3, FABP7, TNF-alpha, Gro-alpha, BDNF and GFAP. The study cohort included three groups of PD patients: the first treated with standard L-Dopa-based therapy, the second with deep brain stimulation (DBS) and L-Dopa-based maintenance therapy, and the last of untreated patients in the early stage of PD. A group of matched controls was also investigated.
Results: We found an extensive dysregulation of lipid profile in PD patients compared to controls. Specifically, we found elevated triglycerides (TG) levels in all PD patients, increased phosphatidylcholine (PC-O) only in untreated patients and lower levels of sphingomyelin (SM) in two treated groups compared to healthy subjects. Interestingly, we also observed a downregulation of Ether-linked Lyso-phosphatidyl-ethanolamine (LPE-O) and fatty acid (FA) in DBS compared to L-Dopa-treated patients. Furthermore, untreated patients showed a decreased level of FABP3 and FABP7 markers of lipid mobilization and catabolism, while only DBS patients showed an increase in TNF-α, marker of neuroinflammation.
Conclusions: These data, although preliminary, may be encouraging to extent this analysis to a larger cohort of patients to discover new biomarkers for therapeutic drug monitoring and identify novel targets that will improve long-term treatments for PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1122 / #1717

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PERFORMANCE OF A SEED AMPLIFICATION ASSAY FOR MISFOLDED ALPHA-SYNUCLEIN IN CEREBROSPINAL FLUID AND BRAIN TISSUE IN RELATION TO LEWY BODY DISEASE STAGE AND PATHOLOGY BURDEN

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Piero Parchi[1,2], Giuseppe Mario Bentivenga[1], Angela Mammana[2], Simone Baiardi[1], Marcello Rossi[2], Alice Ticca[1], Franco Magliocchetti[2], Andrea Mastrangelo[1], Sabina Capellari[1]
[1]University of Bologna, Department Of Biomedical And Neuromotor Sciences, Bologna, Italy, [2]IRCCS, Instituto Delle Scienze Neurologiche Di Bologna, Bologna, Italy

Aims: 1) To evaluate the diagnostic performance of a seed amplification assay for misfolded alpha-synuclein (αSyn SAA) in antemortem CSF of patients with a neuropathological diagnosis. 2) To study the relationship between SAA kinetic parameters, the number of αSyn brain seeds and the LBD burden assessed by immunohistochemistry.
Methods: We tested 269 antemortem CSF samples and 138 serially diluted brain homogenates from patients with LBD in different stages by the αSyn Real-Time Quaking-Induced Conversion (RT-QuIC) SAA. Moreover, we looked for LB pathology by αSyn immunohistochemistry in a consecutive series of 604 Creutzfedt-Jakob disease (CJD)-affected brains.
Results: CSF αSyn RT-QuIC showed 100% sensitivity in detecting LBD in limbic and neocortical stages. The assay sensitivity was significantly lower in early stages (37.5% in Braak 1 and 2, 73.3% in Braak 3) or focal pathology (50% in amygdala-predominant). The number of CSF αSyn RT-QuIC positive quadruplicate fluorescence curves significantly correlated with the LBD stage. Brain αSyn RT-QuIC showed higher sensitivity than immunohistochemistry for detecting misfolded αSyn. In the latter, the kinetic parameter lag phase (time to threshold) strongly correlated with the αSyn seed concentration. Finally, incidental LBD prevalence was 8% in the CJD cohort.
Conclusions: The present results indicate that (a) CSF αSyn RT-QuIC has high specificity and enough sensitivity to detect all patients with LB pathology at Braak stages >3 and most of those at stage 3; (b) Brain deposition of misfolded αSyn precedes the formation of LB and Lewy neurites; (c) αSyn RT-QuIC provides "quantitative" information regarding the LB pathology burden, with the lag phase and the number of positive replicates being the most promising variables to be used in the clinical setting.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1123 / #400

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

MIRO1 AS A NOVEL PERIPHERAL DRUG-RESPONSIVE BIOMARKER FOR PD PATIENT IDENTIFICATION AND SEGMENTATION

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Sean Pintchovski, Atossa Shaltouki, Eric Beattie, Chung-Han Hsieh, Wesley Sun, Bill Shrader
Acurex Biosciences, Biology, San Carlos, United States of America

Aims: Defects in mitophagy, the process for recycling damaged mitochondria, are a major pathological driver of Parkinson's disease (PD) and other neurodegenerative disorders. The protein Miro1 must be released from mitochondria for normal mitophagy to proceed. Interestingly, Miro1 retention was discovered in post-mortem PD brain tissues and PD patient iPSC dopaminergic neurons. Additionally, Miro1 retention was observed in PD patient fibroblasts, serving as a novel peripheral biomarker to distinguish healthy from PD subjects. This study has two objectives: 1. Determine whether the Miro1 biomarker is detectable in more clinically tractable peripheral blood mononuclear cells (PBMCs) from PD subjects. 2. Evaluate the efficacy of Acurex's therapeutic compound CU-00048 to trigger Miro1 release from damaged mitochondria in PBMCs from PD subjects.
Methods: Establish a robust *ex vivo* mitophagy assay to quantify Miro1 protein levels in PBMCs obtained from PD patients and age- / sex-matched healthy controls.
Results: The Miro1 biomarker was observed in PBMCs collected from both sporadic and genetically defined (G2019S LRRK2) PD subjects. Treatment with Acurex's best-in-class Ca_V3 calcium channel antagonist, CU-00048, effectively rescued Miro1 levels in both PD subgroups.
Conclusions: Preliminary findings suggest that the PBMC Miro1 assay is a high-fidelity clinical biomarker, enabling the rapid identification and segmentation of PD subjects. Miro1 rescue by CU-00048 could identify potential clinical responders and determine their optimal drug dosage, thereby significantly reducing risk in early clinical trials. Through larger longitudinal studies, the Miro1 biomarker will improve our understanding of disease progression in pre-symptomatic PD subjects, enabling targeted treatment at the earliest disease stages. The innovative PBMC Miro1 biomarker test is poised to advance a new era of precision medicine, significantly boosting the likelihood of therapeutic efficacy and improving the quality of life for PD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1124 / #1065

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

PROFILE OF GLUCOCEREBROSIDASE 1 (GCASE) ACTIVITY AND GLUCOSYLSPHINGOSINE LEVELS IN GBA-PD, PD PATIENTS AND HEALTHY VOLUNTEERS

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Nuno Pires[1], Bruno Igreja[1], Guillermo Castilla-Fernández[2], Wouter Bakker[3], Michel Çakici[3], Maurits Vissers[3], Philip Kremer[3], Daniela Almeida[1], Luís Magalhães[1], Joerg Holenz[1]
[1]BIAL - Portela & C[a], S.A., Research & Development, Coronado, Portugal, [2]BIAL - R&D Investments, S.A., Research & Development, Coronado, Portugal, [3]CHDR, Neurology, Leiden, Netherlands

Aims: Heterozygous glucocerebrosidase 1 (*GBA1*) pathogenic variants are the most common genetic risk factor for Parkinson's disease (PD). The aim of this study was to assess whether glucocerebrosidase (GCase) enzyme activity and glucosylsphingosine (GlcSph) levels (enzyme substrate) differs between GBA-PD and idiopathic PD patients compared to healthy volunteers (Toetsing Online number: NL79102.100.21).
Methods: GCase activity in dried blood spots (DBS) and GlcSph levels in plasma were analyzed from healthy volunteers (n=8), idiopathic PD patients (n=8) and GBA-PD patients (n=8).
Results: No statistically significant intra- and inter-day variability in GCase activity in DBS was observed. GCase activity in DBS was statistically significantly lower in GBA-PD compared with idiopathic PD patients and healthy volunteers [-2.30 (0.67) and -2.70 (0.67) µmol/L mean (SE) difference, p=0.003 and 0.001 respectively], whilst plasma GlcSph levels were statistically higher in GBA-PD patients compared with idiopathic PD patients and healthy volunteers [0.45 (0.15) and 0.54 (0.15) pmol/mL mean (SE) difference, p=0.007 and 0.002 respectively]. No statistically significant differences for GCase activity and plasma GlcSph levels between idiopathic PD patients and healthy volunteers were detected.
Conclusions: Heterozygous *GBA1* mutations had a relevant functional impact on GCase activity in DBS and on GlcSph in plasma. Further studies are being conducted to refine their use as biomarkers in clinical trials targeting GBA-PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1125 / #780

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ASSOCIATION OF PLASMA NEUROFILAMENT LIGHT CHAIN WITH CLINICAL MANIFESTATIONS IN DEMENTIA WITH LEWY BODIES

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Íñigo Rodríguez-Baz[1], Javier Arranz[1], Nuole Zhu[1,2], Sara Rubio[1,2], Elena Vera[1,2], Isabel Sala[1,2], Juan Fortea[1,2], Alberto Lleó[1,2], Daniel Alcolea[1,2]
[1]Sant Pau Biomedical Research Institute, Universitat Autònoma de Barcelona, Sant Pau Memory Unit, Department Of Neurology, Barcelona, Spain, [2]Biomedical Research Network Center for Neurodegenerative Diseases, CIBERNED, Spain, Memory Unit, Barcelona, Spain

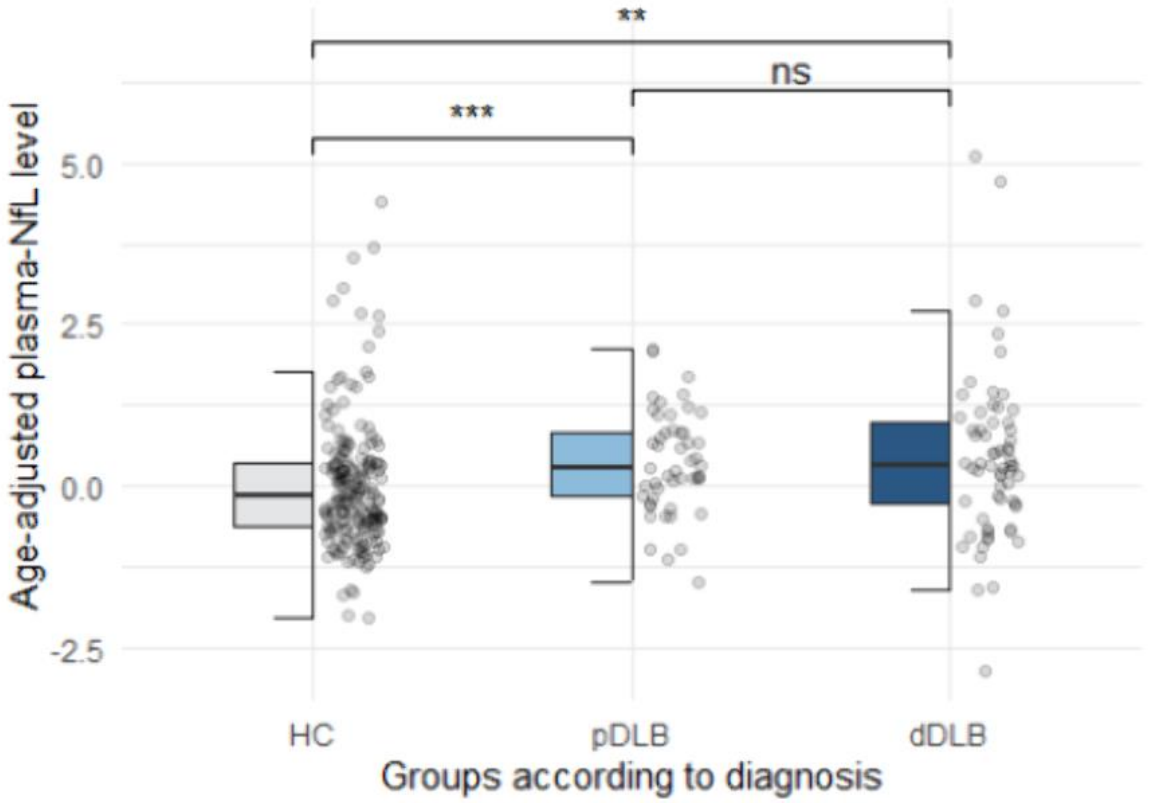
Aims: Our aim was to investigate plasma neurofilament light chain (NfL) level variations in patients with Dementia with Lewy Bodies (DLB) and their correlation with manifested symptoms.
Methods: We assessed NfL levels in plasma samples from patients at prodromal (pDLB) and dementia (dDLB) stages of DLB, along with healthy controls (HC) assessed between 2017 and 2022 at the Sant Pau Memory Unit in Barcelona. Considering the association between NfL concentrations and age in HC, we adjusted NfL by age in DLB patients. We compared concentrations between groups and evaluated their association with the presence of Alzheimer's co-pathology (identified via cerebrospinal fluid biomarkers), core clinical symptoms (cognitive fluctuations, hallucinations, REM sleep behaviour disorder, parkinsonism), and disease severity.
Results: We included 312 participants, comprising 56 with pDLB, 70 with dDLB, and 186 HC. The mean age in our cohort was 63.7±13.6 years, 57.7% female. NfL concentrations were higher in DLB patients (+0.41SD, p=0.002) compared to HC (+0.36SD in pDLB and +0.44SD in dDLB). Having co-existing Alzheimer's pathology had no significant effect on NfL concentration. Likewise, we found no differences based on core symptom presence (neither number nor duration). dDLB patients in the highest quartile of NfL concentrations exhibited poorer cognitive performance on the MMSE, compared to those in the lowest quartile ($\bar{x}$25.7±2.8 Vs $\bar{x}$21.3±5.7;
p=0.013).

Table 1. Demographics

	Healthy control (n=186)	pDLB (n=56)	dDLB (n=70)
Age (years)*	55.5 (11.1)	74.5 (5.4)	76.7 (5.3)
Sex			
Female	118 (63.4%)	30 (53.6%)	32 (45.7%)
Male	68 (36.6%)	26 (46.4%)	38 (54.3%)
Plasma NfL (pg/ml)*	11.7 (13.2)	19.3 (8.7)	28.9 (44.6)
Alzheimer's co-pathology			
A+T+	NA	15 (26.8%)	24 (35.3%)
A-T-	NA	30 (53.6%)	30 (44.1%)
AT intermediate	NA	11 (19.6%)	14 (20.6%)
MMSE score*	29.3 (0.9)	26.2 (2.6)	22.5 (4.6)
Core symptoms presence			
Cognitive fluctuations	NA	33 (64.7%)	49 (79.0%)
Visual hallucinations	NA	21 (38.9%)	45 (66.2%)
RBD	NA	34 (61.8%)	39 (65.0%)
Parkinsonism	NA	51 (91.1%)	69 (98.6%)
Core symptoms accumulation			
One	NA	7 (12.5%)	4 (5.7%)
Two	NA	25 (44.6%)	15 (21.4%)
Three	NA	14 (25.0%)	36 (51.4%)
Four	NA	10 (17.9%)	15 (21.4%)
Duration of symptoms from cognitive impairment (months)			
Cognitive fluctuations**	NA	22.8 (11.4 ; 49.0)	24.0 (5.8 ; 45.1)
Visual hallucinations**	NA	0 (-10.2 ; 40.6)	13.2 (0.0 ; 67.3)
RBD**	NA	-32.0 (-119.4 ; 29.2)	-3.3 (-40.3 ; 7.4)
Parkinsonism**	NA	12.7 (2.0 ; 36.2)	6.3 (0.0 ; 33.4)
UPDRS-III score*	NA	20 (12.3)	20.8 (9.2)

**Mean (SD), **median (25p ; 75p). pDLB=prodromal dementia with Lewy bodies; dDLB=dementia with Lewy Bodies in the dementia stage; MMSE= Mini-mental state examination; NA = Not applicable; NfL= neurofilament light chain; RBD=REM sleep Behaviour Disorder; UPDRS-III=Unified Parkinson's Disease Rating Scale-Part III.*

Figure 1. Plasma neurofilament light chain concentration according to diagnosis.



HC=Healthy controls; pDLB=prodromal dementia with Lewy bodies; dDLB=dementia with Lewy Bodies in the dementia stage; NfL= neurofilament light chain.

Conclusions: Our results suggest that plasma NfL concentrations increase in DLB patients as early as in prodromal disease stages and may be linked to cognitive performance in dementia stages.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1126 / #994

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ASSOCIATION BETWEEN PLASMA AMYLOID-B BIOMARKER AND NEUROPSYCHOLOGICAL SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Yuji Saitoh[1,2], Kotaro Hattori[3], Yuji Takahashi[1]
[1]National Center of Neurology and Psychiatry, Neurology, Kodaira, Tokyo, Japan, [2]Tokyo Metropolitan Neurological Hospital, Neurology, Fuchu, Japan, [3]National Center of Neurology and Psychiatry, Medical Genome Center, Kodaira, Tokyo, Japan

Aims: Amyloid-β (Aβ) is a major neuropathological hallmark in Alzheimer's disease (AD) and commonly co-exist in Lewy body disease (LBD). Aβ may play an important role in developing neuropsychological symptoms such as a cognitive decline in patients with LBD. As a non-invasive technique, the development of a reliable plasma biomarker detecting Aβ allows us to predict the brain Aβ burden in patients with AD. However, it is not well evaluated whether the plasma Aβ biomarker is associated with neuropsychological symptoms of LBD. The purpose of our study was to investigate the relationship between plasma Aβ biomarker and neuropsychological symptoms in patients with Parkinson's disease (PD).
Methods: Plasma Aβ biomarker composite score, calculated from plasma Aβ precursor protein $(APP)_{669-711}$/ $Aβ_{1-42}$ and $Aβ_{1-40}$/ $Aβ_{1-42}$, originally reported by Nakamura et al. in 2018, were measured in 32 patients with PD. A retrospective review of medical records was performed to identify the comorbidity of the major neuropsychological symptoms in PD, including cognitive decline, delusion, and hallucination, of these patients in the clinical course. We conducted a Chi-squared test to evaluate the association between the plasma Aβ biomarker and neuropsychological symptoms.
Results: Among 32 patients with PD, 10 patients showed the abnormal plasma Aβ biomarker composite score. Chi-squared test with Yates' continuity correction revealed that abnormal composite plasma Aβ biomarker score was significantly associated with the development of both dementia ($\chi^2(1)=7.13$, $p=0.0076$) and hallucinations ($\chi^2(1)=3.85$, $p=0.0498$) in the clinical course, but delusion was not ($\chi^2(1)=0.0831$, $p=0.773$).
Conclusions: In our cohort, abnormal plasma Aβ biomarker composite score predicts the development of cognitive decline and hallucination in patients with PD. Further validation studies are required to confirm these findings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1127 / #1508

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

BIOMARKERS IN PARKINSON'S DISEASE: PAST, PRESENT, AND FUTURE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Pratibha Sharma[1], Rajinder Dhamija[2]
[1]Institute of Human Behaviour and Allied Sciences, Human Behaviour Department, Delhi, India, [2]Institute of Human Behaviour and Allied Sciences, Director And Professor Neurology, Delhi, India

Aims: Background: Parkinson's disease (PD) is a neurodegenerative disease that affects millions of people worldwide. The diagnosis of PD can be challenging due to the lack of specific biomarkers and the reliance on clinical symptoms and medical history.
Methods: This study sheds light on the past, present, and future of biomarkers in PD research.
Results: In the past, researchers have identified several potential biomarkers, including dopamine transporter imaging, CSF biomarkers, and genetic markers. However, these biomarkers lacked the sensitivity and specificity required for accurate diagnosis and monitoring of PD. Currently, significant progress has been made in the field of PD biomarkers, and biomarkers such as alpha-synuclein have shown promise as potential diagnostic and prognostic markers. Imaging techniques, such as PET scans, utilizing ligands that bind to alpha-synuclein aggregates may be useful in diagnosis. CSF biomarkers, including alpha-synuclein, tau, and DJ-1, have shown some potential in detecting PD pathology. However, further validation and standardization are required for their use in clinical practice.
Conclusions: Recent advancements in genomics, proteomics technologies and bioinformatics, may lead to the identification of genetic markers that can predict an individual's risk of developing PD or their disease progression. While the field of PD biomarkers has made significant progress, several challenges need to be addressed. The role of biomarkers in PD diagnosis, risk, and progression has been discussed. The future of PD biomarkers holds great potential, with the development of novel imaging techniques, genetic, and protein biomarkers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1128 / #454

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

DEVELOPMENT AND TESTING OF A GLUCOCEREBROSIDASE ACTIVITY ASSAY TO EVALUATE TARGET ENGAGEMENT OF ALLOSTERIC GCASE ACTIVATORS IN WHOLE BLOOD SAMPLES

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Daniel Ysselstein[1], Maria Nguyen[1], Jennifer Hu[1], Eric Zluhan[1], Eva Thijssen[2], Philip Kremer[2], Mackenzie Hagey[3], Omer Siddiqui[3], Jesse Cedarbaum[3], Jim Sullivan[1], Kevin Hunt[1]
[1]Vanqua Bio, Research And Development, Chicago, United States of America, [2]CHDR, Neurology, Leiden, Netherlands, [3]Vanqua Bio, Developement, Chicago, United States of America

Aims: Heterozygous loss-of-function mutations in the gene *GBA1*, which encodes for glucocerebrosidase (GCase), are a major risk factor for the development of Parkinson's disease (PD). Vanqua Bio has developed novel, small-molecule allosteric activators that significantly increase GCase activity. Current methods to assess GCase activity fail to evaluate GCase activity within the lysosomal environment, where an allosteric activator functions. We aimed to develop and test a novel assay to assess lysosomal GCase activity in fresh blood samples, in order to measure target engagement by the Vanqua GCase activator, VQ-101, in Phase 1 clinical studies.
Methods: An assay to assess lysosomal GCase activity was developed and transferred to two independent labs. Intra-day, before and after food, and inter-day assessment of GCase activity was measured to determine natural fluctuations in GCase activity and to understand potential food effects in a Phase 0 study of healthy volunteers (HV) and GBA-PD patients. Activation of GCase by VQ-101 in peripheral blood from HV, iPD, and GBA-PD subjects was assessed by spiking VQ-101 into blood samples and assessing GCase activity. Finally, non-human primates (NHPs) were dosed with VQ-101 and GCase activity was assessed longitudinally.
Results: The GCase activity assay was successfully transferred to independent labs with consistent measurements obtained across both sites. Minimal intra- and inter-day fluctuations in GCase activity was observed with no evidence of a food effect. Concentration-dependent activation of GCase was observed after spike of VQ-101 into fresh blood samples from HV, iPD, and GBA-PD subjects. Lastly, NHPs dosed with VQ-101 demonstrated robust activation of GCase over 24 hours.
Conclusions: We have developed a robust assay to measure live-cell GCase activity in humans that will enable assessment of target engagement by GCase activators in early clinical development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1129 / #435

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

ASSOCIATION OF CSF BIOMARKERS WITH DAT SPECT AND MIBG CARDIAC SCINTIGRAPHY IN PARKINSON'S DISEASE

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ryosuke Shimasaki[1], Masanori Kurihara[1,2], Keiko Hatano[1], Ryoji Goto[1], Kenichiro Taira[1], Ryoko Ihara[1], Mana Higashihara[1], Yasushi Nishina[1], Masashi Kameyama[3,4], Atsushi Iwata[1,2]
[1]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Department Of Neurology, Tokyo, Japan, [2]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Integrated Research Initiative For Living Well With Dementia, Tokyo, Japan, [3]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Department Of Diagnostic Radiology, Tokyo, Japan, [4]Tokyo Metropolitan Institute for Geriatrics and Gerontology, Research Team For Neuroimaging, Tokyo, Japan

Aims: Cerebrospinal fluid (CSF) concentrations of homovanillic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA), the dopamine and serotonin metabolites, had been shown to decrease in Parkinson's disease (PD). The aim of this study was to evaluate the relationships between these CSF biomarkers and imaging biomarkers, striatal dopamine transporter (DAT) SPECT using ^{123}I-ioflupane and cardiac scintigraphy using ^{123}I-MIBG (MIBG), in PD patients.
Methods: We retrospectively reviewed 58 patients with drug-naïve PD receiving DAT SPECT, MIBG, and lumbar puncture from September 2021 to August 2023. The Z-score of the bilateral averaged striatal DAT standard binding ratio (averaged-SBR Z-score) was measured with DAT SPECT, and MIBG was judged as positive or negative results by expert readings.
Results: Mean age was 75.5 ± 8.7 years old. Thirty-one were male and 27 were female. Thirty-four were MIBG-positive and 24 were MIBG-negative. Averaged-SBR Z-score was -3.41±1.01. HVA was 25.2±12.5 ng/ml and 5-HIAA was 14.2±5.3 ng/ml. Significant difference was observed in 5-HIAA ($t=3.80$, $p<0.001$) between MIBG-positive and MIBG-negative groups. Logistic regression analysis with MIBG-negative or MIBG-positive as the dependent variable and age, sex, HVA and 5-HIAA as independent variables showed no significant difference in age, sex and HVA, but a significant difference in 5-HIAA (odds ratio=0.747, $p=0.005$). Averaged-SBR Z-score correlated with HVA ($r=0.484$, $p<0.001$) and 5-HIAA ($r=0.365$, $p=0.005$). Multiple regression analysis with averaged-SBR Z-score as the dependent variable and age, sex, HVA and 5-HIAA as independent variables showed no correlation in age, sex and 5-HIAA, but a correlation in HVA ($t=3.539$, $p<0.001$).
Conclusions: Our study showed that striatal DAT binding associated with HVA and cardiac MIBG associated with 5-HIAA. These results suggest some pathophysiological links between serotonin concentration in the central nervous system and degeneration of the cardiac sympathetic systems.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1130 / #637

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

A NOVEL PS129 ALPHA-SYNUCLEIN SIMOA HOMEBREW ASSAY THAT POTENTIALLY CAPTURES THE PATHOLOGICAL FORM OF ALPHA-SYNUCLEIN.

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Jeroen Vanbrabant[1], Leentje Demeyer[1], Cindy François[1], Giovanni Bellomo[2], Anna Lidia Wojdała[2], Davide Chiasserini[3], Lorenzo Gaetani[2], Lucilla Parnetti[2], Erik Stoops[1]
[1]ADx NeuroSciences, R&d, Gent, Belgium, [2]University of Perugia, Laboratory Of Clinical Neurochemistry, Section Of Neurology, Department Of Medicine And Surgery, Perugia, Italy, [3]University of Perugia, Section Of Physiology And Biochemistry, Department Of Medicine And Surgery, Perugia, Italy

Aims: The detection of alpha-synuclein phosphorylated at serine129 (pS129Syn) in human biofluids remains challenging considering its low abundance and the complexity of alpha-synuclein diversity in the pathology of synucleinopathies. However, the potential of pS129Syn as a biomarker of synucleinopathy is established in tissues. Our work describes a novel Simoa Homebrew immunoassay for detection of pS129Syn in human cerebrospinal fluid (CSF) using a monoclonal antibody (mAb) pair with documented specificity.
Methods: Specificity of the pS129Syn mAb (code#RD-091) and pan alpha-synuclein mAb (code#RD-006) was assessed by mapping the epitopes using (phosphorylated) synthetic peptides. For the novel assay, a number of analytical performance parameters were evaluated, i.e.: measuring range, precision, LLOQ and specificity, using commercially sourced non-clinical CSF.
Results: The pS129syn antibody was mapped in the region aa128-138 (not containing tyrosine125), suggesting a different (phospho-)specificity when compared to reference mAb MJF-R13 that maps in the aa125-131 region. Pan alpha-synuclein mAb RD-006 has an epitope in the aa 99-110 region. The Simoa Homebrew assay displayed an average intra- and inter-assay variability of 1.3%CV and 12.9%CV, respectively, for a 3-member CSF QC-panel. For all samples measured (CSF: n=21; plasma: n=19), the pS129syn concentrations were within the measuring range of the assay (0.25 to 25 pg/mL). The assay was specific for pS129Syn up to 10.000 pg/mL of spiked recombinant alpha-synuclein in remnant CSF.
Conclusions: A prototype Simoa Homebrew pS129Syn assay was established, based on an antibody pair characterized for pS129Syn specificity. Our results suggest that this novel pS129Syn prototype assay may detect pathological pS129Syn species. Further clinical exploration of this assay is warranted, e.g., by testing a cohort of paired CSF-plasma samples characterized by an alpha-synuclein seed amplification assay.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1131 / #1527

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

EXPLORING INTESTINAL ALTERATIONS IN PARKINSON`S DISEASE THROUGH STOOL ANALYSIS OF PATIENTS

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Martin Weidenfeller[1], Verena Schmitt[1], Alexandra Cosma[1], Magdalena Bolsinger[1], Franz Marxreiter[1], Mario Zaiss[2], Patrick Süß[1], Friederike Zunke[1], Stefan Wirtz[3], Jürgen Winkler[1], Wei Xiang[1]
[1]University Hospital Erlangen, Molecular Neurology, Erlangen, Germany, [2]University Hospital Erlangen, Internal Medicine 3, Erlangen, Germany, [3]University Hospital Erlangen, Medicine 1, Erlangen, Germany

Aims: Parkinson's disease (PD) is characterized by prodromal gastrointestinal (GI) inflammatory symptoms. Acumulating evidence points to a gut-to-brain spread of PD associated mediators. Analyzing patient stool offers a unique, non-invasive approach to uncover GI-tract changes. This study delved into whether gut content affects the brain through investigating the response of astrocytes to PD stool extracts. Moreover, we explored alterations in PD stool samples by focusing on i) the quantity of eukaryotic and prokaryotic cells, ii) calprotectin levels as a GI inflammation marker, iii) protein acetylation (PA) linked to gut inflammation, and iv) microbiota composition.
Methods: To assess astrocytic responses, primary mouse astrocytes were exposed to stool extracts, and glutamate transporter 1 (GLT1) expression was assessed via RT-PCR. Cell composition in the stool was analyzed by estimating prokaryotic and eukaryotic cells using PCR for 16S and 18S rRNA genes, respectively. Calprotectin and PA levels were measured through immunoblotting. Microbiome analysis was performed using 16S rRNA sequencing.
Results: Astrocytes exposed to PD stool extracts exhibited significantly reduced GLT1 expression compared to controls. PD stool samples showed an increase of prokaryotic cells and a significant decrease in eukaryotic cells. Elevated calprotectin levels and reduced PA levels were observed in PD stool. Altered microbiota in PD stool were observed, with *Faecalibacterium* consistently decreased.
Conclusions: Our findings suggest that PD stool contains mediators affecting astrocytes differently compared to control stool extracts. We also observed significant changes in stool cell composition, protein patterns, and microbiota in PD-derived stool. While stool composition may not fully reflect GI alterations, our data supports the potential of stool analysis as a surrogate and stratification method for PD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1132 / #2953

Poster Topic: *Theme C: α-Synucleinopathies / C04.f. Imaging, Biomarkers, Diagnostics: CSF, blood, body fluid biomarkers*

A NOVEL SEEDING AMPLIFICATION IMMUNOASSAY (SAIA) APPROACH FOR DETECTING ALPHA-SYNUCLEIN AGGREGATES IN CSF

POSTERS: C04.F. IMAGING, BIOMARKERS, DIAGNOSTICS: CSF, BLOOD, BODY FLUID BIOMARKERS

Ilham Abdi[1], Indulekha Sudhakaran[1], Simona Ghanem[1], Nishant Vaikath[1], Nour Majbour[1], Vasilios C. Constantinides[2], Elisabeth Kapaki[2], George Paraskevas[2], Wilma Van De Berg[3], Daniel Erskine[4], Kostas Vekrellis[5], Michael Schlossmacher[6], Omar El-Agnaf[1]
[1]Qatar Biomedical Research Institute, Qatar Foundation, Neurological Disorder Research Center, Doha, Qatar, [2]School of Medicine, National and Kapodistrian University of Athens, Eginition Hospital, First Department Of Neurology, Athens, Greece, [3]Vrije Universiteit Amsterdam, Amsterdam UMC, Section Clinical Neuroanatomy And Biobanking, Department Of Anatomy And Neurosciences,, Amsterdam, Netherlands, [4]Newcastle University, Ageing Research Laboratories, Newcastle upon Tyne, United Kingdom, [5]Biomedical Research Foundation of the Academy of Athens, Division Of Basic Neurosciences, Athens, Greece, [6]University of Ottawa, Brain And Mind Research Institute, Ottawa, Canada

Aims: The lack of sensitive and specific biomarkers for α-synucleinopathies, such as Parkinson's disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB), presents a significant challenge in diagnostics and disease monitoring. We aimed to develop and characterize a novel diagnostic assay, Seeding Amplification ImmunoAssay (SAIA), for its quantitative, highly sensitive, and disease-specific detection of alpha-synuclein seeds in synucleinopathies
Methods: SAIA was assessed for its analytical performance in a pilot study using brain homogenates from PD, MSA, DLB cases, and age-matched controls. Additionally, SAIA's application was explored in cerebrospinal fluid (CSF) samples from discovery cohort of PD subject and controls.
Results: SAIA demonstrated remarkable performance in amplifying and detecting α-synuclein seeds in brain homogenates, with dilutions up to 6,400-fold and detection thresholds as low as 0.5 attogram. The assay effectively distinguished synucleinopathies from non-synucleinopathies and controls, achieving sensitivities and specificities between 80-100%, as evidenced by area under the curve values exceeding 0.9. Notably, SAIA also revealed a positive correlation between CSF α-synuclein seed levels and disease severity in PD patients, as measured by the Unified Parkinson's Disease Rating Scale.
Conclusions: The development of SAIA marks a significant step forward in the field of synucleinopathy research. Its ability to quantitatively and specifically detect α-synuclein seeds in both brain homogenates and CSF demonstrates its potential as a reliable diagnostic and disease monitoring tool.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1133 / #2200

Poster Topic: *Theme C: α-Synucleinopathies / C04.g. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

SLEEP PHENOTYPES OF SYNUCLEINOPATHY AND TAUOPATHY IN PARKINSONISM

POSTERS: C04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Nils Briel[1,2], Céline Marti[1], Heide Baumann-Vogel[1,3], Rositsa Neumann Poryazova[1,4], Philipp Valko[1,5,6], Esther Werth[1,4,6], Christian Baumann[1,6,7], Simon Schreiner[1,6,7]
[1]University Hospital Zurich, Department Of Neurology, Zurich, Switzerland, [2]Ludwig-Maximilians-University, Center For Neuropathology And Prion Research, Munich, Germany, [3]Clienia Schlössli, Privatklinik Für Psychiatrie Und Psychotherapie, Oetwil am See, Switzerland, [4]Bellevue Medical Group, Neurozentrum Oerlikon, Zurich, Switzerland, [5]Klinik Hirslanden, Klinik Für Neurologie, Zurich, Switzerland, [6]University of Zurich, Center Of Competence Sleep & Health Zurich, Zurich, Switzerland, [7]*, Contributed Equally, Zurich, Switzerland

Aims: Neurodegenerative parkinsonism is mainly caused by neuropathologically defined alpha-synucleinopathy (Syn) or tauopathy (Tau). To date non-invasive and easily accessible antemortem biomarkers of underlying pathology are a major unmet need. Sleep-wake disturbances are highly prevalent in neurodegenerative disorders and attract growing interest. In fact, rapid-eye-movement (REM) sleep behavior disorder (RBD) is a strong predictor of underlying alpha-synucleinopathy. However, little is known about non-REM (NREM) sleep features across different types of parkinsonism. Here, we explored whether sleep features from polysomnography differentiate suspected tauopathy or synucleinopathy in patients with neurodegenerative parkinsonism.
Methods: We performed a retrospective single-center analysis of polysomnography recordings from 198 patients with a clinical diagnose of neurodegenerative parkinsonism with suspected Syn (20 DLB, 100 PD, 45 MSA) or Tau (27 PSP, 6 CBS). Sleep features were compared across groups and used in unsupervised clustering.
Results: Tau patients showed less REM sleep, less NREM stage 2, more wake after sleep onset and less sleep efficiency than Syn patients (all $p<0.001$). We also found differences in sleep parameters between diagnostic groups, showing a gradient towards worse sleep from Lewy body disorders (DLB+PD) to atypical parkinsonism (MSA+PSP+CBS). Clustering allowed differentiation of Syn vs. Tau patients based on polysomnography features.
Conclusions: NREM sleep features differ between neurodegenerative parkinsonism with suspected Syn or Tau. These findings suggest that neurodegeneration of sleep-wake regulatory brain regions might differ according to proteinopathy, in addition to RBD-related brainstem involvement as a feature of Syn. Sleep phenotypes derived from polysomnography could be of value as antemortem biomarkers for proteinopathy and clinical diagnosis in neurodegenerative disorders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1134 / #1462

Poster Topic: *Theme C: α-Synucleinopathies / C04.g. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

BRAIN-FIRST VS. BODY-FIRST SUBTYPES OF PARKINSON'S DISEASE: EEG-BASED FUNCTIONAL FEATURES AND THEIR PATHOPHYSIOLOGICAL CONSEQUENCES

POSTERS: C04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Matteo Conti[1], Andrea Guerra[2], Roberta Bovenzi[1], Mariangela Pierantozzi[1], Alessandro Stefani[1]
[1]University of Rome "Tor Vergata", Department Of Systems Medicine, Rome, Italy, [2]University of Padua, Department Of Neuroscience, Padova, Italy

Aims: Recent research suggests that isolated REM sleep behavior disorder prior to parkinsonism (pRBD) is a sign of the body-first subtype of Parkinson's disease, in which synucleinopathy starts in the peripheral autonomic nervous system. Instead, in the brain-first subtype, synucleinopathy would initially arise in limbic areas. Functional connectivity (FC) could improve the understanding of pathophysiological features of these subtypes. The aim of this study is to analyze changes in FC between PD patients with and without pRBD, by means of high-density EEG (HD-EEG).
Methods: We enrolled 74 subjects, including 28 early-stage PD patients without pRBD (PD^{pRDB-}), 20 with pRBD (PD^{pRBD+}) and 24 healthy controls (HC). HD-EEG was recorded using a 64-channels system, and a source-reconstruction method was used to identify brain regions activity. Cortical FC in theta, alpha and beta bands was analyzed based on weighted phase-lag index. Potential FC changes between HC, PD^{pRDB-} and PD^{pRBD+} were assessed using network-based statistics.
Results: With respect to HC, PD patients showed hypoconnected networks in theta and alpha band, involving prefronto-limbic-temporal and fronto-parietal areas, respectively. When comparing the PD^{pRDB-} and PD^{pRBD+} subgroups, we found a lower FC in alpha frequency band in PD^{pRBD-}, which involved a network composed by temporo-parietal, frontal and sensorimotor areas (t=2.5, p=0.025).
Conclusions: Reduced FC in alpha band we found in PD^{pRBD+} patients may be linked to an early alteration of brainstem cholinergic pathway, which projects widely to the cortex, in patients with the body-first PD subtype. Furthermore, given that alpha rhythm abnormalities play a role in PD dementia, our data of an early alpha FC impairment in frontal and temporo-parietal areas in PD^{pRBD+} support the hypothesis that patients with the body-first subtype are more likely to progress to dementia than brain-first PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1135 / #2283

Poster Topic: *Theme C: α-Synucleinopathies / C04.g. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

EXPLORING NEUROPHYSIOLOGICAL EEG INDICATORS IN A RAT MODEL OF 6-OHDA-INDUCED PARKINSON'S DISEASE

POSTERS: C04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Jun-Qi Huang[1,2], Sheng Ke Lin[1], Chi-Wei Kuo[2], Hou-Hsuan Lee[2], Tsung-Hsun Hsieh[2]
[1]Chang Gung University, Department Of Biomedical Sciences (master's Program In Clinical Trials Assessment), Taoyuan City, Taiwan, [2]Chang Gung University, School Of Physical Therapy And Graduate Institude Of Rehabilitation Science, Taoyuan City, Taiwan

Aims: Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterized by the degeneration of dopaminergic nigrostriatal neurons. It has been observed that electroencephalography (EEG) can detect abnormalities in dopaminergic subcortical-cortical networks in PD. However, it remains inconclusive whether EEG abnormalities can serve as sensitive indicators for PD. This study developed an EEG recording platform to investigate whether abnormal quantitative EEG parameters can be monitored in a rat model of PD induced by 6-hydroxydopamine (6-OHDA).
Methods: To induce Parkinsonian rat model, we injected 6-OHDA into the left medial forebrain bundle (MFB) to selectively eliminate dopaminergic neurons. Four electrodes were concurrently implanted to collect signals from the frontal and parietal lobes. EEG recordings, combined with wireless data transmission, were monitored two weeks after the 6-OHDA injection, followed by the analysis of differences in power spectral density across various frequency bands (delta, theta, alpha, beta, gamma, and high frequency).
Results: The results of quantitative EEG demonstrate that, compared to rats with sham PD lesion, PD rat exhibited lower power in frequencies of low gamma (30~48 Hz) and high gamma (52~95 Hz), while no obvious differences were observed among the delta (0.5~4 Hz), theta (4~8 Hz), alpha (8~13 Hz), and beta (13~30 Hz) bands.
Conclusions: Our preliminary findings suggest that 6-OHDA-induced neurodegeneration leads to a decrease in gamma power in EEG profiles, implying that it could serve as a potential indicator for monitoring disease progression and assessing the efficacy of intervention protocols in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1136 / #2690

Poster Topic: *Theme C: α-Synucleinopathies / C04.h. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric, behavioral and motor tests*

IMPACT OF RATER CHANGE ON DATA VARIABILITY IN MDS-UPDRS PART III TOTAL SCORE IN PARKINSON'S DISEASE TRIALS

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

Barbara Echevarria[1], Matthew Welch[2], Selam Negash[2], Catarina Cunha[1], Christopher Randolph[3]
[1]WCG Clinical Research Solutions, Clinical Science, Munich, Germany, [2]WCG Clinical Research Solutions, Clinical Data Analytics, Princeton, United States of America, [3]WCG Clinical Research Solutions, Chief Scientific Officer, Princeton, United States of America

Aims: The MDS-UPDRS part III is the most widely used tool to measure changes in motor function over time in clinical trials of Parkinsons Disease (PD). This study evaluates the impact of rater change in visit-to-visit score variability on the MDS-UPDRS part III total score in PD clinical trials.
Methods: Data from six multinational clinical trials of early PD (H&Y I-III) were analyzed. MDS-UPDRS part III motor assessments conducted by site raters were arranged according to visit sequence and divided into two groups: Rater Change (different raters administered subject's consecutive visits) and No Rater Change (same rater administered consecutive visits). The two groups were matched on mean interval times between visits using random sampling. Visit-to-visit absolute score changes for Part III total score were calculated, and frequency distributions were evaluated.
Results: Welch corrected, two sample t-tests were conducted to compare score changes between rater change groups. For MDS-UPDRS part III, the Rater Change group showed a higher mean visit-to-visit score change (N = 2,523, mean = 6.7, SD = 5.53) compared to the No Rater Change (N = 7,553, mean = 4.1, SD = 3.74) group. This group difference reached statistical significance (t = 22.31, *df* = 3325.45 , $p < 0.0001$). Rater Change and No Rater Change groups did not differ significantly on mean interval times (t = 1.80, df = 3891.41, p = .07).
Conclusions: Findings from the study indicate significantly higher score changes when there is a rater change between visits than not for MDS-UPDRS motor assessments. These results highlight the importance of rater consistency in reducing variability in an effort to improve data quality in PD trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1137 / #744

Poster Topic: *Theme C: α-Synucleinopathies / C04.h. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric, behavioral and motor tests*

USING WEARABLE DEVICES TO ASSESS RESPONSE TO MEDICATION IN DE NOVO PARKINSON'S DISEASE

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

Maksymilian Brzezicki[1], Niall Conway[2], Charalampos Sotirakis[1], James Fitzgerald[1], Chrystalina Antoniades[1]
[1]University of Oxford, Ndcn, John Radcliffe Hospital, Level 6, Oxford, United Kingdom, [2]University of Oxford, Ndcn, Oxford, United Kingdom

Aims: Patients not yet receiving medication provide insight to drug-naïve early physiology of Parkinson's Disease (PD). Decisions to start medication and assessment of response to its initiation can be challenging for physicians and patients alike. To identify objective, sensor-derived features of upper limb bradykinesia, postural stability, and gait that can inform decision-making in a movement disorder clinic.
Methods: We used a single finger sensor to identify upper limb features and an array of six body-worn sensors to measure postural stability and gait. Patients were tested over nine visits, at three-monthly intervals, as part of a standard neurological examination.
Results: Three upper limb bradykinetic features (finger tapping speed, pronation supination speed, and pronation supination amplitude) and three gait features (gait speed, arm range of motion, duration of stance phase) were found to progress in unmedicated early-stage PD patients. In all features, progression was masked after the start of medication. There was no change in Montreal Cognitive Score and Mini Mental State Examination scores.
Conclusions: Commencing antiparkinsonian medication is known to lead to masking of progression signals in clinical measures in de novo PD patients. In this study, we show how this effect can be measured using digital devices. The testing kit can be used in movement disorder clinics to inform decision-making and progression monitoring in early PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1138 / #2246

Poster Topic: *Theme C: α-Synucleinopathies / C04.g. Imaging, Biomarkers, Diagnostics: EEG, brain mapping, MEG*

EEG FRONTAL THETA/BETA RATIO IS ASSOCIATED WITH IMPULSIVITY IN PARKINSON'S DISEASE WITH IMPULSE CONTROL DISODERS.

POSTERS: C04.G. IMAGING, BIOMARKERS, DIAGNOSTICS: EEG, BRAIN MAPPING, MEG

Juan Francisco Martín-Rodriguez[1], Elena Iglesias Camacho[2], Francisco Gómez-Campos[2], Pablo Franco-Rosado[1], Silvia Jesús[1], Daniel Macías-García[1], Laura Múñoz-Delgado[1], Astrid Adarmes-Gómez[1], Fátima Carrillo[1], Pablo Mir[1]
[1]Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain, Unidad De Trastornos Del Movimiento, Servicio De Neurología Y Neurofisiología Clínica, Seville, Spain, [2]Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain, Unidad De Trastornos Del Movimiento, Servicio De Neurología Y Neurofisiología Clínica, Seville, Spain

Aims: Parkinson's disease (PD) patients treated with dopaminergic agonists (DAs) often develop impulse control disorders (ICDs). This study investigated the role of oscillatory brain activity in PD patients with and without ICDs.
Methods: Thirty-six participants were divided into three groups: healthy controls (HCs), PD patients with ICDs (PD+ICDs), and PD patients without ICDs (PD-ICDs). Resting state EEG was recorded from all participants, and PD patients underwent two recording sessions, one during regular DA treatment (ON) and another after an overnight washout of DA replacement therapy (OFF)
Results: PD+ICDs patients in the OFF condition showed increased theta (θ) power in the central region compared to HCs. These patients also showed decreased central θ activity and θ/β ratio, as well as increased central-parietal beta (β) activity in the ON condition. Trait impulsivity correlated with frontal θ/β ratio in the ON condition in PD+ICDs patients, and with frontal and parietal θ/β in the OFF condition in PD-ICDs patients. Differences in central θ were detected between PD+ICDs in the OFF condition and HCs in frontal regions, and between PD+ICDs in the ON and OFF conditions. Additionally, parietal sources of β oscillations showed a treatment effect in the PD+ICD group, with increased β activity in the ON condition.
Conclusions: These findings suggest that PD+ICDs patients have a distinctive neurophysiological profile characterized by altered θ and β oscillations. This profile is sensitive to dopaminergic treatment and shares similarities with other disorders characterized by high trait impulsivity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1139 / #540

Poster Topic: *Theme C: α-Synucleinopathies / C04.h. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric, behavioral and motor tests*

IDENTIFYING PARKINSONISM IN MILD COGNITIVE IMPAIRMENT

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

Paul Donaghy[1], Rishira Fernando[1], Calum Hamilton[1], Rory Durcan[1], Sarah Lawley[1], Sally Barker[1], Joanna Ciafone[1], Nicola Barnett[1], Kirsty Olsen[1], Michael Firbank[1], Gemma Roberts[2], Jim Lloyd[2], George Petrides[2], Sean Colloby[1], Louise Allan[3], Ian Mckeith[1], John O'Brien[4], John-Paul Taylor[1], Alan Thomas[1]
[1]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [2]Newcastle Hospitals NHS Foundation Trust, Nuclear Medicine, Newcastle upon Tyne, United Kingdom, [3]University of Exeter, Centre For Research In Ageing And Cognitive Health, Exeter, United Kingdom, [4]University of Cambridge, Department Of Psychiatry, Cambridge, United Kingdom

Aims: Clinical parkinsonism is a core diagnostic feature for mild cognitive impairment with Lewy bodies (MCI-LB) but can be challenging to identify. A five-item scale[1] derived from the UPDRS has been recommended for the assessment of parkinsonism in dementia.[2] This study aimed to determine whether the five-item scale is effective in identifying parkinsonism in people with MCI.
Methods: Participants with MCI from two cohorts (n=146) had a physical examination including the Unified Parkinson's Disease Rating Scale and [123I]-FP-CIT SPECT striatal dopaminergic imaging. Participants were classified as having parkinsonism (P+) or no parkinsonism (P-) based on a consensus of three clinicians, and with abnormal striatal dopaminergic imaging (D+) or normal imaging (D-). The five-item scale was the sum of tremor at rest, bradykinesia, action tremor, facial expression, and rigidity scores from the UPDRS. The ability of the scale to differentiate participants with clinically identified parkinsonism and abnormal striatal dopaminergic imaging (P+D+) and no parkinsonism with normal imaging (P-D-) was examined.
Results: The five-item scale had an AUROC of 0.92 in Cohort 1, but the 7/8 cut-off defined for dementia had low sensitivity to identify P+D+ participants (sensitivity 25%, specificity 100%). Optimal sensitivity and specificity was obtained at a 3/4 cut-off (sensitivity 83%, specificity 88%). In Cohort 2, the five-item scale had an AUROC of 0.97, and the 3/4 cut-off derived from Cohort 1 showed sensitivity of 100% and a specificity of 82% to differentiate P+D+ from P-D- participants.
Conclusions: The five-item scale is effective to identify parkinsonism in MCI, but a lower threshold must be used in MCI compared with dementia. **References** Ballard et al. *Acta Neurol Scand* 1997;**96**:366-71. Thomas et al. *Int J Geriatr Psychiatry* 2018;**33:**1293-1304.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1140 / #775

Poster Topic: *Theme C: α-Synucleinopathies / C04.h. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric, behavioral and motor tests*

RESTING-STATE FUNCTIONAL CONNECTIVITY ASSOCIATED WITH SOCIO-COGNITIVE DYSFUNCTION IN NON-DEMENTED PARKINSON'S DISEASE

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

Giulia Funghi, Giuseppe Rabini, Claudia Meli, Luca Turella, Jorge Jovicich, Costanza Papagno, Alessandra Dodich
University of Trento, Center For Mind/brain Sciences (cimec), Rovereto, Italy

Aims: Social cognition (SC) deficits have been reported in Parkinson's disease (PD), but the characterization of these deficits and their underlying neural correlates remains limited. The aim of this study is to evaluate alterations in the recognition of complex mental states from faces in this population using a novel task and to explore their neural correlates.
Methods: Twenty-two PD patients (M:11; age in years: 66.9±7.2, education in years: 11.0±3.9, MOCA: 23.4±4.2) were enrolled. All patients underwent a basic clinical and neuropsychological assessment and performed the Facial Complex Expressions (FACE) test. Patients were classified as impaired (PD-SOC, n=7) or unimpaired (PD-CON, n=15) according to their performance on the FACE test, based on Italian normative data. Resting-state functional magnetic resonance imaging (rs-fMRI) was used to investigate functional connectivity (FC) within the emotion understanding network using both ROI-to-ROI and seed-based connectivity analyses, both across the entire PD sample and comparing PD-SOC vs. PD-CON.
Results: ROI-to-ROI connectivity analyses revealed a positive association between FACE test performance and BOLD co-activation of the right and left amygdala (p-FDR=0.003). Similarly, seed-based correlation analyses revealed significant clusters of FC between the left amygdala and the right temporal pole (peak p-FDR=0.025), the left insular cortex (peak p-FDR=0.025) and the right amygdala (peak p-FDR=0.015). The same regions showed a lower FC in PD-SOC compared to PD-CON.
Conclusions: This study demonstrated clinically relevant complex mental state recognition deficits in PD patients, associated with functional changes in emotion-related brain regions. FC results highlight the critical role of the bilateral amygdala in PD patients' FACE test performance and extend the neural network for complex mental state recognition to include the left insular cortex and the right anterior temporal pole.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1141 / #1380

Poster Topic: *Theme C: α-Synucleinopathies / C04.h. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric, behavioral and motor tests*

EFFECT OF DOPAMINERGIC TREATMENT ON COGNITIVE CONTROL MEASURED BY OCULOMOTOR BEHAVIOR AND STROOP TASK IN PARKINSON'S DISEASE: A PILOT STUDY

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

Lenka Hapáková, Zuzana Košutzká, Šimon Janovič
Comenius University Faculty of Medicine University Hospital Bratislava, 2nd Department Of Neurology, Bratislava, Slovak Republic

Aims: To study how dopaminergic treatments, affect cognitive control in Parkinson's disease (PD) over three visits with escalating dosages.
Methods: Ten drug-naive patients diagnosed with PD (median age = 59.5, IQR = 7.25 years) without dementia (mean MoCA = 25.5, IQR = 5.5) were enrolled. All patients initiated dopaminergic treatment, with Levodopa (n=4) and Pramipexol (n=6), administered during three visits (baseline, one-month, and three-month follow-up) with incremental dosages. The protocol for each visit involved eye-tracking, assessing latencies of prosaccades and antisaccades, express saccades (<130ms), errors, gain, and speed. A screening neuropsychological battery was employed, which included a tablet-based Numeric Stroop test with congruent and incongruent conditions. We analyzed statistical differences among the 3 measurements using rank-transformed data and analysis of variance.
Results: Significant measurement effect was observed for express prosaccades index ($F = 3.76$, $p < 0.05$), and numeric Stroop both in congruent and incongruent conditions ($F = 5.2$, $p < 0.05$), ($F = 4.77$, $p < 0.05$). The express prosaccade index significantly decreased from the second (median = 16.75, IQR = 15.9) to the third (median = 3.36, IQR = 5.68) measurement, $p < 0.05$. Numeric Stroop tasks showed reduced reaction times between the second (median = 1408.4, IQR = 327) and third (median = 1175.5, IQR = 459.9) measurements for congruent, and between the second (median = 1275.13, IQR = 389.27) and third (median = 954.03.5, IQR = 372.86) measurement for incongruent condition.
Conclusions: Initially impaired cognitive control showed improvement with dopaminergic treatment in the third assessment, seen in reduced express prosaccades and Stroop reaction times. Eye tracking demonstrated its potential as a sensitive clinical tool compared to other neuropsychological tests which did not exhibit significant differences.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1142 / #1721

Poster Topic: *Theme C: α-Synucleinopathies / C04.h. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric, behavioral and motor tests*

LONG-TERM DEMENTIA PREVALENCE IN PARKINSON'S DISEASE: GLASS HALF-FULL?

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

Julia Gallagher[1], Janel Fedler[2], Caroline Gochanour[3], Roseanne Dobkin[4], Dag Aarsland[5], Roy Alcalay[6,7], Matthew Barrett[8], Chelsea Caspell-Garcia[2], Ryan Cho[2], Lana Chahine[9], Alice Chen-Plotkin[1], Christopher Coffey[2], Nabila Dahodwala[1], Jamie Eberling[10], Alberto Espay[11], James Leverenz[12], Irene Litvan[13], Eugenia Mamikonyan[14], James Morley[15], Irene Richard[16], Liana Rosenthal[17], Andrew Siderowf[1], Tanya Simuni[18], Michele York[19], Allison Willis[1], Sharon Xie[20], Daniel Weintraub[14]

[1]University of Pennsylvania, Neurology, Philadelphia, United States of America, [2]University of Iowa, Clinical Trials Statisitcal & Data Management Center,, Iowa City, United States of America, [3]The University of Iowa, Neurology, iowa City, United States of America, [4]Rutgers University, Psychiatry, New Brunswick, United States of America, [5]Institute of Psychology, Psychiatry & Neuroscience (IoPPN), King's College London, Department Of Old Age Psychiatry, London, United Kingdom, [6]Laboratory of biomarkers and genomic of neurodegeneration,, Tel-aviv Medical Center, Tel Aviv, Israel, [7]Columbia University, Department Of Neurology, New York, United States of America, [8]Virginia Commonwealth University, Neurology, Richmond, United States of America, [9]University Pittsburgh, Neurology, Pittsburgh, United States of America, [10]Michael J Fox Foundation, Research Resources, New York, United States of America, [11]University of Cincinnati, Neurology, Cincinnati, United States of America, [12]Cleveland Clinic, Neurology, Cleveland, United States of America, [13]University of California San Diego, Neurology, San Diego, United States of America, [14]University of Pennsylvania, Psychiatry, Philadelphia, United States of America, [15]Philadelphia Veteran's Affairs, Parkinson's Disease Research, Education And Clinical Center, Philadelphia, United States of America, [16]University of Rochester, Neurology, Rochester, United States of America, [17]Johns Hopkins University, Neurology, Baltimore, United States of America, [18]Northwestern University, Neurology, Chicago, United States of America, [19]Baylor College of Medicine, Section Of Neurology, Houston, United States of America, [20]University of Pennsylvania, Biostatistics And Epidemiology, Philadelphia, United States of America

Aims: To determine long-term, cumulative dementia prevalence rates in PD using data from two large, ongoing, prospective observational studies.
Methods: The Parkinson's Progression Markers Initiative (PPMI) and a longstanding PD research clinical core at the University of Pennsylvania (Penn) were observed. PPMI enrolls *de novo*, untreated PD participants at baseline, and Penn enrolls a convenience cohort from a large clinical center. For PPMI a cognitive battery and MDS-UPDRS Part I are administered annually, and the site investigator assigns a cognitive diagnosis annually. At Penn a comprehensive cognitive battery is administered either annually or biennially, and a cognitive diagnosis is made by consensus. Kaplan-Meier (KM) survival curves were fit for time from PD diagnosis to stable dementia diagnosis for each cohort, using assigned cognitive diagnosis of dementia as the primary endpoint, and MoCA score <21 and MDS-UPDRS Part I cognition score ≥3 as secondary endpoints (for PPMI). Cumulative dementia prevalence by PD disease duration was tabulated for each study and endpoint.
Results: For the PPMI cohort, 417 PD participants were seen at baseline; estimated cumulative probability of dementia at year 10 disease duration were: 7% (site investigator diagnosis), 9% (MoCA) or 7.4% (MDS-UPDRS Part I cognition). For the Penn cohort, 389 PD participants were followed over time, with 184 participants (47% of cohort) eventually diagnosed with dementia. The KM curve for the Penn cohort had median time to dementia diagnosis =15 years (95% CI: 13-15) disease duration; the estimated cumulative probability of dementia was 27% at year 10, 50% at year 15, and 74% at year 20.

Conclusions: Results from two large, prospective studies suggest that dementia in Parkinson disease occurs less frequently, or later in the disease course, than often-cited previous research studies have reported.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1143 / #2084

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

EXPANDING THE RESOURCES FOR PARKINSON'S DISEASE DRUG DISCOVERY: ACCELERATING MEDICINES PARTNERSHIP IN PARKINSON'S DISEASE

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Sri Ramulu Pullagura[1], Christine Swanson-Fischer[2], Debra Babcock[2], Alessio Travaglia[1]
[1]Foundation for the National Institutes of Health, Neuroscience, North Bethesda, United States of America, [2]National Institute of Neurological Disorders and Stroke/NIH, Division Of Neuroscience, Bethesda, United States of America

Aims: The Accelerating Medicines Partnership® (AMP®) program for Parkinson's Disease (PD), launched in 2018, fosters collaboration among government, industry, and non-profits to enhance our understanding of PD. Its key goals include identifying disease mechanisms, discovering diagnostic and prognostic biomarkers, and validating targets for PD treatment.
Methods: AMP PD's research plan involves comprehensive molecular and clinical profiling of patient data and biosamples to find and validate PD biomarkers. This includes sharing harmonized molecular and clinical data, such as genome sequencing, transcriptomics, and proteomics to identify new targets, disease subtypes, and predictive markers for PD progression. AMP PD uses eight well-characterized cohorts and collaborates with the Global Parkinson's Genetics Program (GP2).
Results: Currently, AMP PD has collected extensive data from 10,807 participants across eight cohorts by September 2023. This includes 3,537 PD subjects (1,469 with known mutations), 4,337 healthy controls (1,615 with known mutations), and 2,933 subjects with other diagnoses. Longitudinal blood-based transcriptomics data is available for 3,277 participants, while whole genome sequencing data covers 10,418 subjects, and targeted proteomics involves 413 participants. Additional data, such as single-cell sequencing in post-mortem tissue, blood-based transcriptomics, and unbiased proteomics from blood and CSF, will be accessible in late 2023/early 2024.
Conclusions: AMP PD's platform, hosted on Google Cloud, promotes data sharing, supports efficient analysis, reduces costs, and encourages collaboration, facilitating the discovery of PD biomarkers for clinical trials and therapy development. This presentation highlights scientific breakthroughs made possible by AMP PD, emphasizing genomics, proteomics, and post-mortem tissue sequencing research for biomarker discovery. It also underscores the potential of AMP PD data for broader scientific exploration now and as the program moves into its next phase

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1144 / #1725

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

AUTONOMIC FUNCTIONS AND DOPAMINERGIC CORRELATES IN DEMENTIA WITH LEWY BODY: A PRELIMINARY STUDY

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Chiara Giuseppina Bonomi[1], Camilla Rocchi[2], Caterina Motta[1], Chiara Serafini[1], Agostino Chiaravalloti[3], Alessandro Martorana[1]
[1]University of Rome Tor Vergata, Memory Clinic, Rome, Italy, [2]University of Rome Tor Vergata, Neurology Unit, Rome, Italy, [3]University of Rome Tor Vergata, Nuclear Medicine Unit, Rome, Italy

Aims: Both autonomic failure and nigrostriatal denervation are well-known features of Dementia with Lewy Body (DLB). However, the relationship between the two has been poorly investigated. We aimed to assess cardiovascular and sudomotor autonomic function tests (AFTs) in DLB and to evaluate the relationship between AFTs and ^{123}I-ioflupane dopamine transporter uptake at single photo-emission computed tomography (DAT-SPECT).
Methods: 15 DLB patients and 20 healthy controls (HC) underwent head-up tilt-test (HUTT), Valsalva Maneuver, deep-breathing, cold-face, hand-grip test (HG), electrochemical skin conductance (ESC). DLB patients also underwent DAT-SPECT, we used the DaTQUANT software for semi-quantitative analysis.
Results: DLB patients showed lower delta heart rate at 3rd minute of HUTT (p=0.016), Valsalva Ratio (p<.001) and Overshoot (p=0.004), lower delta systolic (ΔSBP, p=0.002) and diastolic blood pressure (ΔDBP, p<.001) at HG, lower inspiration-espiration difference at deep-breathing (p=0.004), and lower hands-feet ESC than HC (both p=0.003). Of all the AFTs, only HG responses correlated with striatal DaTQUANT measures: HG ΔDBP strongly inversely correlated with bilateral uptake of ^{123}I-FP in the anterior (Right: rho -0.691, p 0.004; Left: rho -0.676, p 0.006) and posterior putamen (Right: rho -0.769, p<.001; Left: rho -0.663, p 0.007).
Conclusions: Despite the absence of overt orthostatic hypotension, DLB patients showed covert dysautonomia encompassing adrenergic and parasympathetic dysfunction. Moreover, the functioning of sympathetic peripheral efferent pathways to vessels, reflected by HG ΔDBP, was inversely associated with nigrostriatal denervation. This could suggest the presence of different profiles of peripheral-predominant vs central-predominant impairment in DLB patients

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1145 / #2760

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

OPTIMAL DIGITAL ENDPOINT SELECTIONS OF MOVEMENT IN PARKINSON'S DISEASE

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Kristen Sowalsky, Vrutangkumar Shah, Fay Horak
Clario, Medical & Scientific Affairs, Portland, United States of America

Aims: Wearable sensors enable precise, sensitive, and reliable digital endpoint capture of movement impairment in Parkinson's disease (PD). As there are thousands of digital movement endpoints available for use in clinical trials, selecting those most optimal per each unique study can be challenging. We offer guidelines, aligned with regulatory guidance, and supported by the latest scientific evidence.
Methods: An approach to selecting the best digital movement outcome for a clinical trial is outlined considering the following criteria: 1) meaningfulness to participants 2) sensitivity/specificity to disease 3) related to the conventional stage of disease/progression and patient-reported scales 4) reflective of pathophysiology and 5) sensitivity to change. A review of the literature on gait and balance digital outcomes for newly diagnosed PD was performed.
Results: Digital endpoints of gait captured with inertial sensors on the feet, lower back, and wrists have the most scientific supported. The majority of evidence is available from short walking and standing tasks performed in a controlled setting, while evidence for passive, real-world data is growing. Specifically, measures including foot strike angle, turn velocity, arm swing reduction/asymmetry, gait variability, and sway jerkiness reflect the outlined criteria for early PD. Measures of bradykinesia and tremor, while having more limited evidence, are also promising. However, the hypothesized effect of the therapy under investigation must also be considered, as the sensitivity of specific gait and balance endpoints to change differ by treatment due to the underlying pathophysiology.
Conclusions: Digital endpoints of movement impairment specific to early PD are meaningful to patients, more sensitive to disease progression than conventional clinical scales, and a critical tool in the future success of clinical trials to provide effective treatments for PD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1146 / #1017

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

REDUCED VARIABILITY IN CARDIAC R-R INTERVAL AS A PREDICTOR OF PARKINSON'S DISEASE

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Laura Vacca[1], Daniele Bravi[2], Margherita Torti[1], Stefania Proietti[1], Maria Francesca De Pandis[3], Rossella Rotondo[3], Fabiana Radicati[1], Miriam Casali[1], Giuseppe Rosano[4], Fabrizio Stocchi[2]
[1]IRCSS HSR La Pisana, Ctc, Rome, Italy, [2]IRCSS HSR La Pisana, Ctc, Rome, Italy, [3]San Raffaele Cassino, Neurology, Cassino, Italy, [4]IRCSS HSR La Pisana, Cardiology, Rome, Italy

Aims: Non Motor Symptoms in Parkinson's disease are resulting from neurodegerative processes that also involves the peripheral autonomic nervous system. Cardiovascular changes have been recognised to affect all stage of ethe disease plus suggested as potential prodromal sign. The aim of the present study was to evaluate the changes in the heart rate variability as predictor of disease onset
Methods: Fisrt Degree relatives, with age between 50 to 75 years, of individuals with established diagnosis of Parkinson's disease underwent a 10 min electrocardiogram and followed up over 10 years by phone check to report any changes in their health status Primary objective was to evaluate Heart rate variability . Subjects were also clinically investigated about the presence of depression, constipation, hyposmia and RBD like sleep disorders
Results: 324 subjects have been enrolled. 204 subjects eligible for analyss (44 screening failure, 76 excluded to to poor ECG output) . Outcome data did not reveal any significant abnormalities in heart rate variability in such population. A subgroup of 31 participants with heart rate variability papameter below the 5th percentile was identified, however no-one from this subgroud expereinced the occurence of parkinsons's disease symptoms. Study confirmes previous data showing a reduction of heart rate variability with increasing age.
Conclusions: The Heart rate Variability of first degree relatievs of parkinson's disease patients did not differ from the reference ranges of healthy population, therefore such parameter does not seem to represent a reliable biomarker for prodromal Parkinson's disease. However , given the heterogeneicity of teh disease, lack of clinical and imaging biomarkers , additional studies involving more accurate and sensitive EEg methdologies associated to confirmatory imaging and or biofluid markers are needed

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1147 / #2653

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

ARTIFICIAL INTELLIGENCE OPPORTUNITIES FOR VOICE DIAGNOSTICS OF PARKINSON'S DISEASE (BRAINPHONE PROJECT)

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Zuleykha Zalyalova[1], Diana Khasanova[2], Ildar Khasanov[3], Guzal Ilina[2]
[1]Kazan State Medical University, Department Of Neurology, Kazan, Russian Federation, [2]Republican Centre for Movement Disorders, -, Kazan, Russian Federation, [3]LLC Brainphone, -, Kazan, Russian Federation

Aims: The work was carried out within the framework of BRAINPHONE project for voice diagnostics of Parkinson's disease (PD) with artificial intelligence (AI) method. The method used is convolutional neural network (CNN), trained with 1000 unique audiorecords of voices of PD patients vs healthy volunteers (50/50%). The aim of the study was the assessment of quality metrics of AI method in comparison with MDS clinical criteria of PD.
Methods: For validation test 10% from training sample was selected: balanced sample with 50 PD patients (25 early and 25 advanced stages) and 50 healthy volunteers. From the sample were excluded patients with atypical and other types of parkinsonism and with disorders associated with speech disturbances. Data was collected in June-July 2023 in the Republican Centre for Movement Disorders (Kazan, Tatarstan Republic, Russia). All patients were assessed at first by 2 experienced parkinsonologists and then with the trained CNN. The specialist's diagnosis was made on the MDS clinical criteria of PD with output "PD" or "non-PD". The trained CNN output was "possible PD" (counted probability of 0.5 and higher) and "non-PD" (counted probability less than 0.5).
Results: The sensitivity of trained CNN was 80.1%, the specificity – 92.3%. According to literature for MDS clinical criteria of PD the sensitivity is 82,6-94,5% and the specificity is 57,8-88,5% [1,2].
Conclusions: Compared with clinical criteria voice diagnostics via trained CNN shows comparable results in sensitivity and better results in specificity. Potentially, diagnostics using trained CNN can be applied as a screening tool. The limitations of the study are balanced testing sample (50/50% vs 99,5-98/0.5-2% of PD and healthy persons in real-life depending on age and area); people with speech disturbances and other types of parkinsonism were excluded.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1148 / #1207

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

AUTORADIOGRAPHY CHARACTERIZATION OF NOVEL ALPHA-SYNUCLEIN RADIOLIGANDS [3H]TG1-90B,[3H]M503-1619 AND [3H]HY-2-15 IN HUMAN POST MORTEM BRAIN.

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Dinahlee Saturnino Guarino[1], Kuiying Xu[2], Guilong Tian[1], Ho Young Kim[1], Virginia Lee[3], Kelvin Luk[4], Robert Mach[1]
[1]Perelman School of Medicine, University of Pennsylvania, Radiology, Philadelphia, United States of America, [2]Adesis, Chemistry, Wilmington, United States of America, [3]University of Pennsylvania, Pathology & Lab Medicine, Philadelphia, United States of America, [4]University of Pennsylvania, Pathology And Laboratory Medicine, Philadelphia, United States of America

Aims: To examine region- and substrate-specific autoradiographic patterns of alpha-synuclein radioligands targeting Sites 2 and 9, and to determine whether there is off-target binding to other amyloid/non-amyloid proteins.
Methods: We applied [^{3}H]Tg1-90B (Site 2), [^{3}H]M503-1619 (Site 9) and [^{3}H]HY-2-15 (Site 9) *in vitro* real-time autoradiography and immunohistochemistry studies to postmortem samples from patients with a definite pathological diagnosis of Parkinson disease, dementia with Lewy Bodies, Multiple system atrophy, Alzheimer disease, frontotemporal lobar degeneration-tau (progressive supranuclear palsy and corticobasal degeneration) and elderly controls free of pathologic changes of neurodegenerative disease. Brain tissue sections were stained for a-syn, Aβ, tau and compared to [^{3}H]Tg1-90B, [^{3}H]M503-1619 and [^{3}H]HY-2-15 autoradiography on adjacent sections.
Results: Our data indicate that [^{3}H]Tg1-90B displayed specific binding in PD, DLB and MSA tissue. [^{3}H]M503-1619 binds to a-syn inclusions found in PD, DLB brain but not in MSA; conversely [^{3}H]HY-2-15 autoradiography showed the opposite pattern. However, specific binding of the radioligands was also observed in tissue from AD, PSP, CBD cases indicating binding to tau pathology, that was confirmed by tau immunostaining.
Conclusions: Our observations derived from combined autoradiography and immunohistochemistry, indicate that the Site 2 ligand Tg1-90B is able to detect α-syn inclusions present both in PD and MSA patient. M503-1619 preferentially recognize α-syn aggregates in PD, and DLB brain tissue over α-syn lesions in MSA patients. In contrast, HY-215 autoradiography support its potential use for imaging α-syn in MSA patients. Our results suggest that compounds targeting Site 2 ligands may be a “pan-a-syn” radiotracer (i.e., targeting both PD and MSA), whereas radiotracers targeting Site 9 show specificity for PD or MSA. The reason for the disease specificity of Site 9 ligands is not clear at this time

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1149 / #2208

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

CHARACTERIZING PARKINSON'S MOTOR FLUCTUATIONS USING WEARABLE DEVICES

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Witney Chen, Tiffany Jansen, Aiden Arnold, Ro'Ee Gilron
Rune Labs, Neuroscience, San Francisco, United States of America

Aims: Generate algorithmic approaches to detect and characterize motor fluctuations in Parkinson's disease using wearable device data.
Methods: Wearable data from 900+ subjects with Parkinson's disease were analyzed to characterize the prevalence and dynamics of medication-induced motor fluctuations. Subjects wore an Apple Watch and carried an iPhone to continuously monitor tremor, dyskinesia, gait and mobility, vitals, and sleep. We filtered for subjects with data for at least 10 days and >8 hours per day. We quantified periodicity using frequency decomposition methods, identifying spectral peaks above statistical chance thresholds. The periods of the identified cycles were validated against patient-reported medication schedules. We generated statistical features of the periodicity, which were used to cluster subjects as fluctuators versus non-fluctuators and to assess cycle dynamics over time.
Results: Periodic fluctuations in tremor and dyskinesia were successfully identified in unevenly sampled time series data from tremor-dominant subjects. The prevalence, cadence, and magnitude of motor fluctuations varied across subjects, and we found fluctuators and non-fluctuators in our cohort (Figures 1, 2). The algorithm was affected by patient phenotype, consistency in medication times, complexity of medication regimen, and data quantity per subject.

Figure 1

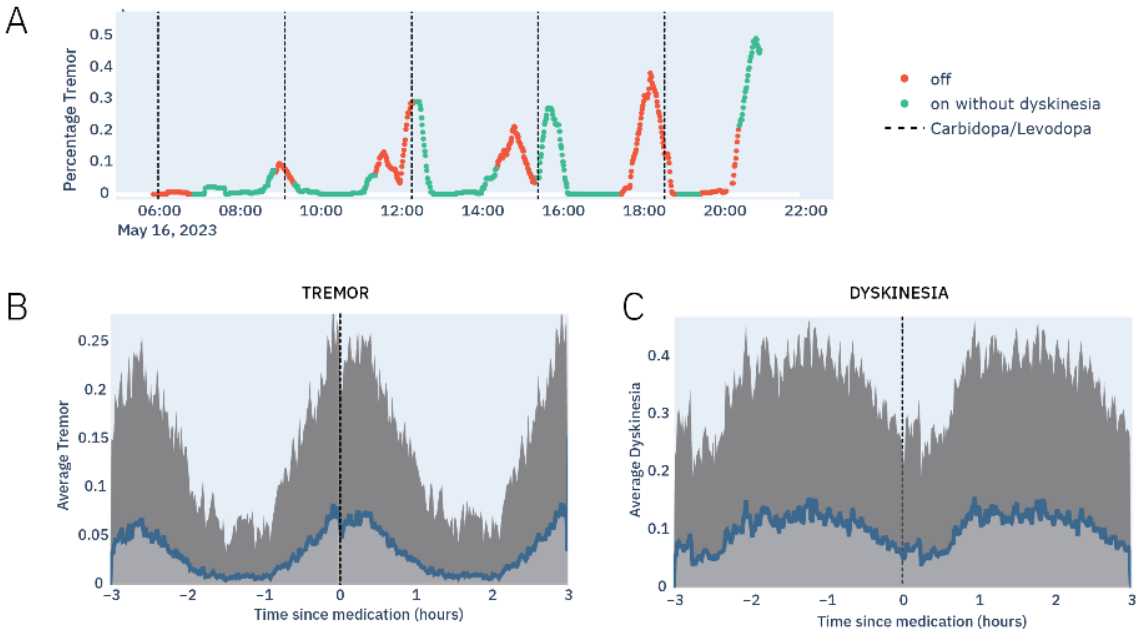


Figure 1. Wearable data from a single subject example *with* medication-induced motor fluctuations. Percent of recorded time with resting tremor fluctuates throughout a representative day, corresponding with medication times and the subject's motor diary responses (A). Dose response curves of tremor (B) and dyskinesia (C) in response to carbidopa/levodopa, indicating a 3 hour fluctuation cycle.

Figure 2

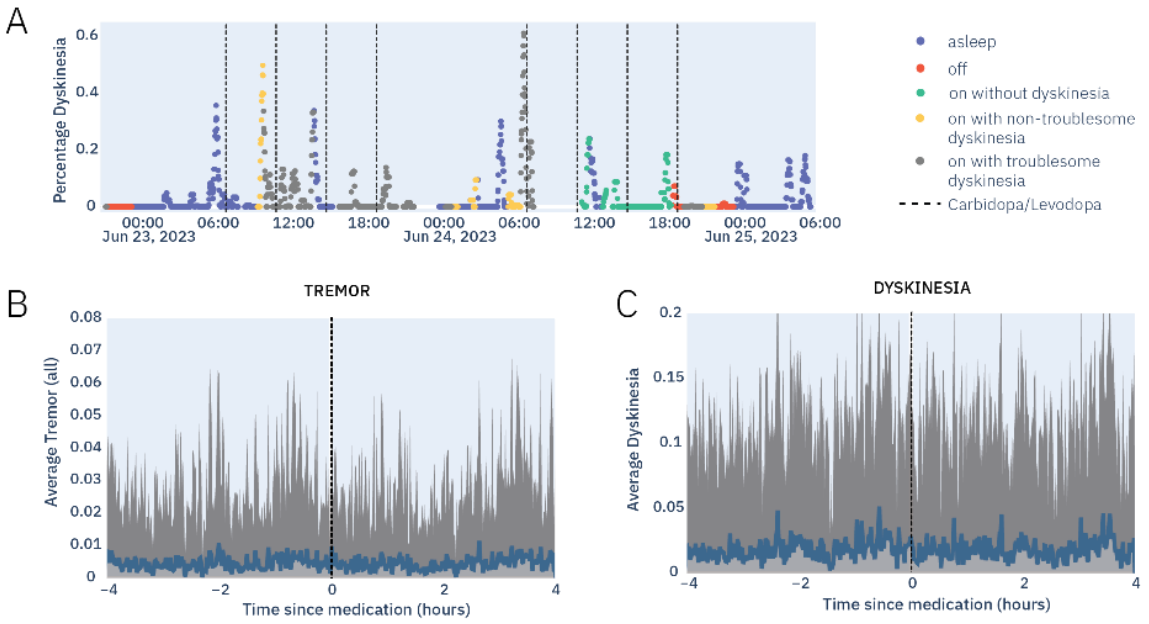


Figure 2. Wearable data from a single patient example *without* medication-induced motor fluctuations. Percent of recorded time with dyskinesia fluctuates throughout a representative day, but these do not consistently correspond with medication times and patient's motor diary responses (A). Dose response curves of tremor (B) and dyskinesia (C) do not indicate clear fluctuations in response to carbidopa/levodopa.

Conclusions: Data-driven approaches successfully identify motor fluctuators using wearable devices. Continuous monitoring can be used to quantify the cadence and magnitude of fluctuations, assess the change over time, and assess responses to therapeutic interventions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1150 / #2354

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

DEVELOPMENT OF THE JAPANESE VERSION OF GASTROINTESTINAL DYSFUNCTION SCALE FOR PARKINSON'S DISEASE (GIDS-PD)

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Fukiko Kitani-Morii[1], Takuma Ohmichi[1], Etsuro Nakanishi[2], Ryosuke Takahashi[2], Yuzo Fujino[1], Shoko Ohtomo[1], Toshiki Mizuno[1], Takashi Kasai[1]
[1]Kyoto Prefectural University of Medicine, Neurology, Kyoto, Japan, [2]Kyoto University Graduate School of Medicine, Neurology, Kyoto, Japan

Aims: Patients with Parkinson's disease (PD) exhibit a wide range of gastrointestinal dysfunctions, but until now, there has been no disease-specific scale to assess their severity. The Gastrointestinal Dysfunction Scale for Parkinson's Disease (GIDS-PD) was introduced in 2021 as a self-administered questionnaire comprising 12 items to evaluate constipation, bowel irritability, and upper gastrointestinal symptoms in PD patients, with scores ranging from a minimum of 1 point to a maximum of 108 points.
Methods: With permission from the Movement Disorder Society, our team initiated the development of the Japanese version of GIDS-PD in August 2022.
Results: Initially, we created the Japanese version from the English version of the original paper (Mov Disord. 2021;36:2358-2366). An independent team then conducted a back-translation of this Japanese version into English, and the Translation Review Subcommittee of the MDS confirmed the equivalence between the original and back-translated versions. In a pre-cognitive test involving 10 PD patients and 10 assessors whose native language is Japanese, the comprehensibility of all items in the Japanese version exceeded an average score of 5 out of 6 points (with 6 points indicating very good understanding and 1 point indicating very poor understanding). Following another round of review by the MDS, the provisional Japanese version of GIDS-PD was posted on the MDS website, making it available for general clinical use.
Conclusions: The provisional use of the Japanese version of GIDS-PD is now possible. Currently, we are conducting field tests with 100 PD patients and 30 healthy individuals using the provisional Japanese version of GIDS-PD. This will allow us to compare its similarity to the original article.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1151 / #1369

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

COMPARISON BETWEEN P2X7R, MAO-B AND TSPO IMAGING BIOMARKER IN ALZHEIMER'S DISEASE AND TAUOPATHY BRAINS

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Yanyan Kong[1], Cinzia Maschio[2], Fang Xie[1], Uwe Konietzko[2], Hongjun Jin[3], Yihui Guan[1], Roger Nitsch[2], Ruiqing Ni[2]
[1]Fudan University, Pet Center, shanghai, China, [2]University of Zurich, Institute For Regenerative Medicine, Zurich, Switzerland, [3]Sun Yat-Sen University, Guangdong Provincial Engineering Research Center Of Molecular Imaging, Zhuhai, China

Aims: Neuroinflammation plays an important role in Alzheimer's disease and primary tauopathies include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD). The aim of the current study is to compare the patterns of purinergic P2X7R tracer [^{18}F]GSK1482160 with monoamine-oxidase B (MAO-B) tracer [^{18}F]SMBT-1 and translocator protein (TSPO) tracer [^{18}F]DPA-714 in the brain of disease models.
Methods: MicroPET scans were performed using [^{18}F]GSK1482160, [^{18}F]SMBT-1, [^{18}F]DPA-714, as well as [^{18}F]flobetapir (amyloid-beta) and [^{18}F]PM-PBB3 (tau) in widely used mouse models of Alzheimer's disease (including APP/PS1, 5×FAD and 3×Tg mice), 4-repeat tauopathy mice (rTg4510), and age-matched wild-type mice at young and middle ages. Immunofluorescence staining was performed on the postmortem brain tissues from non-demented controls, patients with AD, PSP and CBD, as well as from the aforementioned mouse models.
Results: We found increased P2X7R levels by [^{18}F]GSK1482160 in the cortex, basal forbrain, amygdala of 7-month-old rTg4510 mice compared to wild-type mice, but not in the other models (APP/PS1, 5XFAD, 3XTg mice) at both young and middle ages. In comparison, increased regional MAO-B levels indicated by [^{18}F]SMBT-1 was observed in the middle aged rTg4510, APP/PS1, 5XFAD mice compared to wild-type mice but not in 3xTg mice, Increased regional TSPO levels indicated by [^{18}F]DPA-714 was observed n the middle aged rTg4510 and 5XFAD mice compared to wild-type mice, but not in APP/PS1 and 3xTg mice. Postmortem studies showed increased levels of P2X7R, glial fibrillary acidic protein (GFAP) and Iba1 in the brain tissues from the hippocampus from AD, striatum from PSP and CBD.
Conclusions: The findings provide in vivo imaging evidence for diverse patterns of P2X7R using [^{18}F] GSK1482160 compared to MAO-B and TSPO imaging in the brain of Alzheimer's disease and tauopathy models.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1152 / #2654

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

LOW-BURDEN DIGITAL SPEECH BIOMARKERS FOR EARLY DIAGNOSIS AND PROGNOSIS IN PARKINSON'S DISEASE: STUDY DESIGN AND PROTOCOL

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Alexander Jäck[1,2], Ebru Baykara[3], Mira Fischer[1,2], Urban Fietzek[1], Alexander Bernhardt[1,2], Alexandra König[3], Johannes Tröger[3], Günter Höglinger[1,2], Johannes Levin[1,2]
[1]German Center for Neurodegenerative Diseases, Dzne, Munich, Germany, [2]LMU University Hospital, Department Of Neurology, Munich, Germany, [3]ki:elements GmbH, Clinical Research, Saarbrücken, Germany

Aims: In collaboration with ki:elements, this study seeks to identify and validate digital speech biomarkers for Parkinson's Disease (PD) through AI empowered remote assessments. Building on ki:elements' prior work, the focus is on detecting early-stage Parkinson's, tracking progression, and assessing levodopa responsiveness. A subproject will further validate digital speech biomarkers against established molecular biomarkers including Tau, Amyloid and Lewy-Type Synuclein.
Methods: The study will commence as a 12-month observational research, aiming to include 100 patients and 100 healthy controls, building on established cohorts with multiparametric deep phenotyping established at LMU Munich. In addition to extensive clinical phenotyping, this study will collect comprehensive speech data remotely through ki:element's Mili mobile app. Combined with gold standard measures and advanced speech analysis using AI, this data will help to investigate speech and language based phenotypes for PD patients, capturing motor, cognitive, and mood symptoms.
Results: Study Design, no results yet. Possible preliminary data by March
Conclusions: The intricate diagnostic landscape of PD is riddled with challenges due to its reliance on clinical motor-function criteria and poor prognostic assessments. The emergence of non-motor symptoms as precursors to motor impairments showcases the complexity of PD's clinical manifestation. Considering the precursory and progressive nature of speech alterations AI and machine learning also offer immense promise in establishing reliable digital biomarkers. By delving into both speech alterations and molecular biomarkers in an exploratory subproject we seek to shed light on the underlying pathomechanisms of speech and linguistic changes in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1153 / #1838

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

THE SYNUCLEIN ONE STUDY: CUTANEOUS ALPHA-SYNUCLEIN DEPOSITION IN DEMENTIA WITH LEWY BODIES AND MILD COGNITIVE IMPAIRMENT

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Christopher Gibbons[1], Todd Levine[2], Bailey Bellaire[3], Roy Freeman[1]
[1]Harvard Medical School, Beth Israel Deaconess Medical Center, Neurology, Boston, United States of America, [2]HonorHealth, Neurology, Scottsdale, United States of America, [3]CND Life Sciences, Neurology, Scottsdale, United States of America

Aims: The Synuclein-One study is an NIH-funded 30-site multicenter trial that included 50 patients with dementia with Lewy bodies (DLB) and 27 with mild cognitive impairment. Here we report the detection of cutaneous phosphorylated alpha-synuclein (P-SYN) in patients with DLB and MCI. An unmet need exists for a validated, well-characterized, simple, reproducible biomarker of synuclein pathology. The number of individuals with neurodegenerative diseases continues to grow and misdiagnosis within and among synuclein and non-synuclein dementias continues to occur, resulting in incorrect medication choices, iatrogenic complications, inaccurate prognostication and patient frustration.
Methods: After signed consent, study participants completed neurologic examinations (MDS-UPDRS, Hoehn and Yahr scale), medical history review, cognitive evaluation (MOCA), orthostatic vital signs and neurodegenerative disease questionnaires. DLB was defined using consensus criteria. MCI was defined as MOCA score of 18-25. Skin biopsies at the distal leg, distal thigh and posterior cervical sites were performed on all participants with quantitation of P-SYN and intra-epidermal nerve fiber density (IENFD).
Results: In the 50 DLB participants (MDS-UPDRS 68±28, Hoehn and Yahr 2.4±1.0, MOCA 16±5.4), P-SYN was detected in 48/50 (96%). Of 27 participants with MCI (MDS-UPDRS 3.5±6.0, Hoehn and Yahr 0.1±0.4, MOCA 23±2.8), P-SYN was detected in 8/27 (30%). Detection of P-SYN in healthy controls is 3.3%.
Conclusions: Cutaneous P-SYN testing is a sensitive and specific test for phosphorylated alpha-synuclein in patients with DLB. The detection of P-SYN in individuals with MCI is 10-times that of the healthy population. Longitudinal follow up of MCI participants is needed to understand the long-term implications of these results and the risk of co-pathology associated with other conditions such as Alzheimer's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1154 / #1787

Poster Topic: *Theme C: α-Synucleinopathies / C04.h. Imaging, Biomarkers, Diagnostics: Cognitive, psychometric, behavioral and motor tests*

GAIT ALTERATIONS FROM PRODROMAL TO EARLY-STAGES OF PARKINSON'DISEASE: A MOBILE HEALTH TECHNOLOGY SUPERVISED MULTICENTER STUDY

POSTERS: C04.H. IMAGING, BIOMARKERS, DIAGNOSTICS: COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS

Cinzia Zatti[1], Andrea Pilotto[1], Clint Hansen[2], Andrea Rizzardi[1], Marcello Catania[1], Robbin Romijnders[2], Leandro Purin[1], Maria Pasolini[3], Eva Schaeffer[2], Andrea Galbiati[4], Luigi Ferini-Strambi[4], Daniela Berg[2], Maria Rizzetti[5], Walter Maetzler[2], Alessandro Padovani[1]
[1]University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy, [2]Christian-Albrechts University, Neurology, Kiel, Germany, [3]ASST Spedali Civili, Neurophysiology Unit, Brescia, Italy, [4]IRCCS San Raffaele Scientific Institute, Clinical Neurosciences, Neurology-sleep Disorders Centre, Milan, Italy, [5]FERB Onlus, Parkinson's Disease Rehabilitation Center, Trescore Balneario, Italy

Aims: Gait alterations are prominent features of Parkinson's disease (PD), whereas their onset and progression is still theme of debate. Idiopathic REM sleep behavioral Disorder (iRBD) is the condition with the highest risk of conversion into PD and other alpha-synucleinopathies, and might present with subtle gait alterations. Aim of the study was to analyze gait temporal and spatial parameters in PD spectrum from the prodromal to the overt phase and to compare these to treated PD and healthy controls.
Methods: The prospective multicenter study included consecutively individuals with PSG-confirmed iRBD without parkinsonism, drug-naïve PD patients (nPD), early-stage treated PD (tPD) patients and healthy controls (HC). Each individual underwent assessment of motor and non-motor symptoms and cognitive status. All individuals underwent supervised gait assessment using mobile health technology (MHT) at normal, fast pace and during dual-task performances.
Results: The study included 208 subjects, namely 23 iRBDs, 60 nPD, 60 tPD and 65 HC. In normal gait, nPD and iRBD, but not tPD showed increased step time compared to HC. In gait at fast speed, nPD and tPD, but not iRBD exhibited increased step time compared to HC. In dual task gait, iRBD, nPD and tPD showed increased step time in comparison to HC. In all gait tasks, both nPD and tPD, but not iRBDs exhibited shorter step length compared to HC.
Conclusions: This study showed that gait temporal parameters are more sensitive to change especially in dual-task conditions in prodromal phases of the disease. Conversely, step length is a good parameter in detecting the overt phase. The findings also suggest an impact of treatment on parameters in normal gait with less impact on fast and dual task gait. Further studies are warranted to confirm these findings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1155 / #2947

Poster Topic: *Theme C: α-Synucleinopathies / C04.i. Imaging, Biomarkers, Diagnostics: Other*

CAMPTOCORMIA FOLLOWING PRAMIPEXOLE IN A PARKINSON'S DISEASE PATIENT

POSTERS: C04.I. IMAGING, BIOMARKERS, DIAGNOSTICS: OTHER

Debi Das[1], Amit Shankar Singh[2], Jeenendra Singhvi[3], Jaslovleen Kaur[3]
[1]Fortis Hospital, Emergency And Critical Care, Mohali, India, [2]Forits Hospital, Neurology, Mohali, India, [3]Fortis Hospital, Neurology, Mohali, India

Aims: To report a case of severe and reversible camptocormia following oral pramipexole therapy in a Parkinson's disease patient.
Methods: A 79-year-old male, with a known case of Parkinson's disease presented in the clinic with 3-year complaints of progressive stooped posture on standing, with anterior bending on walking, without any history of backache or fall. This bending improves when he stands with back support or lies down suggesting camptocormia. For Parkinson's disease, the patient was on oral syndopa plus (levodopa plus carbidopa) 125 mg three times a day, pramipexole 0.25 mg three times a day, amantadine 100 mg two times a day, and his tremors, bradykinesia and rigidity were significantly controlled. There was no history of any psychiatric drug intake or any symptoms suggesting atypical parkinsonism in the past. On examination, the patient walks with significant anterior bending, with left-hand dystonic posturing while walking. On lying down posture improves, and no spinal deformity or tenderness over the back is present.
Results: On evaluation, blood tests and imaging of the brain and spine were normal. In view of camptocormia developing in Parkinson's disease patients without the use of any neuroleptic agent, the patient's pramipexole is withdrawn, and his anterior bending improved significantly following this. Syndopa CR 250 mg at night was added and amantadine was further increased to control his Parkinson's disease symptoms.
Conclusions: Dopamine agonists can cause induce or aggravate camptocormia but the exact pathophysiology is unknown. Truncal dystonia, rigidity, and/or proprioceptive disintegration are the possible central mechanisms of camptocormia. How pramipexole, a dopamine agonist causing camptocormia is debatable, but identification of this rare, but important cause of camptocormia should always be considered if other causes are ruled out.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1156 / #1750

Poster Topic: *Theme C: α-Synucleinopathies / C05.a. Genetics, Epidemiology: Whole genome sequencing*

GENOMIC INSIGHTS INTO PARKINSON'S DISEASE OF A LARGE ITALIAN COHORT

POSTERS: C05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

Agata Fant[1], Francesco Musacchia[1], Sara Trova[1], Andrea Gaudio[2], Lucia Trevisan[3], Fabio Landuzzi[1], Luca Pandolfini[4], Andrea Cavalli[1], Edoardo Monfrini[5], Alessio Di Fonzo[6], Manuela Vecchi[1], Paola Mandich[2], Stefano Gustincich[1]
[1]Istituto Italiano di Tecnologia, Cmp3vda, Aosta, Italy, [2]IRCCS Ospedale Policlinico San Martino, Uoc Genetica Medica, Genova, Italy, [3]University of Genoa, Department Of Neuroscience, Rehabilitation, Ophthalmology, Genetics And Maternal And Child Health, Genova, Italy, [4]Istituto Italiano di Tecnologia, Center For Human Technologies (cht), Genova, Italy, [5]Dino Ferrari Center, Neuroscience Section, Department Of Pathophysiology And Transplantation University Of Milan, Milano, Italy, [6]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milano, Italy

Aims: Parkinson's disease (PD) is heterogeneous both clinically and genetically with complex phenotypes and different progressive course. Despite recent advancements in the identification of both rare and common variants contributing to disease onset and risk, a comprehensive evaluation of the whole genome landscape in subjects with PD will improve our knowledge of this condition. The study aims at deciphering the genetic impact of coding and non-coding regions of the genome on Parkinson's disease in Northern Italy. Therefore, we are actively recruiting patients diagnosed with Parkinson's disease and expect to collect hundreds of cases in the next years. The overall goal of the study is to integrate genome sequencing into clinical practice.
Methods: Whole genome sequencing is performed on PD subjects with short-read (Illumina) and/or long-read (Oxford Nanopore) technologies. Bioinformatic analysis is performed using the NVIDIA Clara™ Parabricks® pipeline with BWA-Mem automatized and parallelized on GPUs. We also developed a consensus pipeline for SV analyses.
Results: We sequenced hundreds of subjects on the Illumina platform and we are performing long-read sequencing on a selected group of subjects. In a subset of cases, we identified pathogenic and risk variants in known causative genes, and candidate variants in non-coding regions of the genome.
Conclusions: We are sequencing the genome of a large Italian cohort of subjects with Parkinson's disease. The integration of short- and long-read sequencing will allow the identification of novel mutations and mechanisms/pathways in unsolved clinical cases with Parkinson's disease. Additionally, the characterization of causative repeat expansions, structural variants, and epigenetic modifications on native DNA with Nanopore technology will further expand our understanding of Parkinson's disease. Overall, this study will facilitate the integration of genome sequencing in clinical practice.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1157 / #1091

Poster Topic: *Theme C: α-Synucleinopathies / C05.a. Genetics, Epidemiology: Whole genome sequencing*

BLACK AND AFRICAN AMERICAN CONNECTIONS TO PARKINSON'S DISEASE STUDY

POSTERS: C05.A. GENETICS, EPIDEMIOLOGY: WHOLE GENOME SEQUENCING

Peter Wild Crea[1,2], Mary Makarious[2,3], Kristin Levine[1,4], Daniel Vitale[5,6], Mathew Koretsky[7], Michael Nalls[1,8], Zih-Hua Fang[9], Deborah Hall[10], Tao Xie[11], Mahesh Padmanaban[11], Ejaz Shamim[12,13,14], David Standaert[15], Marissa Dean[15], Elizabeth Disbrow[16], Ashley Rawls[17], Justin Solle[18], Naomi Louie[18], Kimberley Billingsley[2,19], Pilar Alvarez Jerez[2,3], Dena Hernandez[2], Sampath Arepalli[2], Laksh Malik[1], Abigail Miano-Burkhardt[1,2], Hampton Leonard[20,21], Hirotaka Iwaki[1,8], Cornelis Blauwendraat[2,22], Andrew Singleton[2,22], Sara Bandres Ciga[1]
[1]National Institutes of Health, Center For Alzheimer's And Related Dementias, Bethesda, United States of America, [2]National Institute on Aging, Laboratory Of Neurogenetics, Bethesda, United States of America, [3]UCL Movement Disorders Centre, University College London, London, United Kingdom, [4]Data Tecnica International, Data Tecnica International, Washington, United States of America, [5]DataTecnica LLC, Datatecnica, Washington, DC, United States of America, [6]National Institutes of Health, Center For Alzheimers And Related Dementia, Rockville, United States of America, [7]National Institutes of Health, Center For Alzheimer's And Related Dementias, Rockville, United States of America, [8]Data Tecnica LLC, Data Tecnica Llc, Washington, United States of America, [9]German Center for Neurodegenerative Diseases, Dzne, Tübingen, Germany, [10]Department of Neurological Sciences, Rush University Medical Center, Chicago, United States of America, [11]University of Chicago Medicine, Department Of Neurology, Chicago, United States of America, [12]National Institute of Neurological Disorders and Stroke, Human Motor Control Section, Bethesda, United States of America, [13]Kaiser Permanente Mid-Atlantic States, Department Of Neurology, Largo, United States of America, [14]Kaiser Permanente, Midatlantic Permanente Research Institute, Rockville, United States of America, [15]University of Alabama at Birmingham, Department Of Neurology, Birmingham, United States of America, [16]Department of Neurology, LSU Health Shreveport, Lsu Health Shreveport Center For Brain Health, Shreveport, United States of America, [17]University of Florida Norman Fixel Institute for Neurological Diseases, Neurology Movement Disorders, GAINESVILLE, United States of America, [18]Michael J. Fox Foundation for Parkinson's Research, Department Of Clinical Research, New York, United States of America, [19]Bldg T44, 9000 Rockville Pike, Center Of Alzheimer's And Related Dementias, Card, Nih, Bethesda, United States of America, [20]Center for Alzheimer's and Related Dementias, National Institutes Of Health, Bethesda, United States of America, [21]DataTecnica, Na, Washington, United States of America, [22]National Institute on Aging and National Institute of Neurological Disorders and Stroke, National Institutes of Health, Center For Alzheimer's And Related Dementias, Bethesda, United States of America

Aims: BLAAC PD is a multi-center study recruiting Black and African American individuals with Parkinson's Disease (PD) and healthy controls. BLAAC PD aims to provide a platform for replication studies to explore the relevance of genetic findings reported in other populations and investigate genotype-phenotype correlations. The ultimate goal is to create a foundational cohort to assess diverse aspects of PD in this historically excluded population and serve as a model for diversity and equity in research.
Methods: BLAAC PD collects samples from six sites across the United States. A total of 167 cases and 220 controls have been collected. Following DNA extraction, samples are genotyped and imputed, followed by ancestry assessment through a pre-trained machine learning model based on reference sample series. A comprehensive assessment was conducted to investigate known and novel genetic contributors
Results: Our analyses showed consistent differences in variant frequencies, magnitude of effects and

risk alleles for disease-causing mutations in PD known genes including SNCA, VPS35, LRRK2, PRKN, PINK1, DJ1 and GBA. Additionally, we screened genetic risk loci known to be associated with PD in multiple ancestral populations including over 100 loci. We also assessed structural variants in early-onset and familial PD cases.

Conclusions: These findings highlight the need for diverse representation in genetic research. Insufficiently diverse genetic data may exacerbate health disparities once translated to the clinic. BLAAC PD will help resolve the cross-ancestry applicability of drug targets, treatments and preventative measures by elucidating the genetic architecture of disease in African and African admixed ancestries and also providing a platform for replication studies of previous work in other populations. Looking ahead, BLAAC PD plans to continue recruiting and genotyping participants to serve as a foundational cohort for diverse genetic studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1158 / #603

Poster Topic: *Theme C: α-Synucleinopathies / C05.b. Genetics, Epidemiology: Disease-causing mutations*

LONG-READ SEQUENCING TO IDENTIFY UNREVEALED SECOND HIT IN AUTOSOMAL RECESSIVE PARKINSON'S DISEASE

POSTERS: C05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Kensuke Daida[1,2], Manabu Funayama[2], Kimberley Billingsley[3], Laksh Malik[4], Breeana Baker[4], Mayu Ishiguro[2], Hiroyo Yoshino[2], Yuanzhe Li[2], Kenya Nishioka[2], Cornelis Blauwendraat[1], Nobutaka Hattori[2]
[1]NIH, Laboratory Of Neurogenetics, Bethesda, United States of America, [2]Juntendo University, 2-1-1 Hongo Bunkyo, Tokyo, Japan, [3]Bldg T44, 9000 Rockville Pike, Center Of Alzheimer's And Related Dementias, Card, Nih, Bethesda, United States of America, [4]National Institutes of Health, Center For Alzheimer's And Related Dementias, Bethesda, United States of America

Aims: *PRKN* is the most frequent genetic cause of young-onset Parkinson's disease (YOPD). Approximately 3% of the YOPD is carrier of two damaging *PRKN* alleles. Many patients with YOPD are still genetically unresolved and some have only heterozygous variants in *PRKN* identified by conventional sequencing methods such as multiplex ligation-dependent probe amplification (MLPA) and short-read sequencing. Our previous study identified a 7.4 Mbp inversion in *PRKN* using long-read sequencing. We hypothesized that some YOPD patients with heterozygous variants of *PRKN* gene will likely have complex structural variants like inversions in the *PRKN* gene as an unrevealed second damaging variant which is difficult to identify using short-read sequencing. Thus, we aimed to elucidate the role of complex *PRKN* structural variants using long-read sequencing.
Methods: Parkinson's disease (PD) patients with age at onset younger than 50 were screened genetically by short-read amplicon sequencing and MLPA to identify potential causal variants in the causative genes for PD. Oxford Nanopore long-read sequencing was performed to patients who only have one heterozygous variants in *PRKN*.
Results: 37 PD patients were identified to have heterozygous *PRKN* variants (Female: Male = 23:14, Age at onset = 34.5 ± 9.34) including 14 patients with point mutations and 23 with exon deletion or duplication. Oxford Nanopore long-read DNA sequencing has been performed on all 37 patients and we have got enough data so far for the analysis (Overall output; 95.2 ± 21.73 Gb, N50 20.9 ± 4.55 kb).
Conclusions: Complex structural variants may exist as a second hit in heterozygous *PRKN* carriers with YOPD. Long-read sequencing can be an effective tool to identify complex structural variants in genetically unresolved patients with PD and will expand the role of *PRKN* in YOPD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1159 / #733

Poster Topic: *Theme C: α-Synucleinopathies / C05.b. Genetics, Epidemiology: Disease-causing mutations*

IDENTIFICATION OF NOVEL CANDIDATE GENES FOR LATE ONSET PARKINSON'S DISEASE: POLYGENIC MODEL OF INHERITANCE AND PARKINSON'S DISEASE RISK

POSTERS: C05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Teresa Esposito[1,2], Federica Carrillo[2], Giorgio Fortunato[2], Laura Ianiro[1], Nicola Modugno[1], Sara Pietracupa[1], Luigi Pavone[1], Teresa Nutile[2], Danilo Licastro[3], Nicole Piera Palomba[1]
[1]IRCCS Neuromed, Neurology, Pozzilli (IS), Italy, [2]Institute of Genetics and Biophysics CNR, Biomedicine, Napoli, Italy, [3]AREA Science Park, Argo Open Lab Platform For Genome Sequencing, Trieste, Italy

Aims: We have recently reported the identification of new rare gene variants in Parkinson's disease (PD) patients that support polygenic contribution to the disease. Here we aimed at extending the analysis to new families to identify novel genes that could increse the power of this diagnostic test.
Methods: Whole exome sequencing was performed in a cohort of 1150 Italian individuals including 850 PD patients (23 families and 804 independent patients) and 300 healthy subjects.
Results: Family-based approach of 23 PD families identified polygenic inheritance of rare (MAF<0.01) and deleterius (CADD>20) variants in 22 PD candidate genes including: *ATP10B, ACMSD, ANKK1, ANKRD50, DBH, DNAJC13, EIF4EBP1, GIGYF2, GRK5, HTRA2, LRRK2, MAN2C1, PACSIN1, PINK1, RHOT2, SH3GL2, SLC6A3, SMPD1, SNCAIP, SPG11, SYNJ1, TMEM175*. All these genes are expressed in human dopaminergic neurons and are involved in pathways potentially deregulated in PD. The co-inheritance of multiple rare variants (≥ 2) in a panel of 36 PD genes, selected combining data from this study with our published work, may predict PD occurrence in about 50% of patients, both familial and sporadic cases, with high significance (PD *sv* cnt, $p = 1.6 \times 10^{-6}$; familial PD *vs* cnt, $p = 3.9 \times 10^{-8}$; sporadic PD *vs* cnt, p = 0.0002). Furthermore, patients carrying ≥ 2 variants showed higher risk of manifesting cognitive decline (p=0.0008) and an erlier age at onset of the disease (p=0.01). LRRK2 mutation carriers showed higher risk of manifesting levodopa induced dyskinesia (p=0.009). MRI volumetric analysis in a subset of patients carrying ≥ 2 variants showed significant increase of red nucleous (p=0.007), coudate (p=0.01) and cortical thickness (p=0.01) volumes.
Conclusions: Our data underline the importance of rare variants in the genetics of PD and may be relevant for its prediction, diagnosis and treatment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1160 / #1212

Poster Topic: *Theme C: α-Synucleinopathies / C05.b. Genetics, Epidemiology: Disease-causing mutations*

RARE VARIANT PATHWAYS: ANALYZING GENE SET BURDEN OF BIOLOGICAL PATHWAYS ASSOCIATED WITH RARE VARIANTS IN PARKINSON'S DISEASE.

POSTERS: C05.B. GENETICS, EPIDEMIOLOGY: DISEASE-CAUSING MUTATIONS

Vanessa Pitz[1], Allen Fu[2], Sara Bandres Ciga[3], Andrew Singleton[4], Mary Makarious[5], Cornelis Blauwendraat[6]
[1]National Institutes of Health, Integrative Neurogenomics Unit, Laboratory Of Neurogenetics, Bethesda, United States of America, [2]National Institutes of Health, Molecular Genetics Unit, Laboratory Of Neurogenetics, Bethesda, United States of America, [3]National Institutes of Health, Center For Alzheimer's And Related Dementias, Bethesda, United States of America, [4]National Institutes of Health, Molecular Genetics Unit, Laboratory Of Neurogenetics, Center For Alzheimer's And Related Dementias, Bethesda, United States of America, [5]National Institute on Aging, Laboratory Of Neurogenetics, Bethesda, United States of America, [6]National Institutes of Health, Integrative Neurogenomics Units, Laboratory Of Neurogenetics, Center For Alzheimer's And Related Dementias, Bethesda, United States of America

Aims: This study aims to elucidate the biological pathways associated with Parkinson's disease (PD) by analyzing rare genetic variant classes and their cumulative burden within gene sets. Exploring rare genetic variants (frequency <1%) as potential causes or significant risk factors for PD has been challenging. Burden tests assess the combined burden of rare and protein-altering variants in specific gene sets, shedding light on crucial biological pathways related to PD.
Methods: Using data from AMP-PD and the UK Biobank, we categorized variant classes based on SnpEff and LOFTEE predictions regarding impact and prediction scores. Statistical analyses utilized burden test algorithms, with adjustments specific to each dataset. Variant classes were defined based on SnpEff and LOFTEE predictions, including missense, moderate or high impact, high confidence loss of function, and Combined Annotation Dependent Depletion (CADD) PHRED score>20 variants. We used gene-sets from the Molecular Signatures Database (MSigDB) and applied custom burden test scripts (SKAT-O and CMC WALD) to each variant class and MAFs <1% and <0.01%.
Results: We conducted rare and ultra-rare variant pathway analyses on 3,090 canonical pathway gene sets: UKB contributed most gene sets with all 3,090 being present, 2,679 of which were found in AMP-PD. We report pathways significantly associated with PD, based on: passing multiple test correction at P<1.6e-05, generating robust statistical outputs, and remaining significant in a meta-analysis of both data sets.
Conclusions: Despite numerous gene associations with PD, our understanding of biological processes and networks remains incomplete. This extensive rare variant burden pathway analysis provides a valuable tool for identifying crucial biological pathways in PD. The results hold potential for guiding functional prioritization and discovering potential therapeutic targets for PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1161 / #1288

Poster Topic: *Theme C: α-Synucleinopathies / C05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

CO-INFLUENCE OF SEX AND GBA GENOTYPE ON THE PHENOTYPE OF PARKINSON DISEASE PATIENTS

POSTERS: C05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Micol Avenali[1], Silvia Caminiti[2], Pierfrancesco Mitrotti[2], Ilaria Palmieri[3], Giada Cuconato[4], Luca Gallo[2], Rosaria Calabrese[5], Caterina Galandra[3], Cristina Tassorelli[1], Roberta Zangaglia[6], Fabio Blandini[7], Enza Maria Valente[8]
[1]University of Pavia, Department of Brain and Behavioral Sciences, Irccs Mondino Foundation, Pavia, Italy, [2]University of Pavia, Department Of Brain And Behavioral Sciences, Pavia, Italy, [3]IRCCS Mondino Foundation, Neurogenetics Research Centre, Pavia, Italy, [4]University of Pavia, Department Of Molecular Medicine, Pavia, Italy, [5]IRCCS Mondino Foundation, Irccs Mondino Foundation, Pavia, Italy, [6]IRCCS Mondino Foundation, Parkinson Disease And Movement Disorders Unit, Pavia, Italy, [7]University of Pavia, Department of Brain and Behavioral Sciences, Ca' Granda Irccs Foundation, Ospedale Maggiore Policlinico, Milan, Pavia, Italy, [8]University of Pavia, Department of Molecular Medicine, Irccs Mondino Foundation, Neurogenetics Research Centre, Pavia, Italy

Aims: To investigate the potential interaction of sex and GBA mutations on the phenotype of patients with Parkinson Disease (PD).
Methods: GBA-relatedPD and nonGBA-PD underwent a comprehensive clinical characterization (MDS-UPDRS-I-IV, MOCA, SCOPAUT, UPSIT, RBDSQ, BDI and HADS-A). Clinical scores were compared between PD groups. Clustering analysis based on genetic status, demographic and clinical measures was applied to delineate new subgroups. Subgroup analysis according to GBA mutations severity was also performed.
Results: 53 GBA-PD (56% males) and 83 nonGBA-PD (64% males) were enrolled. Within GBA-PD, 10 subjects carried mild, 18 severe, 15 risk and 10 unknown variants. GBA-PD were similar to nonGBA-PD expect for significantly younger age at disease onset and higher BDI and HADS-A scores. Comparison analysis stratified by sex showed that GBA-PD males diverged significantly from nonGBA-PD males in terms of depressive symptoms, while females were comparable in the two groups. Cluster analysis based on combined clinical parameters allowed splitting the entire sample into 2 clusters, which discriminated mainly nonGBA-PD males (Cluster1), from the remaining groups (all females and GBA-PD males - Cluster 2). Dysautonomia, mood and sleep disorders were the most relevant features influencing the clustering process. Interestingly, a significantly higher proportion of mild and severe GBA mutations belonged to Cluster 1, while most of risk variants fell in Cluster 2.
Conclusions: This study highlights the intricate interplay between sex, genetic status, and non-motor features of PD. In this cohort, GBA status was associated with distinct non-motor features (particularly mood disorders), with overt sex-related differences. While these data warrant replication in independent cohort, they emphasize that the interplay of sex and genetic status need to be considered when stratifying PD patients, for improving more accurate precision medicine approaches.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1162 / #1724

Poster Topic: *Theme C: α-Synucleinopathies / C05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

AQUAPORIN 4 SINGLE NUCLEOTIDE POLYMORPHISMS AFFECT SLEEP AND COGNITIVE CLINICAL PHENOTYPE IN PATIENTS WITH PARKINSON'S DISEASE

POSTERS: C05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Edoardo De Natale[1], Alana Terry[1], Heather Wilson[1], Holly Wright[1], Julie Wollaston Moss[1], Laurence Knowles[1,2], Flavia Niccolini[3,4], Sura Albayati[5], Marios Politis[1]
[1]University of Exeter Medical School, Neurodegeneration Imaging Group, London, United Kingdom, [2]Royal Devon University Healthcare NHS Foundation Trust, Department Of Neurology, Exeter, United Kingdom, [3]Queen Elizabeth Hospital, Department Of Neurology, London, United Kingdom, [4]Frimley Park Hospital, Department Of Neurology, Frimley, United Kingdom, [5]East Kent University Hospitals NHS Foundation Trust, Department Of Neurology, Ashford, United Kingdom

Aims: We present preliminary results of an ongoing large cross-sectional cohort study on patients with Parkinson's disease (PD) to assess the role of single nucleotide polymorphisms (SNPs) in the Aquaporin 4 (AQP4) gene, an essential gene for the function of the glymphatic system, in determining clinical phenotypes of PD.
Methods: 176 PD patients consecutively enrolled across three sites in southern England performed a thorough in-person and online assessment of motor and non-motor symptoms, with particular focus on the sleep – Parkinson's disease Sleep Scale (PDSS); Epworth Sleepiness Scale (ESS); Insomnia Severity Index (ISI); and cognitive performance – Montreal Cognitive Assessment (MoCA) and Cambridge Neuropsychological Test Automated Battery (CANTAB). Venous blood was collected and analysed for detection of variants on SNPs of the AQP4 gene.
Results: Carriers of the rs162007 and rs162009 SNPs presented higher scores on the ESS (p=0.01 and p=0.02, respectively) and worse performance on the One-Touch Stockings of Cambridge test (OTS) assessing executive function (z-score p=0.016 and p=0.02, respectively). Homozygosity for the rs3875089 SNPs associated with worse sleep performance as assessed with the ISI (p=0.024), and PDSS (p=0.04). Carriers of the rs9951304 SNP displayed worse executive function on the OTS (p=0.009). Conversely, homozygosity for the rs3763040 SNP yielded better sleep scores on the ESS scale (p=0.045). and carriers of the rs72878787 SNP, better cognitive performance on the MoCA (p=0.026). This latter SNP was also associated with worse depressive symptoms as assessed with the Beck Depression Inventory II scale (BDI-II, p=0.015). Homozygous rs3875089 SNP carriers showed significantly higher total scores on NMSS (p=0.017).
Conclusions: These preliminary results provide evidence of a role of AQP4 SNPs in determining PD phenotypes mainly associated with altered sleep and cognition.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1163 / #8

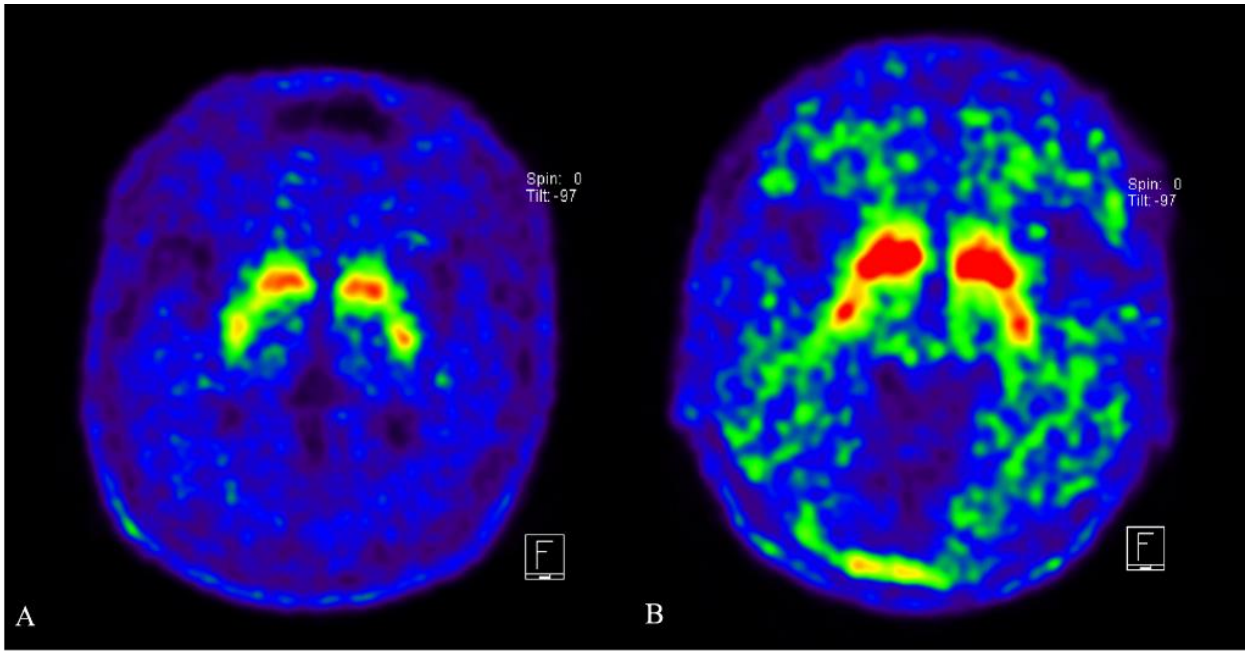
Poster Topic: *Theme C: α-Synucleinopathies / C05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

NOVEL COMPOUND HETEROZYGOUS ATP10B MUTATIONS IN A FAMILY WITH EARLY ONSET PARKINSON'S DISEASE

POSTERS: C05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Da Eun Jeong[1], Min Ju Kang[1], Kyuhwan Shim[2]
[1]Central Veterans Hospital, Neurology, Seou, Korea, Republic of, [2]Gachon University, Department Of Bionano Technology, Seongnam-si, Korea, Republic of

Aims: Novel pathogenic gene, ATPase phospholipid transporting 10B (ATP10B) mutations are established casuse of autosomal recessive early onset Parkinson's Disease(EOPD) or dementia with Lewy bodies (DLB). ATP10B mutations participate in contribute to loss-of-function mechanism resulting in a dysregulated lipids glucosylceramide(GluCer) and phosphatidylcholine(PC) homeostasis. That induces lysosomal degradation, which contributes to the aggregation of alpha-synuclein.
Methods:



(A. Son and B. Mother) 18F-FP-CIT PET imaging shows bilateral posterior putamen with relative sparing of the ventral putamen decreased uptake with relative sparing of the ventral putamen. In genetic analysis, identical novel ATP10B mutation were revealed. This is the first report of familial PD with ATP10B mutation in south Korea.
Results: The mutation could affect the structural changes by the alternation of the intra-molecular interactions with other amino acids. 3D structure and interactions between amino acids were predicted from wild-type and mutant protein sequences (Figure 3). The 3D structure of wild-type protein was obtained from the AlphaFold database. Wild-type and mutant amino acids are presented, and the predicted interaction with other structura ladjacent amino acid was indicated and connected by the dashed line. The substitution from Arg303 to Trp303 led to the contraction of cavity volume of the protein.

In addition, the interaction between Arg303 and Arg1043 was disappeared when mutant Trp303 was replaced. On the other hand, ATP10B protein is a transmembrane protein in the lysosome, which may be caused by membrane instability by mutation.

Conclusions: To our knowledge, this is the korean report of ATP10B variant in parkinson's disease family. We suggest that genetic screening panel for should be provided in Korean PD patients with strong family history, including ATP10B mutation, for appropriate genetic counselling and improve the diagnostic accuracy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1164 / #1239

Poster Topic: *Theme C: α-Synucleinopathies / C05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

UNCOVERING GENOMIC ASSOCIATIONS WITH DATA-DRIVEN PAIN TRAJECTORIES IN PERSONS WITH PARKINSON'S DISEASE

POSTERS: C05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Shiying Liu[1], Douglas Gunzler[1,2], Steven Gunzler[3], Dana Crawford[1,4], Farren Briggs[5]
[1]Case Western Reserve University, Population And Quantitative Health Sciences, Cleveland, United States of America, [2]Case Western Reserve University School of Medicine, Center For Health Care Research And Policy, Cleveland, United States of America, [3]University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, Neurological Institute, Cleveland, United States of America, [4]Case Western Reserve University, Cleveland Institute For Computational Biology, Cleveland, United States of America, [5]University of Miami Miller School of Medicine, Department Of Public Health Sciences, Miami, United States of America

Aims: As a prevalent and complex non-motor symptom, pain is experienced by a majority of people with Parkinson's disease (PWP). Our understanding of its genetic underpinnings remains limited, challenging advancements in this area. This study aims to identify the genetic determinants associated with longitudinal pain trajectories in PWP in the early stages of their disease.
Methods: We utilized five clusters previously identified from longitudinal pain trajectories of patient-reported pain with a data-driven approach. Two genome-wide association studies (GWAS) were conducted on 4,159 PWP with European genetic ancestry. The extreme GWAS targeted PWP exhibiting a severe pain trajectory, while the multinomial GWAS encompassed all four trajectories with increasing pain. Both studies drew comparisons with PWP without significant pain over time. We also employed gene-based and pathway-enrichment analytical techniques for holistic insight.
Results: While no variant reached genome-wide significance, suggestive associations warrant further attention in both GWAS. The top hit in the extreme GWAS is rs117108018 (OR=9; $p=2.5x10^{-7}$), a brain tissue eQTL, along with other genic SNP associations, such as *MAPK8*-rs72794357 (OR=4.6; $p=1x10^{-6}$) and *VLDLR*-rs4741753 (OR=2.2; $p=1.5x10^{-6}$), implicating the role in brain development and opioid dependence. For multinomial GWAS, we identified the most significant genetic variant as rs61881484 ($p=2x10^{-7}$) that intersects with a transcription factor peak that targets *CREB1*, a critical element in synaptic plasticity within sensory neurons and is involved in the modulation of neuropathic pain. We also observed genes associated with neurotransmitter regulation and opioid dependence enriched in our findings.
Conclusions: Our findings are consistent with known neuropathic mechanisms and suggest the role of neuropathic pain in contributing to pain severity. Additionally, we observed potential associations for opioid-related pathways in PWP, highlighting potential therapeutic avenues for future investigations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1165 / #1738

Poster Topic: *Theme C: α-Synucleinopathies / C05.c. Genetics, Epidemiology: GWAS, genetic associations, susceptibility & protective genes*

DISSECTING THE GENETIC INTERACTIONS CONTROLLING A-SYNUCLEIN ACCUMULATION IN PARKINSON'S DISEASE

POSTERS: C05.C. GENETICS, EPIDEMIOLOGY: GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES

Esther Muñoz Pedrazo[1], Carles Calatayud Aristoy[1], Sandra Fernandez Gallego[1], Suresh Poovathingal[2]
[1]VIB Center for Brain & Disease Research - KU Leuven, Department Of Neurosciences, Leuven, Belgium, [2]KU Leuven, Neuroscience, Leuven, Belgium

Aims: Genetic risk constitutes complex interactions among numerous genomic loci to affect disease susceptibility. Given the simultaneous involvement of numerous genetic factors, and the difficulty to identify the relevant genes affected by genome-wide association studies (GWAS), it has been notoriously difficult to define the most critical pathways for further functional testing. In this project I will use novel technology to define, in a high throughput and unbiased manner, which GWAS associated genes cause risk in Parkinson's disease (PD) and how their functional and complex genetic interactions are shaped.
Methods: The most recent GWAS of PD identified 90 risk variants across 78 genomic loci. I will use to a novel dual CRISPR inhibition/activation tool that we recently developed to up- and downregulate combinations of genes associated with these GWAS signals in human dopaminergic neurons, the preferentially affected cell type in PD.
Results: We have generated a stable iPSC line that successfully express our CRISPRi/a system in hiPSC- derived neurons The CRISPRi/a system succesfully increase and decrease the expression of genes in hiPSC-derived neurons.
Conclusions: This project takes a conceptual new approach and brings functional insight into GWAS and complex human genetic interactions in a major neurodegenerative disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1166 / #1890

Poster Topic: *Theme C: α-Synucleinopathies / C05.e. Genetics, Epidemiology: Other*

BAYESIAN ESTIMATION OF REM SLEEP BEHAVIOURAL DISORDER PREVALENCE AT THE CANTON LEVEL IN LUXEMBOURG

POSTERS: C05.E. GENETICS, EPIDEMIOLOGY: OTHER

Eduardo Jubal[1], Anna Schritz[1], Gloria Aguayo[2], Olena Tsurkalenko[2], Tainá Marques[3], Clarissa Gomes[4], Magali Perquin[2], Claire Pauly[3], Lukas Pavelka[3], Rajesh Rawal[4], Soumyabrata Ghosh[4], Venkata Satagopam[4], Rejko Krüger[3], Michel Vaillant[1]
[1]Luxembourg Institute of Health, Competence Centre For Methodology And Statistics, Strassen, Luxembourg, [2]Luxembourg Institute of Health, Department Of Precision Health, Strassen, Luxembourg, [3]Luxembourg Institute of Health, Transversal Translational Medicine, Strassen, Luxembourg, [4]University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Belvaux, Luxembourg

Aims: The primary aim is to estimate the true prevalence of REM sleep behavioural disorder (RBD) in Luxembourg. RBD affects an estimated 0.5 to 1.25 percent of the general population and approximately 2 percent in older adults, translating to 40 to 100 million expected patients worldwide. RBD is a known risk factor for Parkinson's disease (PD), and its global prevalence varies due to genetic and environmental factors.
Methods: The Luxembourg national RBD study invited over 300,000 citizens to participate and succeeded in collecting data from 17,000 respondents. However, this raw data likely contains sampling biases. To refine these estimates, we applied a Bayesian Statistics approach using latent class analysis. Specifically, prior information was shaped by a beta density and combined with the data observed by the Luxembourgish study to provide a more robust estimation of the underlying prevalence.
Results: We were able to approximate the latent prevalence of RBD in Luxembourg. Our analysis produced a mean estimated prevalence of 8.2%, with a median of 8.7%. The 95% credible interval for the prevalence ranged from 1.0% to 13.3%. Additionally, test sensitivity and specificity were estimated at a mean of 98.0% and 94.6%, respectively.
Conclusions: The descriptive analysis from the Luxembourg national RBD study provides valuable initial insights but might be limited by potential sampling biases. This Bayesian analysis provides the first canton-level estimation of RBD prevalence in Luxembourg, supported by a robust measure of statistical uncertainty. The model can be updated with new data at both EU and national levels, serving as a robust instrument for current and future epidemiological research.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1167 / #1090

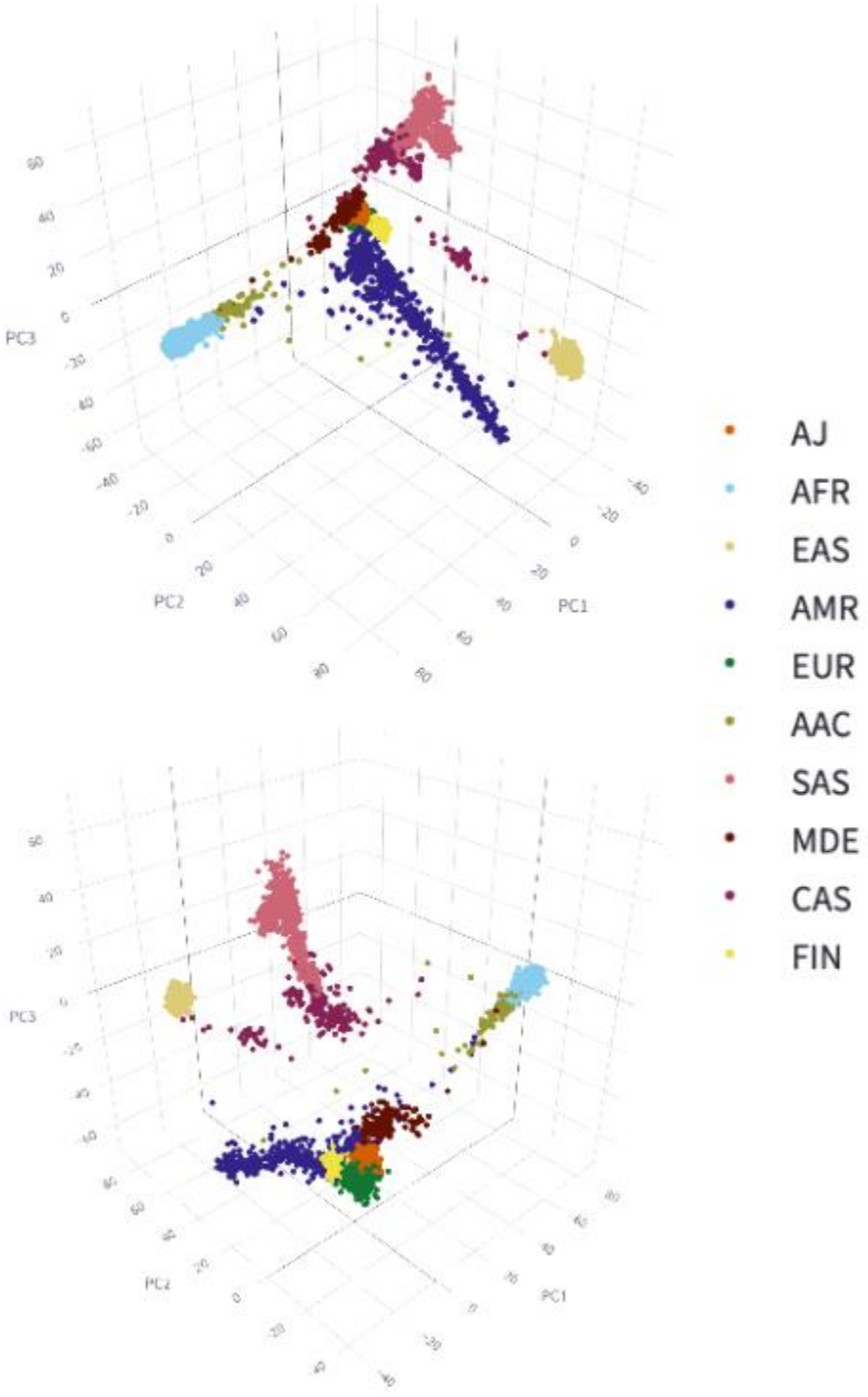
Poster Topic: *Theme C: α-Synucleinopathies / C05.e. Genetics, Epidemiology: Other*

ACCURATE AND DEPLOYABLE GENETIC ANCESTRY PREDICTION FOR NEUROLOGICAL DISORDERS

POSTERS: C05.E. GENETICS, EPIDEMIOLOGY: OTHER

Mathew Koretsky[1], Nicole Kuznetsov[1], Mary Makarious[1,2,3], Hampton Leonard[1,2,4,5], Michael Nalls[1,2,4], Daniel Vitale[1,4]
[1]Center for Alzheimer's and Related Dementias, National Institutes Of Health, Bethesda, United States of America, [2]Laboratory of Neurogenetics, National Institute on Aging, National Institutes Of Health, Bethesda, United States of America, [3]University College London, Ucl Movement Disorders Centre, London, United Kingdom, [4]DataTecnica LLC, Datatecnica Llc, Washington, United States of America, [5]DZNE, Dnze, Tuebingen, Germany

Aims: The genetic architecture of diseases varies across populations. Emphasis has been placed on collecting diverse individual-level data to run genome-wide association studies (GWAS) for different ancestries. Here, we present an accessible machine learning-based approach for genetic ancestry prediction for the NeuroChip and NeuroBooster arrays, which were designed for screening neurological disorders across diverse populations.
Methods: Reference samples from 1000 Genomes Project, Human Genome Diversity Project and an Ashkenazi Jewish population defined ten ancestry groups (Supplementary Figure 1). Common variants were identified between the reference panel and samples genotyped on each array. Principal components fit on these variants were used to train XGBoost classifiers from the reference samples that render predictions on the genotypes. The models are deployed on Docker Hub for researchers to download and use on their own computing infrastructures while staying within GDPR requirements.



Results: Models trained on 24,354 and 39,340 overlapping variants achieved test accuracies of 97.3% for NeuroChip and 98.4% for Neurobooster, respectively. A GWAS performed on African and African admixed individuals that identified a population-specific Parkinson's risk variant in *GBA1* used the NeuroChip model to confirm ancestry for 589 African samples, and the NeuroBooster model for 1,722

African and 1,334 African admixed samples. The NeuroBooster model was also used to predict ancestry for 12,728 Parkinson's cases, 1,674 Alzheimer's and related dementia cases, and 10,533 controls for the Global Parkinson's Genetics Program (GP2).

Conclusions: These models serve as a foundational workflow for studies of Parkinson's and related dementias at GP2 to quantify the impact of diverse genetic datasets in precision medicine studies of neurodegeneration. Future directions include deploying models for accurate prediction on more genotyping chips for researchers to leverage.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1168 / #1127

Poster Topic: *Theme C: α-Synucleinopathies / C05.e. Genetics, Epidemiology: Other*

GENOTOOLS: AUTOMATED GENOTYPE DATA PROCESSING AND GENOME-WIDE ASSOCIATION STUDIES

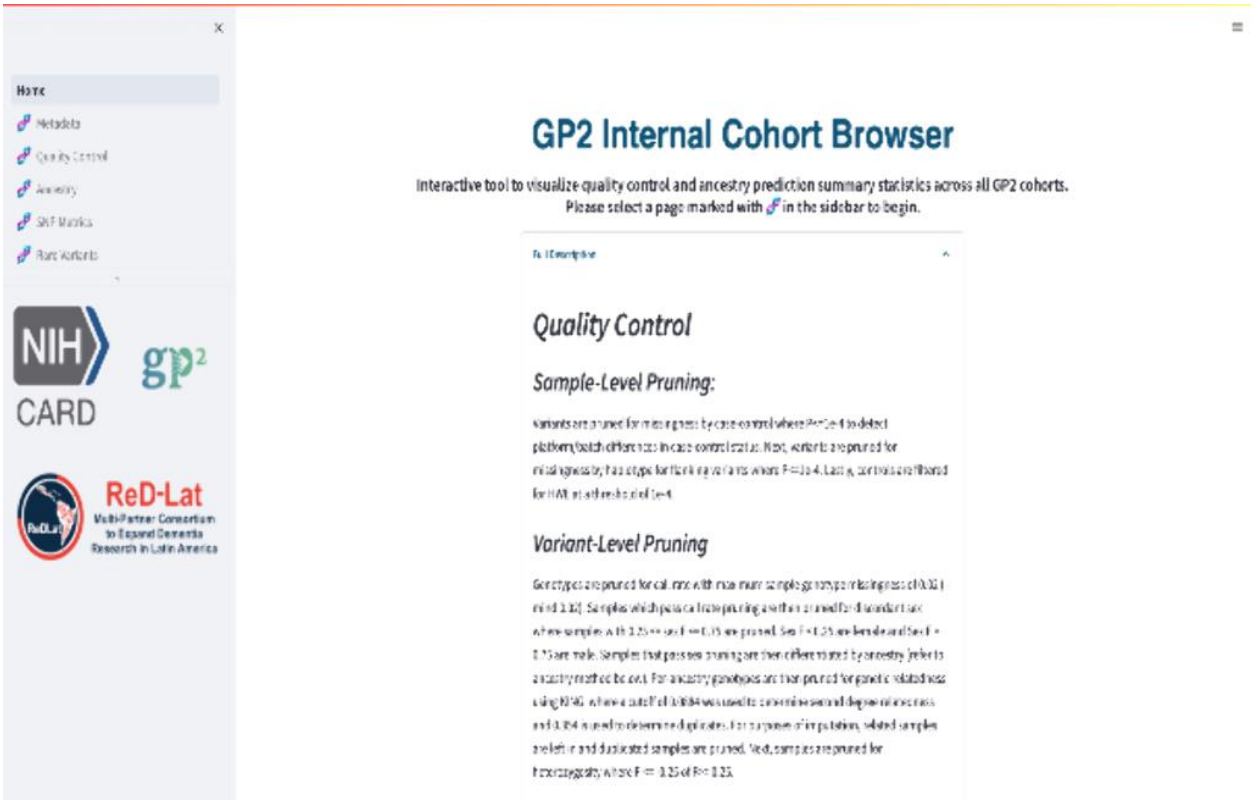
POSTERS: C05.E. GENETICS, EPIDEMIOLOGY: OTHER

Nicole Kuznetsov[1], Mathew Koretsky[2], Daniel Vitale[1,3], Kristin Levine[1,4], Hampton Leonard[1,5,6], Michael Nalls[1,7]
[1]Center for Alzheimer's and Related Dementias, National Institutes Of Health, Bethesda, United States of America, [2]National Institutes of Health, Center For Alzheimers And Related Dementias, Bethesda, United States of America, [3]DataTecnica LLC, Datatecnica, Washington, DC, United States of America, [4]Data Tecnica International, Data Tecnica International, Washington, United States of America, [5]DZNE, Dzne, Tuebingen, Germany, [6]DataTecnica LLC, Datatecnica Llc, Washington, United States of America, [7]Data Tecnica LLC, Data Tecnica Llc, Washington, United States of America

Aims: *GenoTools* is a Python package for automating and scaling genotype quality-control (QC) and genome-wide association study (GWAS) workflows. As larger, more diverse genotype sample sizes are produced, GWAS continues to be standard for nominating variant-trait associations. GenoTools simplifies large-scale, population genetics to produce clean genotypes, summary statistics, and ancestry-specific GWAS.
Methods: GenoTools uses PLINK2, with modifiable values, for missingness, genetic sex, relatedness, heterozygosity, Hardy-Weinberg, and non-random missingness QC. Ancestry is based on reference panels from 1000 Genomes Project, Human Genome Diversity Project, and an Ashkenazi Jewish population. Ancestry prediction incorporates PCA, UMAP, and linear classifiers to assign per-sample ancestry labels. Ancestry-specific GWAS is run, yielding population-specific summary statistics for meta-analysis.
Results: The Global Parkinson's Genetics Program performs data processing using GenoTools. To date, 24,935 samples across ten ancestry groups have passed QC, including 12,728 Parkinson's disease cases, 1,674 Alzheimer's disease and related dementia cases, and 10,533 controls. We developed an accompanying interactive web-application for scientists to examine these results regardless of computational skill. These processed data were also used in a GWAS of African and African-admixed ancestry which identified a novel Parkinson's risk variant in *GBA1*. GenoTools refined GWAS signals for *APOE*, *GBA1*, *SNCA*, and *LRRK2* while leveraging complex ancestry models, as these GWAS signals are enriched within broadly-European, Ashkenazi, and Finnish populations (Table 1).

SNP_ID_hg38	Gene	EUR_freq
19:44907187:G:A	*APOE*	0.404569
1:155236550:A:C	*GBA*	0.29654
12:40277196:C:A	*LRRK2*	0.156912
4:89814855:C:A	*SNCA*	0.250928

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



Choose a release!

5

Choose a cohort!

GP2 Release 5 FULL

GP2 Release 5 FULL

Number of Samples in Dataset

26,728

Number of Samples After Pruning

24,935

NIH CARD

gp2

ReD-Lat
Multi-Partner Consortium to Expand Dementia Research in Latin America

GP2 Release 5 FULL Metadata

Choose an ancestry!

EUR

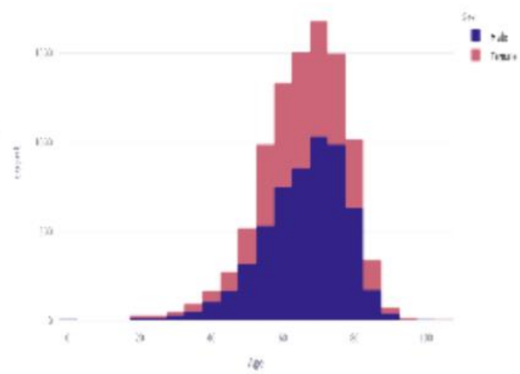
Stratify Age by:

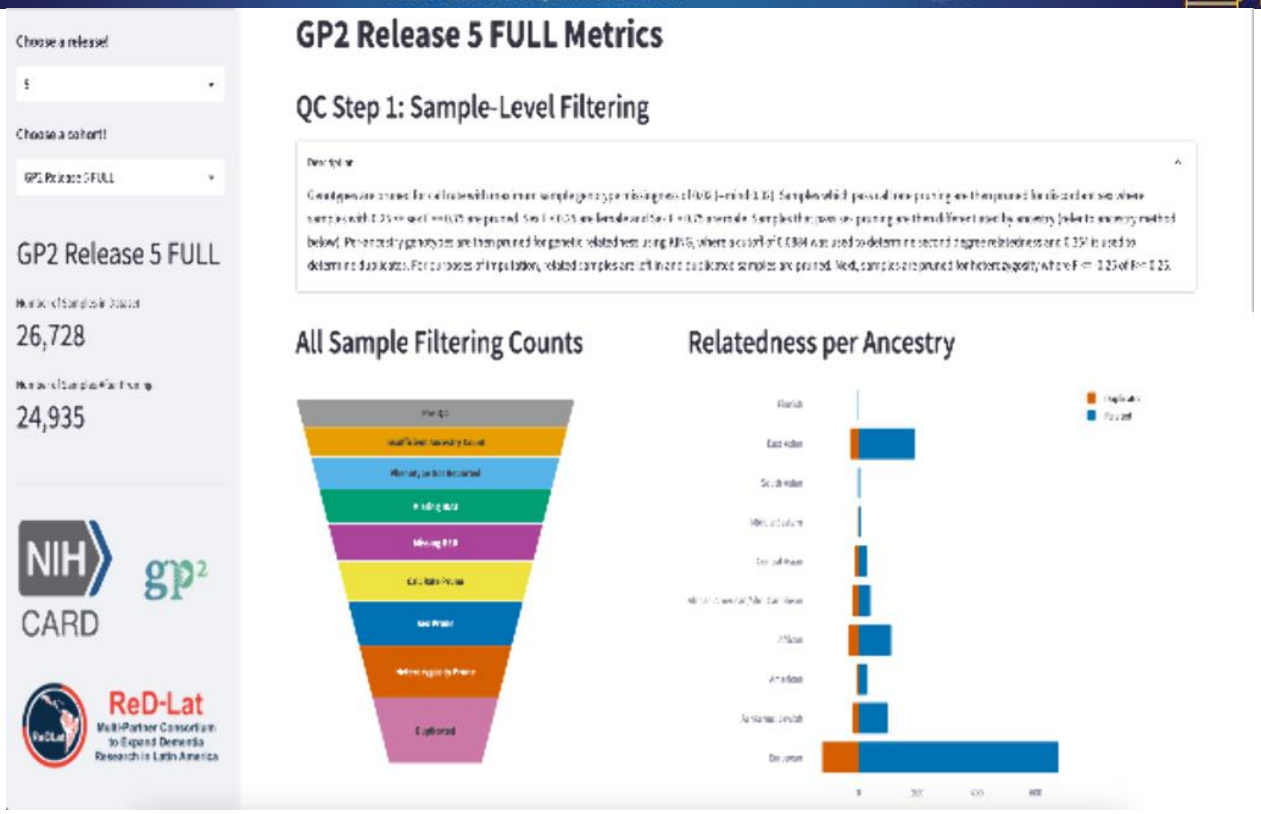
- None
- Sex
- Phenotype

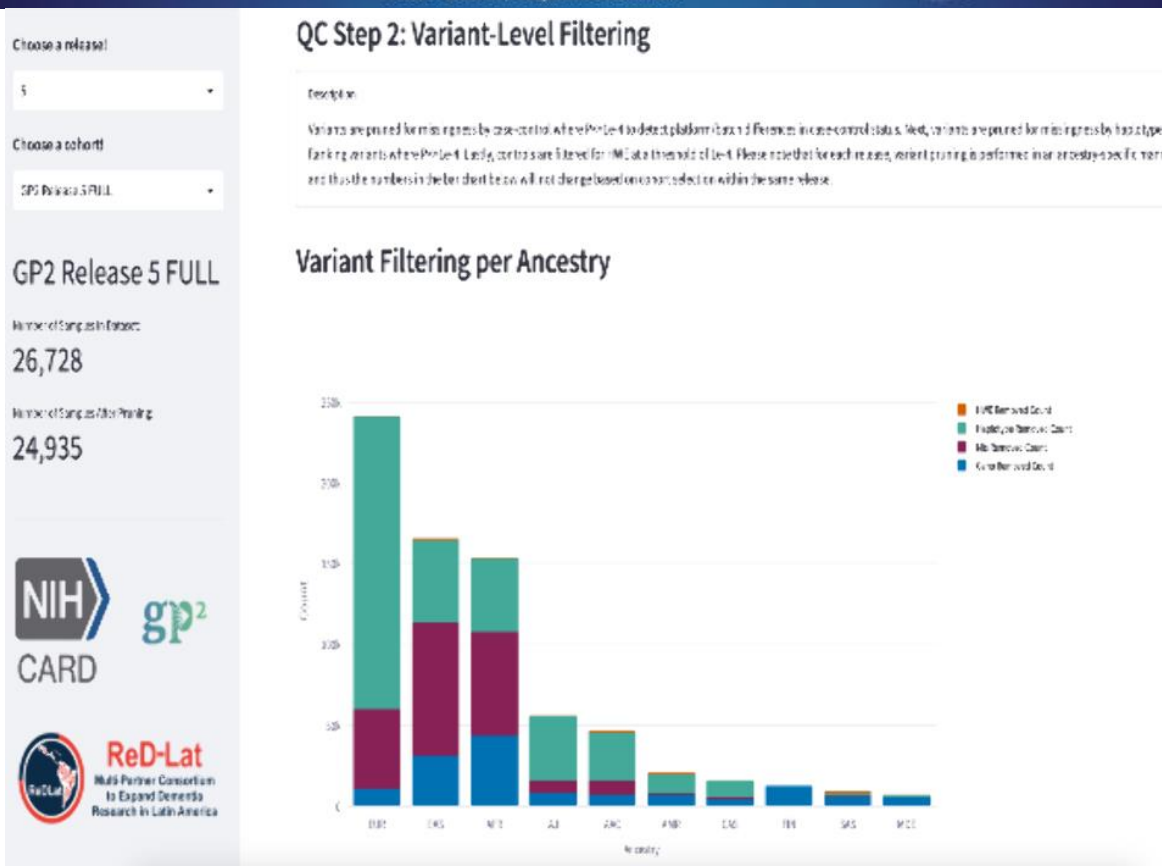
Phenotype Count Split by Sex

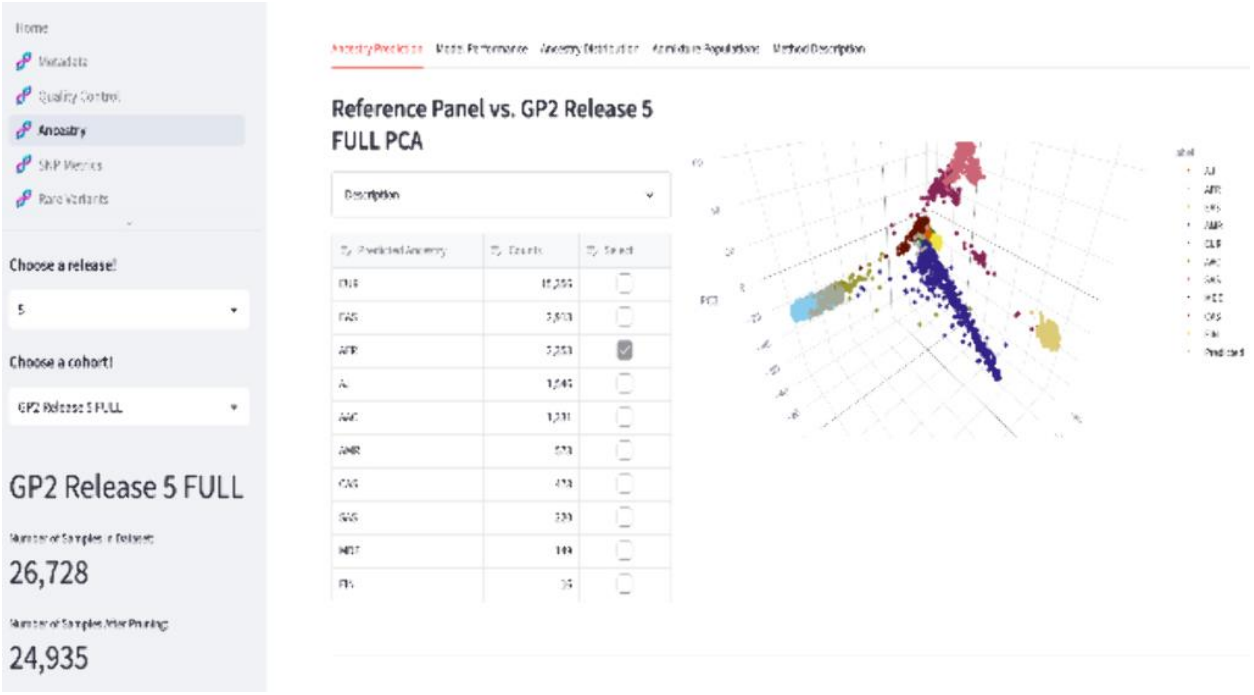
	[illegible]	[illegible]	[illegible]	Total
Male	[illegible]	[illegible]	[illegible]	[illegible]
Female	[illegible]	[illegible]	[illegible]	[illegible]

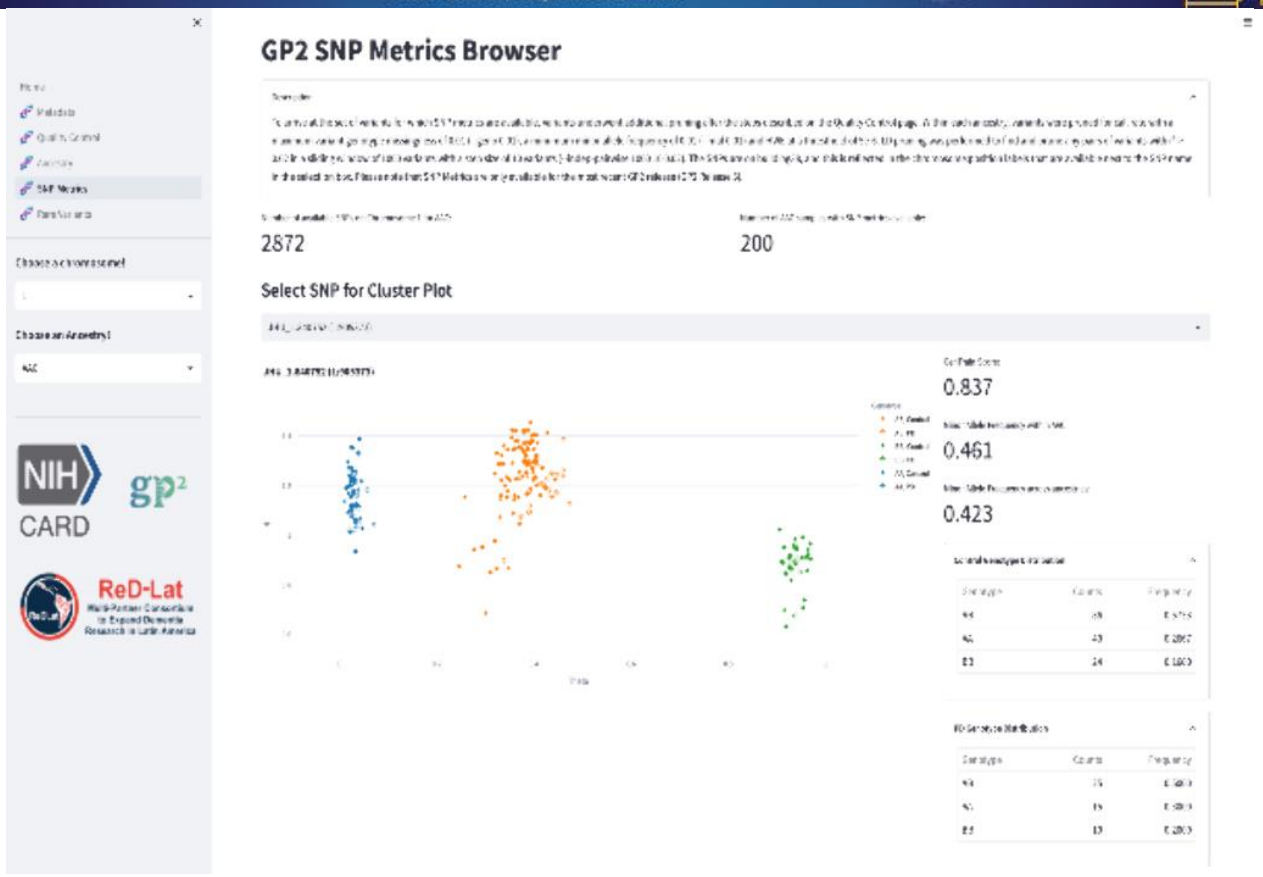
Age Distribution by Sex

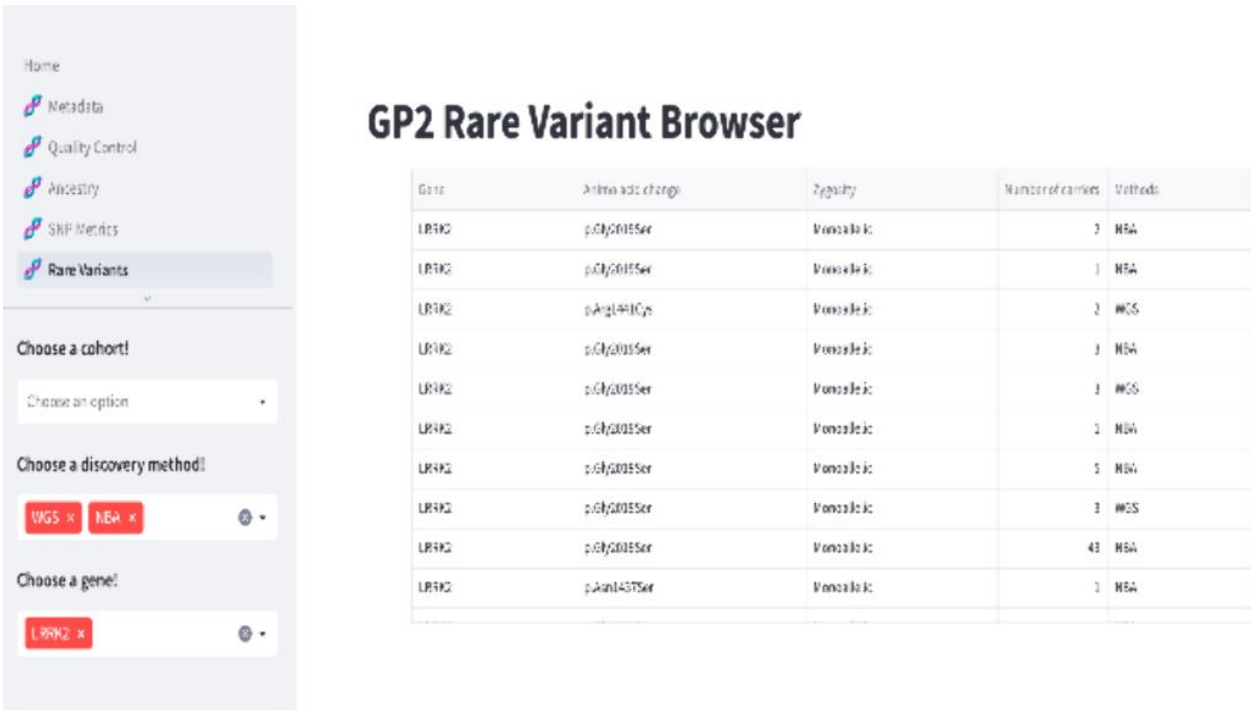



Choose a release!
5
Choose a cohort!
GP2 Release 5 FULL
GP2 Release 5 FULL
26,728
24,935
NIH
CARD
gp2
ReD-Lat
Multi-Partner Consortium to Expand Dementia Research in Latin America
GP2 Release 5 FULL Metrics
QC Step 1: Sample-Level Filtering
All Sample Filtering Counts
Relatedness per Ancestry


Choose a release!
5
Choose a cohort!
GP2 Release 5 FULL
GP2 Release 5 FULL
26,728
24,935
NIH
CARD
gp2
ReD-Lat
Multi-Partner Consortium to Expand Dementia Research in Latin America
QC Step 2: Variant-Level Filtering
Variant Filtering per Ancestry


Home
Metadata
Quality Control
Ancestry
SNP Metrics
Rare Variants
Choose a release!
5
Choose a cohort!
GP2 Release 5 FULL
GP2 Release 5 FULL
26,728
24,935
Reference Panel vs. GP2 Release 5 FULL PCA
Description





Conclusions: GenoTools has shown success in producing high-quality calls at a level

deeper than commonly used in GWAS, with strong computational efficiency leading to discoveries in Parkinson's disease genetics. GenoTools will be broadly used in expediting neurodegenerative disease research and beyond.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1169 / #133

Poster Topic: *Theme C: α-Synucleinopathies / C06.a. Cell, Molecular and Systems Biology: a-synuclein*

POTENTIAL DIRECT ROLE OF SYNUCLEIN IN DOPAMINE TRANSPORT AND ITS IMPLICATIONS FOR PARKINSON'S DISEASE PATHOGENESIS

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: A-SYNUCLEIN

Meewhi Kim[1], Ilya Bezprozvanny[1,2]
[1]UT Southwestern Medical Center, Dept Of Physiology, Dallas, United States of America, [2]Peter the Great St. Petersburg Polytechnic University, Laboratory Of Molecular Neurodegeneration, St Petersburg, Russian Federation

Aims: Parkinson Disease (PD) is a progressive neurodegenerative disorder that is caused by dysfunction and death of dopaminergic neurons. Mutations in the gene encoding α-synuclein (ASYN) have been linked with familial PD (FPD). Despite important role of ASYN in PD pathology, its normal biological function has not been clarified, although direct action of ASYN in synaptic transmission and dopamine (DA^+) release have been proposed. In the present report we propose a novel hypothesis that ASYN functions as DA^+/H^+ exchanger that can facilitate transport of dopamine across synaptic vesicle (SV) membrane by taking advantage of proton gradient between SV lumen and cytoplasm
Methods: To test this hypothesis we performed analysis of alpha-synuclein domain structure and performed computational modeling of interactions between alpha-synuclein and biological membranes.
Results: By bioinformtics anlaysis we discovered close similarity in domain structure of ASYN and pHILP, a designed peptide developed to mediate loading of lipid nanoparticles with cargo molecules. We reasoned that carboxy-terminal acidic loop D2b domain in both proteins binds cargo molecules. By mimicking DA^+ association with E/D residues in D2b domain of ASYN using Tyrosine replacement approach (TR) we have been able to estimate that ASYN is able to transfer 8-12 molecules of dopamine across SV membrane on each DA^+/H^+ exchange cycle. Our results suggest that familial PD mutations (A30P, E46K, H50Q, G51D, A53T and A53D) will interfere with different steps of the exchange cycle. We also predicted that similar impairment in ASYN DA^+/H^+ exchange function also occurs as a result on neuronal aging due to changes in SV lipid composition and size and dissipation of SV pH gradient.
Conclusions: Proposed novel functional role of ASYN provides novel insights into its biological role and its role in PD pathogenesis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1170 / #2488

Poster Topic: *Theme C: α-Synucleinopathies / C05.e. Genetics, Epidemiology: Other*

POPULATION FRACTION OF PARKINSON'S DISEASE ATTRIBUTED TO AVOIDABLE RISK FACTORS

POSTERS: C05.E. GENETICS, EPIDEMIOLOGY: OTHER

Charles Murchison[1], Timothy Sampson[2], David Standaert[1], Haydeh Payami[1]
[1]University of Alabama at Birmingham, Department Of Neurology, Birmingham, United States of America, [2]Emory University, Department Of Cell Biology, Atlanta, United States of America

Aims: Parkinson's disease (PD) is the fastest growing neurological disease with seemingly no means for prevention. While intrinsic risk factors (age, sex, genetics) are inescapable, environmental risk factors are not. This study sought to estimate the fraction of PD which could be reduced if modifiable risk factors were eliminated.
Methods: Several potentially avoidable PD risk factors were simultaneously assessed in a large cohort of persons with PD (N=808) and neurologically healthy controls (N=415). Associations between risk factors and PD were calculated in the presence of, and adjusting for, other risk factors using multivariable logistic regression. Using the adjusted odds ratio, population attributable fraction (PAF) quantified the excess proportion of PD which could have been potentially eliminated if these preventable risk factors had not been present.
Results: Several evaluated risk factors were found to be operative and independently associated with PD, including pesticide/herbicide exposure, repeated blows to the head, and military-related chemical exposure. In addition to identifying repeated blows to the head in sports or military as a potential new risk factor, PAF estimated that 23% of cases of PD in females and 30% in males were attributable to these modifiable risk factors.
Conclusions: Roughly 1/3 of PD cases in men and 1/4 of cases in women were attributed to preventable risk factors and therefore could have been potentially avoided. Critically, sex stratification showed women had no exposure to repeated blows to the head and military-related chemicals when this cohort was growing up. This is no longer the case today and these estimates will change, for better or worse, unless actions are taken to improve environmental and safety standards.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1171 / #474

Poster Topic: *Theme C: α-Synucleinopathies / C06.a. Cell, Molecular and Systems Biology: a-synuclein*

INVESTIGATION OF COMPOUNDS IDENTIFIED IN A HIGH-THROUGHPUT SCREENING IN A PARKINSON'S DISEASE CELL MODEL

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: A-SYNUCLEIN

Svenja Bothe[1], Matthias Höllerhage[1], Claudia Moebius[2], Marc Bickle[3], Günter Höglinger[4]
[1]Hannover Medical School, Department Of Neurology, Hanover, Germany, [2]Max Planck Institute of Molecular Cell Biology and Genetics, Ht-technology Development Studio, Dresden, Germany, [3]Roche Pharma Research & Early Development, Institute Of Human Biology (ihb), Basel, Switzerland, [4]Ludwig Maximilian University, Department Of Neurology, Munich, Germany

Aims: The impact of alpha synuclein (aSyn) in Parkinson's disease (PD) has been long known. However, neither its physiological role nor its pathophysiological mechanism is fully understood and there is no aSyn-specific therapy available yet. Therefore, our goal was to perform a high-throughput screening with 50,000 small chemical compounds to find compound that protected from aSyn-induced toxicity and investigate the mechanism of action of the most potent compounds.
Methods: We used a PD cell model, in which a moderate overexpression of wild-type aSyn in postmitotic dopaminergic neurons (LUHMES) leads to 50% cell death. In this model, we performed a high-throughput screening and identified 25 compounds as potential leads for further drug development. To confirm the findings from the primary screening and to study the aSyn-specifity of the compounds, we performed LDH cell viability assays and cell stainings for apoptosis and neuronal markers. To study the mechanism of action of the compounds we used a cell-free aggregation assay and performed Western blot analyses with different marker proteins of the cellular degradation machinery.
Results: We identified 8 compounds that led to specific protection from aSyn-induced toxicity and selected them to further dissect their mechanism of action. Preliminary results from the aggregation assay showed a reduction in fluorescence intensity signal for 2 compounds, suggesting them to be inhibitors of aSyn aggregation. Western Blot analyses revealed that cells treated with 2 of the compounds had a significant increase on autophagic flux, suggesting a protective mechanism via stimulation of the intracellular degradation of aSyn.
Conclusions: In conclusion, our data suggest that 8 of our initial 25 compound hits lead to aSyn-specific protection in our PD cell model and possibly act by inhibiting the aSyn aggregation or promoting aSyn degradation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1172 / #473

Poster Topic: *Theme C: α-Synucleinopathies / C06.a. Cell, Molecular and Systems Biology: a-synuclein*

INVESTIGATION OF THE ROLE OF NIPSNAP3A AND NIPSNAP3B IN A PARKINSON'S DISEASE CELL MODEL

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: A-SYNUCLEIN

Kristina Losse[1], Matthias Höllerhage[1], Claudia Moebius[2], Marc Bickle[3], Günter Höglinger[4]
[1]Hannover Medical School, Neurology, Hanover, Germany, [2]Max Planck Institute of Molecular Cell Biology and Genetics, Ht-technology Development Studio (tds), Dresden, Germany, [3]Institute of Human Biology (IHB), Roche, Research & Early Development, Basel, Switzerland, [4]Ludwig-Maximilian-University, Neurology, munich, Germany

Aims: In recent years, several risk genes for Parkinson's disease (PD) have been reported to directly or indirectly influence alpha synuclein (aSyn) pathology. In order to discover novel potential genes that modulate aSyn-mediated-neuronal toxicity, we performed a genome-wide siRNA screening in a PD cell model based on aSyn-induced toxicity in human dopaminergic neurons. We found that knockdown of *NIPSNAP3A* and *NIPSNAP3B* protected in this model. Using RNAi and a CRISPR/Cas9 mediated knockout approach, we aimed to confirm the findings from the primary screening, and to explore the protective mechanisms involved.
Methods: For studying the protective efficacy, we performed LDH measurements of medium from the cells as well as Caspase3/7 staining after *NIPSNAP3A* and *NIPSNAP3B* knockdown. For investigating, the intra- and extracellular distribution of aSyn and its aggregation propensity, Western blot analyses were performed. To elucidate possible interactions between aSyn and the identified genes, we investigated the subcellular localisation of NIPSNAP3A and NIPSNAP3B by biochemical fractionation.
Results: LDH measurements and Caspase 3/7 stainings confirmed the protective efficacy of *NIPSNAP3A* and *NIPSNAP3B* downregulation. Western blot analyses indicated higher expression of total and aberrantly phosphorylated aSyn (pS129) after *NIPSNAP3A* and *NIPSNAP3B* knockdown, but no changes of the quantity of aSyn high molecular weight species. One possible explanation for the observed increases in cell viability would be that the intracellular accumulation of pathogenic aSyn prevents spreading of toxic aSyn species to neighbouring cells. Results from biochemical fractionation, revealed a NIPSNAP3A and NIPSNAP3B enrichment in the mitochondrial, nuclear, and membrane fractions.
Conclusions: In conclusion, our results indicate a protective effect against aSyn toxicity of *NIPSNAP3A* and *NIPSNAP3B* downregulation in our PD cell model, and provide preliminary data about the location of NIPSNAP3A and NIPSNAP3B protein in human dopaminergic neurons.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1173 / #2067

Poster Topic: *Theme C: α-Synucleinopathies / C06.a. Cell, Molecular and Systems Biology: a-synuclein*

DISTINGUISHING PHYSIOLOGICAL AND PATHOLOGICAL A-SYNUCLEIN SERINE 129 PHOSPHORYLATION

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: A-SYNUCLEIN

Nagendran Ramalingam, Lisa Brontesi, Shan-Xue Jin, Dennis Selkoe, Ulf Dettmer
Brigham and Women's Hospital/Harvard Medical School, Neurology, Boston, United States of America

Aims: α-synuclein phosphorylation at serine-129 (pS129) is a widely used surrogate marker of pathology in Parkinson's disease and other synucleinopathies. However, we recently demonstrated that pS129 is also a physiological activator of synaptic transmission. In a feed-forward fashion, neuronal activity triggers pS129 that accumulates at synapsin-containing presynaptic boutons but is readily reversible: blocking stimulation normalizes pS129 levels within two hours. Here, we tested whether one can distinguish physiological pS129 from abnormal pS129 observed in α-synuclein dyshomeostasis models.
Methods: Models - *in vitro* (rodent primary neurons from wildtype and *SNCA*$^{-/-}$ rats); Lentiviral transduction; Biochemistry - western blots, subcellular fractionation, and reversible phosphorylation dynamics.
Results: We show that Parkinson's-linked missense mutations in SNCA impact activity-dependent pS129. Under basal conditions, cytosol enriched A30P, H50Q, and G51D exhibited reduced pS129 levels. A53T pS129 levels were similar to wild-type, and E46K pS129 levels were higher. Interestingly, both A30P and E46K pS129 reversibility after stimulation were impaired. For the membrane-enriched amplification of E46K, '3K', dephosphorylation was virtually absent after blocking stimulation, implying reversible pS129 is severely compromised. Importantly, pS129 excess resulting from proteasome inhibition was also associated with reduced reversibility - by neuronal inhibition, kinase inhibition, or phosphatase activation. The impaired reversible pS129 dynamics we report here are likely to be one of the early changes associated with αS dyshomeostasis, potentially preceding pS129 aggregates.
Conclusions: Our findings suggest that perturbed activity-dependent pS129 dynamics are probably a shared characteristic of pathology-associated αS, with possible implications for synucleinopathy treatment and diagnosis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1174 / #445

Poster Topic: *Theme C: α-Synucleinopathies / C06.a. Cell, Molecular and Systems Biology: a-synuclein*

OVEREXPRESSION-INDUCED NUCLEAR ALPHA-SYNUCLEIN ACCUMULATION

POSTERS: C06.A. CELL, MOLECULAR AND SYSTEMS BIOLOGY: A-SYNUCLEIN

Angela Rollar, Eva Szegö, Shirley Lee, Ayse Ulusoy, Donato Di Monte
DZNE (German Center for Neurodegenerative Diseases), Neurodegeneration And Neuroprotection In Parkinson's Disease, Bonn, Germany

Aims: Pathological accumulation of alpha-synuclein (αSyn)-containing inclusions is a hallmark of Parkinson's disease. αSyn is a synaptic protein and, under normal conditions, is predominantly detected in the form of immunoreactive puncta corresponding to synaptic boutons. The purpose of this study was to assess changes in αSyn localization triggered by increased neuronal αSyn expression. In particular, overexpression-induced changes were investigated within neuronal perikarya as well within neuronal nuclei; the latter analysis was facilitated by a newly developed assay that detected interactions between αSyn and histones.
Methods: Experiments and analyses were carried out in the substantia nigra pars compacta of rats in which αSyn overexpression was triggered by a unilateral intranigral injection of adeno-associated viral vectors delivering human αSyn DNA. Midbrain tissue sections were stained with anti-human-αSyn to detect neuronal protein accumulation. Nuclear αSyn localization was evaluated *in situ* using a proximity ligation assay (PLA). Immunoprecipitation was carried out to detect αSyn-histone interactions in nuclear preparations from rat midbrain tissue.
Results: Neither cytosolic nor nuclear αSyn was detected in non-injected control animals. Quite in contrast, overexpression of human αSyn was associated with robust neuronal accumulation of the exogenous protein. Under this condition, human αSyn could be detected in both neuronal perikarya and nuclei by immunohistochemistry. PLA confirmed this overexpression-induced nuclear accumulation and also indicated interactions of human αSyn with histones. These interactions were confirmed by immunoprecipitation using midbrain nuclei.
Conclusions: Our results provide clear evidence of a relationship between increased αSyn expression, cytosolic protein accumulation and αSyn access into neuronal nuclei. Data also reveal that, once in the nucleus, αSyn closely interacts with histones, indicating a mechanism for potential long-lasting deleterious transcriptional consequences.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1175 / #653

Poster Topic: *Theme C: α-Synucleinopathies / C06.b. Cell, Molecular and Systems Biology: LRKK2, parkin, PINK1, DJ-1 and other PD realted genes*

ANALYSIS OF MUTATIONS IN SNCA, PINK1, PARK7, PRKN, AND LRRK2 GENES AND ASSOCIATION WITH MITOCHONDRIAL DNA VARIANTS IN A GROUP OF PATIENTS WITH PARKINSON'S DISEASE

POSTERS: C06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES

Leonardo Biscetti[1], Tiziana Casoli[2], Salvatore Vaiasicca[3], Belinda Giorgetti[2], Maurizio Cardelli[4], Francesca Marchegiani[5], Giuseppe Pelliccioni[1], Fiorenzo Conti[6]
[1]National Institute for the Care of the Elderly, Istituto Nazionale di Ricovero e Cura dell'Anziano, Istituto a carattere scientifico, INRCA-IRCCS, Ancona, Italy, Medicine, Section Of Neurology, Ancona, Italy, [2]National Institute for the Care of the Elderly, Istituto Nazionale di Ricovero e Cura dell'Anziano, Istituto a carattere scientifico, INRCA-IRCCS, Ancona, Italy, Neurobiology Of Aging, Ancona, Italy, [3]National Institute for the Care of the Elderly, Istituto Nazionale di Ricovero e Cura dell'Anziano, Istituto a carattere scientifico, INRCA-IRCCS, Ancona, Italy, Scientific Direction, Ancona, Italy, [4]National Institute for the Care of the Elderly, Istituto Nazionale di Ricovero e Cura dell'Anziano, Istituto a carattere scientifico, INRCA-IRCCS, Ancona, Italy, Advanced Technology Center For Aging Research, Ancona, Italy, [5]National Institute for the Care of the Elderly, Istituto Nazionale di Ricovero e Cura dell'Anziano, Istituto a carattere scientifico, INRCA-IRCCS, Ancona, Italy, Clinic Of Laboratory And Precision Medicine, Irccs Inrca, Ancona, Italy, Ancona, Italy, [6]Università Politecnica delle Marche, Ancona, Italy, Section Of Neuroscience And Cell Biology, Department Of Experimental And Clinical Medicine, Ancona, Italy

Aims: The aim of the present pilot study was to assess variant of uncertain significance (VUS), and pathogenic mutations in *SNCA, PINK1, PARK7, PRKN*, and *LRRK2* genes and to analyze their possible association with mtDNA variants in Parkinson's disease (PD) patients
Methods: Fifteen PD patients were enrolled for this analysis. Blood samples were obtained from the institutional database of the IRCCS INRCA. *SNCA, PINK1, PARK7, PRKN*, and *LRRK2* specific gene mutations were assessed through an NGS-based custom panel and classified by the Parkinson's disease mutation database (PDmutDB). mtDNA was sequenced using a chip-based resequencing system which detects both homoplasmic and heteroplasmic mtDNA variants (40-60% heteroplasmy), and allows the assessment of low-level heteroplasmy (<10% heteroplasmy) by the REA (ratio of expected alleles) index.
Results: The mutations identified by PDmutDB in the specific genes were classified as benign (44.8%), benign VUS (37.1%), VUS (14.3%), likely benign VUS (2.85%) and pathogenic (0.95%). Mean homoplasmic and heteroplasmic mtDNA variants per PD patient were 22.2±5.1 and 6.5±3.5, respectively. Correlation analysis showed that total number of VUS in our cohort strongly correlated with total mtDNA homoplasmic variants (r=0.8452), and moderately with total (r=0.6002) and D-loop heteroplasmic variants (r=0.6093). Total benign VUS mutations negatively correlated with REA index in *ND4* gene indicating that high values of this kind of mutations were associated with low-level heteroplasmy (r=-0.6667). *PINK1* and *LRRK2* total mutations negatively correlated with REA, *PINK1* with total and with most mitochondrial gene REA, while *LRRK2* only with *ND4* gene REA values.
Conclusions: Our preliminary data suggest that mutations in genes associated with PD might influence mtDNA homo-and heteroplasmic variant burden, thereby supporting the role of mitochondrial dysfunction in PD pathogenesis. Further studies will be necessary to confirm these findings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1176 / #1238

Poster Topic: *Theme C: α-Synucleinopathies / C06.b. Cell, Molecular and Systems Biology: LRKK2, parkin, PINK1, DJ-1 and other PD realted genes*

IDENTIFYING THE BINDING INTERFACES BETWEEN LRRK2 AND ITS PHOSPHATASES

POSTERS: C06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES

Antonio Jesús Lara Ordóñez, Chloé Annicotte, Liesel Goveas, Marie Stoup, Marie-Christine Chartier-Harlin, Nicolas Lebègue, Maxime Liberelle, Jean-Marc Taymans
Univ. Lille, Inserm, CHU Lille, Umr-s 1172-lilncog-lille Neuroscience & Cognition, Lille, France

Aims: Mutations in LRRK2 (Leucine-Rich Repeat Kinase 2) are the most common cause of familial Parkinson´s disease (PD), and variants in this gene increase risk for the sporadic form of the disease.. LRRK2 is phosphorylated by other kinases at a cluster of serines between its ANK and LRR domains, and the phosphorylation status of LRRK2 is related to disease. Studies from our lab have identified subunits of Ser/Thr Protein Phosphatase 1 and 2A (PP1 and PP2A) as phosphatases of LRRK2. However, the binding interface of these phosphatases with LRRK2 is currently unknown.
Methods: Characterization of the binding interface of LRRK2 with its phosphatases using truncated constructs encoding LRRK2 domains with protein-protein interaction techniques such as coimmunoprecipitation, proximity ligation assay and microscale thermophoresis. Site-directed mutagenesis is performed in the domains of LRRK2 interacting with phosphatases to identify the residues that are important for their interaction.
Results: Here we confirm that PPP1CA, PPP2CA and PPP2R2A bind full length LRRK2 and have differential binding preferences towards the different domains of LRRK2.
Conclusions: Our research has identified the regions of binding between LRRK2 and its phosphatases, establishing the groundwork needed to understand the mechanisms of LRRK2 phosphoregulation at the structural level and to modulate LRRK2 complexes with its phosphatases as a strategy to manipulate the phosphorylation status of LRRK2.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1177 / #680

Poster Topic: *Theme C: α-Synucleinopathies / C06.b. Cell, Molecular and Systems Biology: LRKK2, parkin, PINK1, DJ-1 and other PD realted genes*

IDENTIFYING INSTRINSIC DYSFUNCTION IN IPSC-DERIVED MEDIUM SPINY NEURONS FROM PARKINSON'S PATIENTS HARBOURING GBA N370S

POSTERS: C06.B. CELL, MOLECULAR AND SYSTEMS BIOLOGY: LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES

Humaira Noor[1,2], Kaitlyn Cramb[1,3], Lahiru Handunnetthi[2], Richard Wade-Martins[1,3]
[1]Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, (asap), Washington D.C., United States of America, [2]University of Oxford, Nufflied Department Of Medicine, Oxford, United Kingdom, [3]University of Oxford, Department Of Physiology, Anatomy & Genetics, Oxford Parkinson's Disease Centre, Oxford, United Kingdom

Aims: Parkinson's disease (PD) is a movement disorder caused by age-related progressive neurodegeneration. The cardinal motor symptoms are caused by striatal dysfunction and are attributed to the loss of dopamine release by Substantia Nigra pars compacta dopaminergic neurons which heavily innervate the striatum. The medium spiny neurons (MSNs) representing about 90-95% of the striatum are the main postsynaptic afferents of dopaminergic neurons. Despite representing an integral component of the network responsible for movement modulation that is compromised in PD, our understanding of the role of MSN in PD pathophysiology and network dysfunction remains limited. Use of iPSC-derived human MSNs from patients provides a unique opportunity to investigate these human striatal neurons in monoculture and detect early intrinsic dysfunction in PD.
Methods: iPSCs from patients harbouring PD-associated N370S mutation in the GBA gene (n=3) and healthy controls (n=3) have been differentiated into GABAergic MSNs using a 70-day protocol and characterised using immunocytochemistry and RT-qPCR. With the aid of functional analyses like ratiometric fluorescent dye Fura-2 for calcium imaging, seahorse assay for mitochondrial health and multi-electrode array for extracellular electrical activity, we will identify the impact of PD on the health and activity of iPSC-derived MSNs.
Results: iPSC-derived MSNs express specific markers, DARPP32 and GAD67, as early as Day 40, as observed from qPCR and immunocytochemistry data which persisted throughout the maturation period. Preliminary results point to an intrinsic dysregulation in iPSC-derived MSN from PD patients insinuating GBA N370S affects health and function of MSNs.
Conclusions: The highly efficient differentiation protocol results in functional iPSC-derived GABAergic MSN. Preliminary data suggests intrinsic dysregulation in iPSC-derived MSNs from patients that may contribute to PD pathology. Further studies will explore the mechanisms underlying the cell-autonomous dysfunction in these striatal neurons in the context of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1178 / #2975

Poster Topic: *Theme C: α-Synucleinopathies / C06.c. Cell, Molecular and Systems Biology: Network biology, connectome, protein-protein interations*

USING NETRAAI TO DISCOVER PARKINSON'S DISEASE SUBTYPES: GENERATIVE AI REVEALS TRANSCRIPTOMIC PERSONALITIES LINKING MITOCHONDRIAL, MICROBIOME, AND IMMUNE SIGNALING

POSTERS: C06.C. CELL, MOLECULAR AND SYSTEMS BIOLOGY: NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS

Bessi Qorri, Mike Tsay, Larry Alphs, Joseph Geraci
NetraMark, Biotechnology, Toronto, Canada

Aims: Parkinson's disease (PD) and Alzheimer's disease (AD) are two major neurodegenerative disorders with complex and poorly understood etiology. To address the clinical variability of PD and elucidate its underlying mechanisms, we leverage the power of NetraAI, a novel machine learning (ML) system. Our primary objective is to identify genetic drivers within specific PD patient subpopulations and uncover pivotal disease pathways, ultimately enhancing our understanding and treatment strategies.
Methods: Using a transcriptomic dataset consisting of 191 controls and 397 PD patients obtained and assembled from the Michael J. Fox Foundation, we employed NetraAI, powered by its unique Attractor AI algorithms, to identify causal clusters, or variables termed hypotheses explaining specific subpopulations. Cross-hypothesis integration revealed significant variables and pathways linked to PD.
Results: We report on several different hypotheses about the disease, linking mitochondrial function, the microbiome, and the immune response to PD. Importantly, we identify three key genes: *GPATCH2L*, *CLEC1B*, and *IRAK3. Protein-protein interaction networks were used to derive novel proteins of interest, all cl*osely linked to immune-mediated functions. This underscores the pivotal role of the immune system and the immune response in PD pathogenesis, showcasing NetraAI's ability to uncover key variables in disease pathogenesis.
Conclusions: This study highlights the potential of ML to untangle the intricate web of factors contributing to PD, offering insights applicable to other neurodegenerative disorders, including AD. By identifying causal clusters and significant genes in disease pathogenesis, we open new avenues for the diagnosis and treatment of these debilitating conditions. This research not only advances our understanding of the disease but also offers a scientific foundation for future investigations into the role of immune-related factors in neurodegenerative disorders, promising new opportunities for therapeutic interventions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1179 / #2621

Poster Topic: *Theme C: α-Synucleinopathies / C06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

SPATIAL TRANSCRIPTOMICS IN DOWN SYNDROME IDENTIFIES KEY PATHWAYS OF ALZHEIMER'S DISEASE

POSTERS: C06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Emily Miyoshi[1], Samuel Morabito[1], Caden M. Henningfield[1], Negin Rahimzadeh[1], Sudeshna Das[1], Justine Silva[1], Arshi Shahin[1], Mari Perez-Rosendahl[2], Elizabeth Head[3], Vivek Swarup[1]
[1]University of California Irvine, Neurobiology And Behavior, Irvine, United States of America, [2]University of California Irvine, Department Of Pathology And Laboratory Medicine, Irvine, United States of America, [3]University of California Irvine, Pathology & Laboratory Medicine, Irvine, United States of America

Aims: Alzheimer's disease (AD) exhibits substantial molecular heterogeneity, influenced by a complex interplay of environmental and genetic factors. The study aims to unravel the cell-type specific and spatial transcriptomic changes in AD, with a special focus on a subset of Down Syndrome (DS) patients suffering from AD (AD in DS). We intend to explore the congruencies and divergences between sporadic AD (sAD) and AD in DS, thereby providing insights that may bridge current gaps between mouse models and human conditions.
Methods: This investigation employed spatial transcriptomics (ST, 10x genomics visium) along with single-nucleus RNA sequencing (snRNA-seq) to examine cortical tissue samples from early-stage AD, late-stage AD, and AD in DS donors. Concurrently, amyloid plaque and fibril imaging were conducted on the same tissue samples to directly correlate gene expression alterations with pathological features.
Results: Our comprehensive analysis reveals pronounced spatial and cell-type specific changes in gene expression across the spectrum of AD pathology. Notably, the transcriptomic signatures shared remarkable similarities between sAD and AD in DS, indicating potential commonality in disease pathways. Furthermore, integration of amyloid imaging data with ST permitted the establishment of direct associations between shifts in gene expression and the spatial distribution of pathological aggregates.
Conclusions: The findings illuminate the utility of spatial transcriptomics in elucidating the intricate molecular mechanisms underlying AD. Importantly, the study uncovers converging molecular pathways between sAD and AD in DS, reinforcing the utility of AD in DS as an informative model for advancing our understanding of AD pathogenesis at the molecular level.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1180 / #1336

Poster Topic: *Theme C: α-Synucleinopathies / C06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

TRANSCRIPTOMIC ANALYSIS OF SPORADIC PARKINSON'S DISEASE : IDENTIFICATION OF DISEASE SPECIFIC PATHOLOGICAL MARKERS.

POSTERS: C06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Sooyeon Yoo[1,2], Junyoung Chang[3], Kwanghoon Lee[1,2], Seoug-Ik Kim[1,2], Junseo Seo[3], Hwisoo Choi[3], Yu-Mi Shim[1,2], Junil Kim[3], Jae-Kyung Won[1,2], Sung-Hye Park[1,2]
[1]Seoul National University Hospital, Dementia Brain Bank, Seoul, Korea, Republic of, [2]Seoul National University Hospital, Pathology, Seoul, Korea, Republic of, [3]Soongsil University, Systems Biomedical Science, Seoul, Korea, Republic of

Aims: Parkinson's disease (PD) is a common neurodegenerative disease (NDD) characterised by abnormal protein accumulation leading to neuronal death. Research shows that NDDs share a common pathophysiology, including inflammatory responses, reactive gliosis and oxidative stress. Identifying genes that regulate these cellular responses in NDD may aid in diagnosis, understanding the disease environment, predicting disease progression and evaluating therapeutic efficacy.
Methods: We performed single-nucleus RNA sequencing on the substantia nigra of four brains each from sporadic PD and primary age-related tauopathy (PART) to serve as a more appropriate control group from a pathological standpoint. We obtained a total of 32,000 nuclei, integrated these data and used a variety of computational analyses including Seurat DEG, RNA velocity, GSEA, GO, SCENIC and TENET to understand the characteristics of PD. For histological validation in post-mortem tissue, we used single-molecule in situ hybridisation (smISH).
Results: We identified seven major cell types and their specific markers. For neurons, we observed proportional changes in dopaminergic, glutamatergic and GABAergic neurons and identified the disease-associated subpopulation of each neuronal subtype. DEG analysis revealed more pronounced changes in non-neuronal cells such as astrocytes and microglia than in neurons themselves. These changes were associated with reactive glial characteristics and inflammatory responses. For astrocytes and microglia, we performed Monocle-based pseudotime analysis and obtained the two disease-associated trajectories for each. Along with the trajectory, we were able to identify many genes involved in the cellular events of neurodegenerative disease. We constructed the networks for each related cellular process and identified representative transcription factors and their target genes.
Conclusions: We discovered multiple genes that exhibited cell-type-specific expression and underwent disease-associated expression changes, enhancing their potential as pathological markers. These genes have undergone histological validation in postmortem tissues using smISH.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1181 / #1731

Poster Topic: *Theme C: α-Synucleinopathies / C06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

DIFFERENTIAL METASTATES OF DIRECT PATHWAY STRIATAL OUTPUT NEURONS ACROSS THE DEVELOPMENT OF L-DOPA-INDUCED DYSKINESIA: A ROLE FOR ACTIVIN SIGNALING

POSTERS: C06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Henrique De Oliveira Amaral, David Figge, David Standaert, Karen Eskow Jaunarajs
University of Alabama at Birmingham, Department Of Neurology, Birmingham, United States of America

Aims: L-DOPA-induced dyskinesia (LID) is a debilitating, motor side effect arising from chronic dopamine replacement therapy with L-DOPA for the treatment of Parkinson disease (PD). The heterogeneous composition of the striatum, including diverse subpopulations of medium spiny output neurons (MSNs), interneurons, and supporting cells, has complicated the precise identification of the cell(s) underlying LID development and persistence. To elucidate the cellular and molecular mechanisms of LID, we used single nucleus RNA-sequencing (snRNA-seq) to establish a comprehensive striatal transcriptional profile during the development and maintenance of LID.
Methods: Hemiparkinsonian mice were treated with vehicle or L-DOPA for varying durations (1, 5, or 10 d) and nuclei from the striata were processed for snRNA-seq.
Results: Our analysis found that a limited population of dopamine D1 receptor-expressing MSNs (D1-MSNs) arising from both the
patch and matrix compartments were found in three activated metastates. These activated D1-MSN subpopulations displayed a majority of the transcriptional changes previously associated with LID; however, the prevalence and transcriptional behavior of each activated D1-MSN
metastate was directly correlated to the number of L-DOPA administrations. The differentially expressed genes found in these D1-MSNs indicated acute L-DOPA induced multiple plasticity-related transcription factors and regulators of MAPK signaling, while repeated L-DOPA exposure
induced numerous genes associated with synaptic remodeling, learning and memory, and transforming growth factor-ß (TGFß) signaling. Notably, repeated L-DOPA led to a sensitization in the expression of Inhba, a member of the activin/TGFß superfamily, in activated D1-MSNs and
the pharmacological inhibition of its receptor, ALK4, impaired LID development.
Conclusions: Collectively, these data suggest that a distinct subset of D1-MSNs become differentially responsive to L-DOPA. Our data further suggests that TGFß signaling plays an essential role in LID development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1182 / #1348

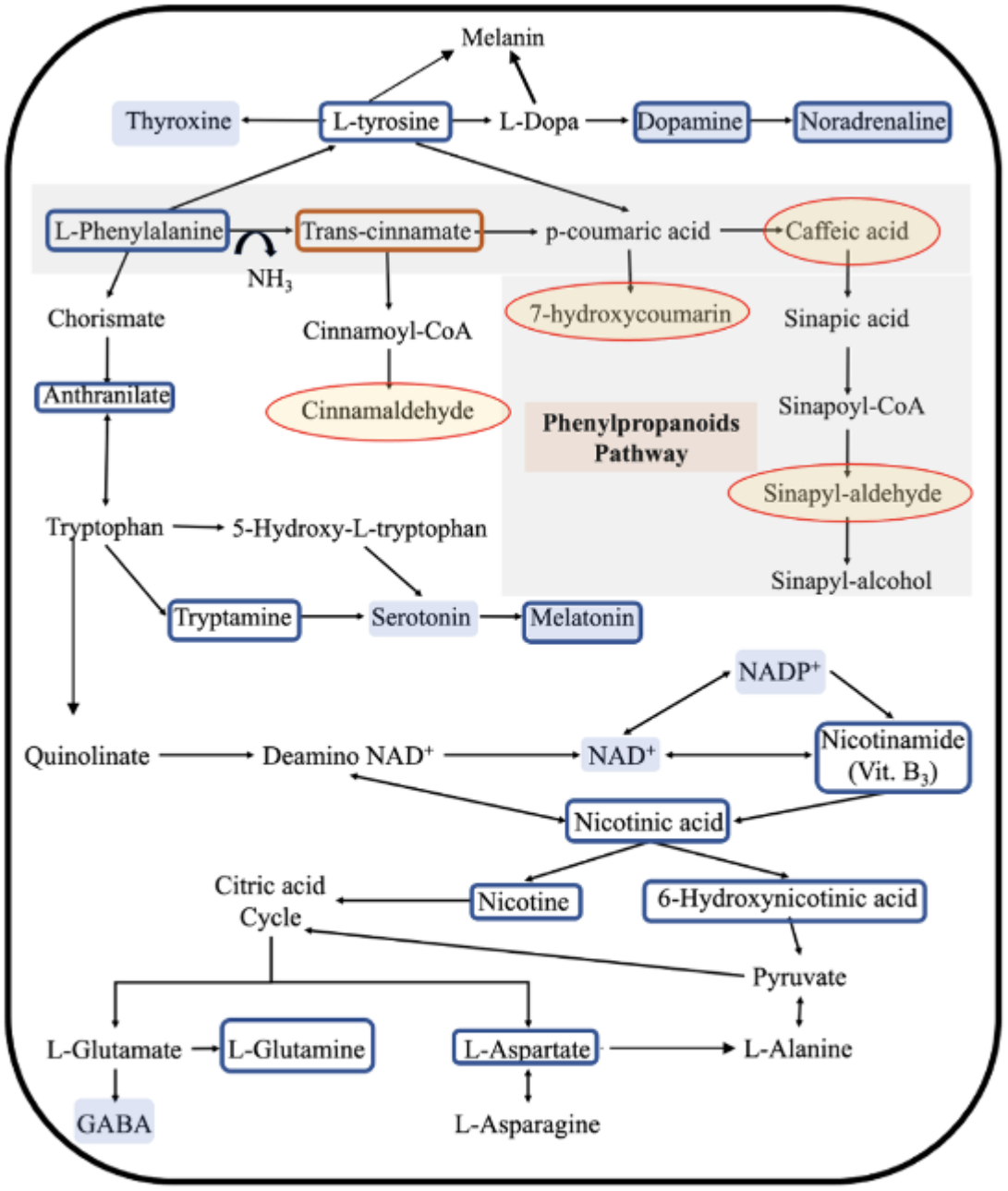
Poster Topic: *Theme C: α-Synucleinopathies / C06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

METABOLOMIC PROFILING REVEALS ALTERED PHENYLALANINE METABOLISM AND A POSSIBLE ROLE OF TRANS-CINNAMATE IN PARKINSON'S DISEASE: A METABOLOMICS STUDY OF AN EGYPTIAN COHORT

POSTERS: C06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Nourhan Shebl[1], Shaimaa El-Jaafary[2], Ayman Saeed[3], Samir Shamma[1], Jaidaa Mekky[4], Lobna Mohamed[4], Hassan El-Fawal[1], Mie Rizig[5], Mohamed Salama[1]
[1]The American University in Cairo, Institute Of Global Health And Human Ecology, Cairo, Egypt, [2]Faculty of Medicine, Cairo University, Neurology, Cairo, Egypt, [3]Research Institute, National Research Centre (NRC), Organic Chemistry, Cairo, Egypt, [4]Faculty of Medicine, Alexandria University, Neurology, Cairo, Egypt, [5]University College London, Institute Of Neurology Queen Square, London, Egypt

Aims: We investigated the metabolic alterations associated with Parkinson's disease (PD) by performing a comprehensive metabolic analysis. Our main objectives were to identify possible changes in the phenylalanine (dopamine precursor) metabolism and its impact on the dopaminergic, adrenergic, serotonergic, and melatonergic pathways; in addition, we tested the hypothesis that phenylalanine metabolism in PD may be shifted toward trans-cinnamate (phenylalanine metabolite) production, affecting the levels of critical neurotransmitters and related metabolites such as tyrosine.
Methods: Plasma samples were collected from 27 PD patients, 18 reference controls, and 8 high-risk controls to perform a non-targeted metabolomics analysis (LC-MS). The analysis focused on assessing the intensities of various metabolites, including trans-cinnamate, phenylalanine, tyrosine, dopamine (DA), norepinephrine (NE), 3-hydroxyanthranilic acid, a metabolite that connects phenylalanine metabolism to that of tryptophan. ANOVA test was performed to assess the significant differences in the metabolites' intensities between the recruited groups.
Results: Our findings revealed significantly higher intensities of trans-cinnamate in PD patients compared to controls. In addition, it also showed significantly lower intensities of phenylalanine, tyrosine, DA, NE, 3-hydroxyanthranilic acid, tryptamine, melatonin, and nicotinamide in PD patients. On the contrary, we did not find any significant difference in the levels of tryptophan among the recruited



This Figure shows the detected alterations in the metabolic pathways for the tackled metabolites. Compared to reference controls, the blue boxes show the metabolites that are significantly lower in patients, while the orange box shows the metabolite that is significantly higher in patients. On the other hand, the yellow shaded circles represent the metabolites that appear in patients only and not in controls, while the blue shaded metabolites are some molecules that may have a role in developing the clinical symptoms of PD.

groups.

Conclusions: Our study provides insights into the metabolic changes associated with PD, particularly in phenylalanine metabolism. The higher levels of trans-cinnamate in PD patients suggest a potential shift in phenylalanine metabolism towards the production of trans-cinnamate, possibly via L-phenylalanine

ammonia lyase (PAL), as opposed to the production of tyrosine. Moreover, Altered phenylalanine metabolism may have downstream effects on neurotransmitter production, including DA, NE, tryptamine, melatonin, and nicotinamide, and may contribute to the neurodegenerative processes seen in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1183 / #1079

Poster Topic: *Theme C: α-Synucleinopathies / C06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

PROBING IRON AND LIPID CHANGES IN NEURODEGENERATIVE DISEASES USING METABOLOMICS ON HUMAN POST-MORTEM TISSUE

POSTERS: C06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Holly Spence, Fiona Read, Fergal Waldron, Jenna Gregory
Institute of Medical Sciences, University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom

Aims: Disruption of inflammation, iron and lipid metabolism pathways have all been implicated to have a role in neurodegenerative diseases including Alzheimer's disease and Parkinson's disease. We therefore hypothesise that iron-mediated lipid peroxidation may act as a cross cutting mechanism underpinning protein misfolding, where those with multi-morbidity proteinopathy may exhibit more generalised iron-mediated lipid peroxidation disruption compared to more specific triggers of single proteinopathies.
Methods: Here, 10 patients with pure AD pathology, 10 patients with pure PD pathology and 10 patients with pure ALS pathology were assessed alongside 10 patients with multi-morbidity proteinopathy (at least 2 of ALS, AD or PD) and 20 age and sex matched controls without any neurological disease. Over 2000 metabolites were assessed in central white matter and motor cortex (BA4) post-mortem tissue.
Results: This large-scale metabolomics study of AD, PD and ALS characterises cross-cutting metabolic dysregulation underpinning neurodegenerative disease.
Conclusions: This could be used as therapeutic targets as well as identifying pathways which could be used for differential diagnosis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1184 / #1297

Poster Topic: *Theme C: α-Synucleinopathies / C06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

SINGLE NUCLEUS MULTIOME OPTIMIZATIONS FOR POSTMORTEM HUMAN BRAIN AND LARGE SCALE MULTIOME PROFILING OF PARKINSON'S DISEASE PROGRESSION REVEAL NOVEL GENE REGULATORY MECHANISMS

POSTERS: C06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Adam Turner, Shreya Menon, Ryan Corces
Gladstone Institutes, University of California, San Francisco, Gladstone Institute Of Neurological Diseases, San Francisco, United States of America

Aims: Parkinson's disease (PD) pathogenesis involves changes to cellular state across many cell types and brain regions. However, the cell-type specific molecular mechanisms involved in PD pathogenesis remain elusive. To enable characterization of these cell type-specific disease alterations, we must develop methods to profile the transcriptomic and gene regulatory landscapes in primary human tissues. Here, we optimized the isolation of nuclei from frozen postmortem brain tissue and the generation of corresponding single-nucleus multi-omic data sets. We highlight key advances on the experimental and computational aspects of large-scale single-nucleus data generation.
Methods: We benchmarked different nuclear isolation protocols and single-nucleus methodologies. We considered standard QC metrics as well as often overlooked metrics such as levels of ambient RNA that confound scRNA-seq analysis. We generated a large multi-omic single-nucleus atlas from 101 individuals (80 PD, 21 control) and 5 brain regions (including the substantia nigra) progressively involved in PD pathogenesis.
Results: Through protocol optimizations, we (1) reduced the presence of ambient RNA in single-nucleus RNA-seq data and (2) reduced the percentage of nuclei corresponding to oligodendrocytes and increased the percentage of nuclei corresponding to neurons. To mitigate batch effects, we implemented an experimental strategy that allows for profiling of multiple individuals simultaneously, leveraging the genotype of each donor to deconvolve donor identity in silico, and benchmarked computational tools to perform this deconvolution. We have also systematically compared data sets generated from freshly isolated nuclei (from frozen brain tissue) and cryopreserved nuclei, finding that cryopreservation substantially reduces data quality.
Conclusions: We have made key optimizations to improve single-nucleus multi-omic data quality from postmortem frozen human brain and applied these optimizations to the generation of a massive-scale dataset with more than 3.5 million nuclei.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1185 / #2681

Poster Topic: *Theme C: α-Synucleinopathies / C06.d. Cell, Molecular and Systems Biology: Metabolomics, transcriptomics, lipidomics, proteomics*

SPATIAL LIPID PROFILING OF THE HUMAN BRAIN REVEALS CHANGES RELATED TO AGEING AND PARKINSON'S DISEASE

POSTERS: C06.D. CELL, MOLECULAR AND SYSTEMS BIOLOGY: METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS

Wendy Heywood[1], Jenny Hallqvist[1], Christina Toomey[2], Simon Eaton[1], Mesfer Al Shahrani[1], Simon Heales[3], Kevin Mills[1], Sonia Gandhi[2]
[1]UCL, Institute Of Child Health, London, United Kingdom, [2]UCL, Queen Square Institute Of Neurology, London, United Kingdom, [3]National Hospital for Neurology & Neurosurgery, Neurometabolic Unit, London, United Kingdom

Aims: Dysregulation of the glycosphingolipid degradation pathway is a known risk factor for developing Parkinson's Disease (PD) as illustrated by the increased risk of PD in GBA heterozygotes. Brain lipid changes are also observed in the brains of sporadic PD patients but to a lesser extent than GBA-PD. Knowledge of how brain lipids change across the human brain anatomically, with age and disease have been relatively poorly studied. We have addressed this by spatially profiling the lipidome across 8 different brain regions and explored how lipids change across regions, with age and in response to PD. Using a multi-omic approach we also identify lipids that are associated with changes of the PD brain proteome.
Methods: We have used high precision tissue sampling with targeted LC-MS/MS lipid panels along a spatio-temporal pathology gradient of early, mid and late stage disease.
Results: All regions demonstrated a specific lipid profile with ceramide showing the least variation. Age affected the profile in the controls and was driven by increased hexosylceramide and ceramides. The parietal and frontal cortices and putamen were most affected by PD with between 18-24% of total lipids showing changes. Lipids driving these changes were mostly gangliosides, hexosylceramide and medium chain ceramides. Early PD changes were observed only in the cerebellum and frontal cortex with increased ceramides, lyso-sphingomyelin and plasmalogens. Multi-omic analysis revealed sphingomyelin C34 and C36 species (which are known to bind to a-synuclein fibrils) correlated significantly with proteins that were altered in early PD. Correlation with mitochondrial complex I activity indicated medium chain ceramides, lyso-phosphocholine and plasmalogens are associated with mitochondrial function in early PD.
Conclusions: The brain lipid profile changes with PD and early lipid changes are associated with ROS production and mitophagy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1186 / #1864

Poster Topic: *Theme C: α-Synucleinopathies / C06.e. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

DNA METHYLATION PROFILING IN DIFFERENT BRAIN CELL TYPES IN PARKINSON'S DISEASE

POSTERS: C06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Anthony Klokkaris, Jonathan Mill, Anna Migdalska-Richards
University of Exeter, Department Of Clinical And Biomedical Sciences, Exeter, United Kingdom

Aims: Much is still unknown about the aetiology of Parkinson's disease (PD). While several risk genes have been identified, there is also growing evidence of epigenetic dysregulation, with a number of recent studies identifying DNA methylation changes in PD brains. However, nearly all research has used bulk brain tissue which masks any cell-type specific epigenetic signatures. We aim to investigate genome-wide DNA methylation alterations in distinct cell types isolated from PD post-mortem brain tissue, and additionally whether DNA methylation varies according to *GBA1* mutation status (the most common PD genetic risk factor).
Methods: Fluorescence-activated nuclei sorting was used to isolate neuronal, oligodendrocyte and other glial cell nuclei from the prefrontal cortex of 129 individuals (36 PD-*GBA1*, 35 PD-non-*GBA1,* 10 control-*GBA1* and 48 control-non-*GBA1*). Nuclear DNA was extracted and bisulfite converted and genome-wide DNA methylation was measured using the Infinium MethylationEPIC BeadChip. Following a quality control pipeline, differential methylation was analysed using linear regression. Individuals were also genotyped using the Infinium Global Screening Array.
Results: Cell-type isolation was largely accurate with the vast majority of samples passing quality control. DNA methylation was analysed, comparing PD and control samples as well as PD-*GBA1* and PD-non-*GBA1*, and cell-type specific differentially methylated positions were identified.
Conclusions: This is one of the first studies to investigate genome-wide DNA methylation alterations across distinct brain cell populations in PD. Additionally, it starts to stratify individuals by *GBA1* status. Future work will involve targeted validation of the top changes and integrating DNA methylation, genetic and microRNA expression data (generated for several of these samples). The findings will shed new insights into genes and biological mechanisms involved in the disease and how these might vary according to cell type and disease subtype.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1187 / #1284

Poster Topic: *Theme C: α-Synucleinopathies / C06.e. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

INTERACTION OF GENETIC VARIANTS AND DNA METHYLATION IN ALZHEIMER'S DISEASE

POSTERS: C06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Younghee Lee[1], Seonggyun Han[2], Soo-Ah Cho[1], Wongyung Cho[1], Karen Eilbeck[2], Hillary Coon[2], Kwangsik Nho[3]
[1]Seoul National University, Veterinary Medicine, Seoul, Korea, Republic of, [2]University of Utah, Biomedical Informatics, Salt Lake City, United States of America, [3]Indiana University School of Medicine, Radiology And Imaging Sciences, Indianapolis, United States of America

Aims: Alzheimer's disease (AD) is a major cause of dementia and among the most complex diseases, featuring various heterogeneous molecular mechanisms. Not only germline genetic but also epigenetic factors (i.e., DNA methylation) contribute to its progression in the human brain; in particular, dysregulation of gene expression by single nucleotide polymorphisms (SNPs) and altered DNA methylation is often observed in AD patients. Although genetic and epigenetic regulators have each independently received intensive study for their roles in AD progression, their interactive contributions are not yet fully understood. In this study, we aimed to elucidate the interplay of genetic loci (i.e., SNPs) and DNA methylation in determining transcript-level expression status in AD.
Methods: We performed an integrative analysis of whole-genome sequencing, RNA-seq, and methylation data from the dorsolateral prefrontal cortex in AD patients (n=361), generated from the Religious Orders Study/Memory and Aging Project. Likelihood ratio tests (LRTs) were performed to determine the statistical significance of differences in transcript expression between linear models with and without the SNP-methylation interaction term.
Results: We identified 179 SNP-methylation pairs as having interactions with statistically significant impacts on the expression of 67 transcripts (63 unique genes) belonging to functional gene sets, including immune-related and post-synaptic assembly pathways. In particular, a number of HLA family genes (*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-DRB5*, *HLA-DPA1*, *HLA-K*, *HLA-DQB1*, and *HLA-DMA*) were observed to have changes associated with this SNP-methylation interplay.
Conclusions: Our study provides a new molecular insight into the crosstalk between genetic and epigenetic elements, in that it concerns transcript expression status in AD. Our findings especially implicate immune-related pathways as targets of these regulatory interactions. SNP-methylation interactions may thus contribute to the molecular complexity underlying immune-related pathogenies in AD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1188 / #1209

Poster Topic: *Theme C: α-Synucleinopathies / C06.e. Cell, Molecular and Systems Biology: Epigenetics, histone modification, DNA methylation*

IDENTIFICATION OF PARKINSON'S DISEASE-ASSOCIATED REGULATORY VARIANT ALTERING SCARB2 EXPRESSION IN HUMAN DOPAMINERGIC NEURONS

POSTERS: C06.E. CELL, MOLECULAR AND SYSTEMS BIOLOGY: EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION

Lasse Sinkkonen[1], Deborah Gerard[1,2], Jochen Ohnmacht[1,2], Borja Gomez-Ramos[1], Nina Baumgarten[3], Aurelien Ginolhac[1], Marie Catillon[1], Alexandar Rakovic[4], Christine Klein[4], Marcel Schulz[3], Thomas Sauter[1], Rejko Krüger[2,5,6]
[1]University of Luxembourg, Department Of Life Science And Medicine, Belvaux, Luxembourg, [2]University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Belvaux, Luxembourg, [3]Goethe University Frankfurt, Institute For Cardiovascular Regeneration, Frankfurt am Main, Germany, [4]University of Lübeck, Institute Of Neurogenetics, Lübeck, Germany, [5]Luxembourg Institute of Health, Transversal Translational Medicine, Luxembourg, Luxembourg, [6]Centre Hospitalier de Luxembourg, Parkinson Research Clinic, Luxembourg, Luxembourg

Aims: Parkinson's disease (PD) is marked by the degeneration of midbrain dopaminergic neurons (mDANs) situated in the substantia nigra. PD risk has been linked to common single nucleotide polymorphisms (SNPs) through genome-wide association studies (GWAS), but the underlying mechanisms remain largely undiscovered. SNPs associated with various traits and diseases are enriched within gene regulatory regions. Alterations in transcription factor binding sites (TFBS), caused by variants located within accessible TFBS, can induce changes in gene expression, contributing to *cis*-regulatory variation.
Methods: To better understand how PD-associated SNPs might impact mDANs, we generated time-series transcriptome and chromatin accessibility profiles of purified mDNAs and astrocytes differentiated from human iPSC-derived neural precursor cells. We integrated these epigenomic profiles with 17 million PD-associated SNPs from PD GWAS repository, employing our novel approach to predict SNPs affecting TF binding in a cell type-specific manner.
Results: An intriguing finding involved a PD-associated SNP that introduced a proximal TFBS for NR2C2 at the promoter of lysosomal membrane protein 2 (SCARB2) in mDANs. SCARB2 is a transporter for glucosylceramidase (GBA), a gene frequently associated with PD. Luciferase assays in human neurons confirmed a reduction in transcriptional activity in the presence of the PD-associated SCARB2 allele that also exhibited reduced chromatin accessibility in mDNAs. Moreover, eQTL analysis of human brain regions revealed a lower expression of SCARB2 in the presence of the PD-associated allele, especially in substantia nigra. Consistently, a knockdown of NR2C2 resulted in increased SCARB2 expression that was accompanied by an increase in the number of mDANs within the neuronal population.
Conclusions: In summary, these findings suggest that NR2C2 may function as a repressor of mDAN differentiation, targeting SCARB2 in the presence of a PD-associated regulatory variant.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1189 / #1229

Poster Topic: *Theme C: α-Synucleinopathies / C06.f. Cell, Molecular and Systems Biology: Other*

NEURONAL HAEMOGLOBIN INDUCES LOSS OF DOPAMINERGIC NEURONS IN MOUSE SUBSTANTIA NIGRA, COGNITIVE DEFICITS AND CLEAVAGE OF ENDOGENOUS A-SYNUCLEIN

POSTERS: C06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Carlotta Bon[1], Chiara Santulli[2], Elena De Cecco[2], Marta Codrich[2], Joanna Narkiewicz[2], Pietro Parisse[3], Fabio Perissinotto[3], Claudio Santoro[4], Francesca Persichetti[4], Giuseppe Legname[2], Stefano Espinoza[1,4], Stefano Gustincich[1]
[1]Istituto Italiano di Tecnologia, Rna Lab, Genova, Italy, [2]SISSA, Area Of Neuroscience, Trieste, Italy, [3]Elettra, Sincrotrone, Trieste, Italy, [4]Universita' del Piemonte Orientale, Department Of Health Sciences And Research Center On Autoimmune And Allergic Diseases (caad), Novara, Italy

Aims: Parkinson's disease (PD) presents the selective loss of A9 dopaminergic (DA) neurons of Substantia Nigra pars compacta (SNpc) and the presence of intracellular aggregates called Lewy bodies. α-synuclein (α-syn) species truncated at the carboxy-terminal (C-terminal) accumulate in pathological inclusions and promote α-syn aggregation and toxicity. Hemoglobin (Hb) is the major oxygen carrier protein in erythrocytes. In addition, Hb is expressed in A9 DA neurons where it influences mitochondrial activity. Hb overexpression increases cells' vulnerability in a neurochemical model of PD in vitro and forms cytoplasmic and nucleolar aggregates upon short-term overexpression in mouse SNpc. In this context, our objective was to study the effects of Hb expression in DA neurons *in vivo*.
Methods: α and β-globin chains were co-expressed in DA cells of SNpc *in vivo* upon stereotaxic injections of an Adeno-Associated Virus isotype 9 (AAV9) and in DA iMN9D cells *in vitro*.
Results: Long-term Hb over-expression in SNpc induced the loss of about 50% of DA neurons, a mild motor impairment and deficits in recognition and spatial working memory. Hb triggered the formation of endogenous α-syn C-terminal truncated species. Similar α-syn fragments were found *in vitro* in DA iMN9D cells over-expressing α and β- globins when treated with pre-formed α-syn fibrils.
Conclusions: Our study positions Hb as a relevant player in PD pathogenesis for its ability to trigger DA cells' loss in vivo and the formation of C-terminal α-syn fragments.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1190 / #587

Poster Topic: *Theme C: α-Synucleinopathies / C07.a. Animal Models: Transgenic rodents*

EXERCISE REVEALS POTENTIAL AS AN EARLY DISEASE-MODIFYING TREATMENT IN A MOUSE MODEL OF PARKINSON'S DISEASE

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Malte Feja[1], Leonie Baldauf[1], Milos Stanojlovic[1], Julia Hankel[2], Christian Visscher[2], Eva Schäffer[3], Daniela Berg[3], Franziska Richter[1]
[1]University of Veterinary Medicine Hannover, Department Of Pharmacology, Toxicology, And Pharmacy, Hannover, Germany, [2]University of Veterinary Medicine, Institute For Animal Nutrition, Hannover, Germany, [3]University Hospital Schleswig-Holstein, Christian-Albrechts University, Department Of Neurology, Kiel, Germany

Aims: Subtle motor and non-motor dysfunctions indicative of beginning Parkinson's disease (PD) are evident before clinical disease diagnosis. Persons of risk developing PD would be willing to determine their risk and change their lifestyle in case of a concrete beneficial approach. Growing evidence indicates the potential of exercise in reducing components of PD-related pathology. We hypothesized that early intervention by exercise has a disease-modifying effect during prodromal phase in our PD mouse model.
Methods: Two-month-old transgenic mice overexpressing human wild-type alpha-synuclein (Thy1-aSyn) and wildtypes were assigned to three groups receiving different intensity levels of exercise on a treadmill. We assessed motor performance and activity, and took fecal and brain samples for analysis of microbiota and PD-related pathology.
Results: Transgenic mice showed motor impairment on challenging beam and vertical pole, reflecting the expected progression of aSyn pathology at this age. Improved vertical pole performance under exercise in wildtypes suggests symptomatic effects, while slightly improved beam performance of transgenics might indicate a disease-modifying potential of exercise. Levels of phosphorylated alpha-synuclein at serine 129, a key feature of PD, were increased in the substantia nigra pars compacta in untrained, but not in trained, Thy1-aSyn mice, indicating a neuroprotective potential of exercise. Intensive training did not induce inflammation, since reactive microglia were not affected. Genotypes did not differ in locomotor open field activity, but untrained transgenics exhibited an anxiety-like phenotype. Intriguingly, intensive training reduced anxiety-like behavior in transgenics to wild-type level.
Conclusions: These results suggest that exercise alleviates early sensorimotor and even non-motor deficits in Thy1-aSyn mice and demonstrate its potential as an early PD-modifying treatment. Increased fecal microbiota diversity in intensively-exercised mice supports a potential role of the gut-brain axis in the underlying pathological mechanisms of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1191 / #1551

Poster Topic: *Theme C: α-Synucleinopathies / C07.a. Animal Models: Transgenic rodents*

HISTOLOGICAL EVALUATION OF COLON TISSUE OF THE TRANSGENIC HA53TTG MOUSE MODEL

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Magdalena Daurer, Joerg Neddens, Roland Rabl, Livia Breznik, Tina Loeffler, Stefanie Flunkert, Manuela Prokesch
QPS Austria GmbH, Neuropharmacology, Grambach, Austria

Aims: Parkinson´s disease (PD) is a multicentric neurodegenerative disorder characterized by the accumulation and aggregation of α-synuclein (α-syn). Mutations in the SNCA gene encoding for α-syn are reported to accelerate α-syn oligomerization and aggregation. Recently, it has been recognized that the brain-gut-axis may play a critical role in PD onset and disease progression. Also, an excessive stimulation of the innate immune system may induce inflammation and contribute to the initiation of α-syn misfolding. Hence, in the current study, we histologically characterized colon samples of transgenic mice expressing human α-syn with A53T mutation.
Methods: Colon tissue of 5.5-month old transgenic hA53Ttg mice and age- and sex-matched non-transgenic littermates was histologically evaluated. Briefly, swiss rolls of colon tissues were prepared, and cryosections immunofluorescently labeled for human alpha-synuclein (ha-syn) as well as inflammation markers, such as CD45, CD68 and Iba1. Also, PGP 9.5 and vimentin were labeled to visualize nervous and connective tissue, respectively. Finally, tissue sections were qualitatively evaluated. Analysis of additional markers is still ongoing.
Results: Qualitative analysis revealed presence of hα-syn in hA53Ttg mice in connective tissue but not nervous tissue. Also, as indicated by positive signals for CD45, CD68, and Iba1, hA53Ttg mouse colon showed elevated inflammation compared to non-transgenic littermates.
Conclusions: In conclusion, this study reveals the impact of hα-syn with A53T mutation in murine colon pathology and emphasizes the importance of enteric inflammatory processes of this PD mouse model. Subsequently, the data indicate a potential use of the A53Ttg mouse model for efficacy studies targeting the observed pathologies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1192 / #858

Poster Topic: *Theme C: α-Synucleinopathies / C06.f. Cell, Molecular and Systems Biology: Other*

ASSESSING THE EFFECT OF THERAPEUTIC FASTING ON THE GUT-BRAIN AXIS IN PARKINSON'S DISEASE

POSTERS: C06.F. CELL, MOLECULAR AND SYSTEMS BIOLOGY: OTHER

Júlia Ortís Sunyer[1], Bérénice Hansen[1], Marek Ostaszewski[1], Polina Novikova[1], Oskar Hickl[1], Susheel Busi[1], Velma Aho[1], Kirsten Roomp[1], Janine Habier[1], Tuesday Lowndes[1], Jordan Caussin[1], Andreas Michalsen[2,3], Etienne Hanslian[2,3], Daniela Koppold[2,3], Brit Mollenhauer[4], Sebastian Schade[5], Cédric Laczny[1], Patrick May[1], Jochen Schneider[1,6,7], Paul Wilmes[1,7]
[1]University of Luxembourg, Luxembourg Centre For Systems Biomedicine, Esch-sur-Alzette, Luxembourg, [2]Charité - Universitätsmedizin Berlin, Institute For Social Medicine, Epidemiology And Health Economics, Berlin, Germany, [3]Immanuel Hospital Berlin, Department Of Internal And Integrative Medicine, Berlin, Germany, [4]University Medical Center Göttingen, Department Of Neurology, Göttingen, Germany, [5]Paracelsus-Elena-Klinik Kassel, Department Of Neurosurgery, Kassel, Germany, [6]Saarland University Medical Center, Department Of Internal Science And Medicine Ii, Homburg Saar, Germany, [7]University of Luxembourg, Department Of Life Sciences And Medicine, Esch-sur-Alzette, Luxembourg

Aims: The human gut microbiome is a complex ecosystem that profoundly impacts the immune, metabolic and neural systems. In diseases with inflammatory signatures such as Parkinson's disease (PD), these can be influenced by numerous factors, including host genetics, lifestyle and diet. A study with a cross-sectional and a longitudinal arm was designed. The cross-sectional arm sets out to leverage multi-omic strategies to understand the relationship between the gut microbiome and the immune system in the context of neuroinflammation. The longitudinal arm investigates the impact of up to 7 days of fasting (maximum 400 kcal/day) followed by 12 months of time-restricted eating on PD patients.
Methods: For the cross-sectional arm, a total of 120 stool samples were collected from individuals with PD (n=60) and concomitant healthy controls (n=60). The longitudinal arm involved stool samples collected from 30 PD patients at regular intervals throughout the course of one year. The flash-frozen stool samples were cryomilled and the extraction of the biomolecular fractions was performed for the different multi-omics analyses.
Results: Using microbiome multi-omics data and contextualized prior knowledge in the Expobiome Map (https://expobiome.lcsb.uni.lu/), we identified several molecules of interest in PD. These include, but are not limited to, β-glutamate, ceramides and flagella-related proteins. Moreover, we are currently tracking the signatures of the identified microbiome-derived molecules in the longitudinal arm to make disease-related predictions and assess the effect of the treatment to alleviate PD-related symptoms.
Conclusions: Our study has identified relevant microbiome-derived molecules that could be of interest as biomarkers for PD and for evaluating the treatment's efficacy. The insights generated through this study will not only expand the knowledge on the PD-associated microbiome but also broaden the number of available therapeutic targets against the disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1193 / #979

Poster Topic: *Theme C: α-Synucleinopathies / C07.a. Animal Models: Transgenic rodents*

PFF AND/OR VIRAL VECTOR BASED MODELS FOR PRECLINICAL PROOF OF CONCEPT STUDIES TARGETING ALPHA-SYNUCLEIN PATHOLOGY

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Sofie Carmans[1], Eline Vonck[2], Wannes Dejonckheere[1], Veerle Baekelandt[2], Tom Cornelissen[1]
[1]reMYND, Cro, Leuven, Belgium, [2]KULeuven, Neuroscience, Leuven, Belgium

Aims: Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is characterized by the accumulation of alpha-synuclein protein aggregates in the brain. Currently a lot of effort is put into studying the involvement of different forms of alpha-synuclein, i.e. monomeric, oligomeric, fibrillar and aggregated forms or different post translational modifications of the protein, and their contribution to disease progression. Targeting alpha-synuclein thus has an important therapeutic value. Since the research field lacks good and consistent animal models for preclinical assessment, we are developing mouse models based on the administration of sonicated preformed fibrils (PFF), either alone or in combination with viral vectors. To increase translatability for treatments which target human alpha-synuclein specifically, the development of models combining **human** PFF's and expression of **human** alpha synuclein via viral vectors is initiated.
Methods: Young wild-type mice are treated with combinations of AAV vectors and recombinant mouse or human PFF's (Stressmarq) via different administration routes. Motor performance is assessed followed by pathologic characterization.
Results: Unilateral and bilateral stereotactic injections in the dorsal striatum of young wild type mice with sonicated **mouse** PFF's showed clear pathology and robust neurodegeneration at varying time points (4-13 weeks) after PFF administration. Modeling **human** PFF spreading in mice is more difficult to acquire, due to the species barrier. Therefore hPPF's were administered via striatal injections after local overexpression of human alpha-synuclein by nigral AAV2/7-human-aSyn viral vector injection in young wild-type mice. Motor performance will be assessed followed by pathologic characterization of the model.
Conclusions: These alpha-synuclein based models can be of great importance to the research field to assess in vivo therapeutic interventions directed against alpha-synuclein pathology and more specifically human alpha-synuclein pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1194 / #2702

Poster Topic: *Theme C: α-Synucleinopathies / C07.a. Animal Models: Transgenic rodents*

ON THE WAY TO A NEW MODEL OF NEURODEGENERATION? FIRST EVIDENCE OF THE EXPRESSION OF GATA1 IN THE BRAIN

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Francesco Emanuele Bellomi[1], Claudia Caturano[1], Martyna Podgajna[1,2], Aleksandra Kaczyńska[1,2], Livia La Barbera[3], Paola Verachi[4], Maria Zingariello[1], Mario Falchi[1,4], Michal Wegrzynowicz[2], Simone Carotti[1], Marcello D'Amelio[3], Giorgio Vivacqua[1]
[1]Campus Bio-medico University of Rome, Microscopic And Ultrastructural Anatomy Laboratory, Rome, Italy, [2]Mossakowski medical research Centre Polish Academy of Sciences, Laboratory Of Molecular Basis Of Neurodegeneration, Warsaw, Poland, [3]Università Campus Bio-Medico di Roma, Laboratory Of Molecular Neurosciences, Rome, Italy, [4]Italian National Istitute of Health (ISS), Laboratory Of Confocal Microscopy, Rome, Italy

Aims: GATA1 is a transcription factor belonging to GATA family and involved in the development and the maturation of the hematopoietic lineage, while there are no clear evidence about the expression of GATA1 in neuronal lineage. A potential role for GATA1 in synucleinopathies has been suggested, since GATA1 regulates the transcription of SNCA gene, encoding for alpha-synuclein (a-syn) in red blood cells. In the present study, we aimed at deciphering the effects of GATA1 knocking down on the expression of a-syn and on the survival of different neuronal subtypes.
Methods: The study was performed using control mice with CD1 background and a mice model of GATA1 knock down (STOCK GATA1tm2Sho/J). Immunohistochemistry, immunofluorescence and RNAscope were used to analyze the expression of GATA1. Stereological count for different neuronal subtypes was performed in the olfactory bulbs and in the midbrain. Finally, the expression levels of a-syn were analysed by ELISA and the morphological features of GATA1 expressing neurons were visualized by Transmission Electron Microscopy (T.E.M.).
Results: The brains of CD1 mice were 21% larger in size than those of GATA1low mice. GATA1 is expressed in discrete brain-stem and telencephalic regions and predominantly in the olfactory bulbs. As expected, expression of GATA1 was reduced in GATA1low mice, where GATA1 expressing neurons appeared shrinker and morphologically altered. Stereological count and ELISA analysis demonstrate that the number of DA neurons and the expression of a-syn were altered in GATA1low mice.
Conclusions: Our results prove, for the first time, that GATA1 is expressed in the central nervous system. Regulation of SNCA gene and contribution to maturation and survival of DA neurons request detailed exploration to decipher the role of GATA1 in neurodegeneration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1195 / #2784

Poster Topic: *Theme C: α-Synucleinopathies / C07.a. Animal Models: Transgenic rodents*

OPTIMISATION OF A MOUSE MODEL FOR PARKINSON'S DISEASE BASED ON THE COMBINATION OF ASYN OVEREXPRESSION WITH ASYN FIBRIL SEEDS

POSTERS: C07.A. ANIMAL MODELS: TRANSGENIC RODENTS

Eline Vonck[1], Chris Van Den Haute[2], Tom Cornelissen[3], Veerle Baekelandt[1]
[1]KULeuven, Neuroscience, Leuven, Belgium, [2]KULeuven, Neurosciences, Leuven, Belgium, [3]reMYND, Cro, Leuven, Belgium

Aims: A-synuclein (αSyn) has been identified as a key protein in the pathophysiology of Parkinson's disease (PD). Since, this protein has gained a lot of interest as a possible biomarker and therapeutic target. Multiple αSyn-based rodent models have been developed, each reproducing specific features of the disease. However a more encompassing model mimicking the full spectrum of pathological and behavioural changes is needed. Therefore, we aim to create an αSyn-based model with increased construct validity by combining two established approaches to model PD, namely AAV-mediated overexpression of human αSyn with addition of human αSyn preformed fibrils (hPFFs).
Methods: Our first combination strategy is based on our established vector model where AAV2/7-CMVeSynapsin-hαSyn is injected in the substantia nigra of wild type mice. We build upon this by either co-injecting or sequentially injecting hPFFs in the striatum four weeks post-injection when stable transgene expression is achieved. Secondly, we are creating a peripheral model by administering vector and hPFFs either intracerebroventricularly (ICV) or intravenously (IV) via tail vein injections. To obtain robust transgene expression in the entire CNS we performed a study comparing different vector capsids using both administration routes.
Results: In our experimental design, local co-administration of hPFFs with vector did not lead to enhanced Lewy-like αSyn pathology or neurodegeneration. Therefore we administered striatal hPFFs when local overexpression is established. Behavioural changes and PD-like pathology will be assessed. In addition, IV administration of self-complementary vector PHP.eB-CMVeSynapsin-GFP was identified as most robust and efficient for targeting the entire CNS including spinal cord.
Conclusions: As current treatment options for PD are symptomatic and cannot halt disease progression or cure it, these αSyn-based models can be valuable in identifying novel therapeutic strategies intervening with human αSyn pathology in PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1196 / #1419

Poster Topic: *Theme C: α-Synucleinopathies / C07.b. Animal Models: Primates, naturally occuring models and brain organoids*

DEVELOPMENT OF AN IN VITRO PARKINSON'S DISEASES MODEL BASED ON 3D HUMAN BRAINSPHERES

POSTERS: C07.B. ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS

Lydia Alvarez Erviti[1], David Pamies[2], Guglielmo Verona[3], Marie-Gabrielle Zurich[2]
[1]Center for Biomedical Research La Rioja, Fundacion Rioja -Salud, Molecular Neurobiology, Logroño, Spain, [2]University of Lausanne, Department Of Biomedical Sciences, Lausanne, Switzerland, [3]University College London, Centre For Amyloidosis, London, United Kingdom

Aims: An important limitation in the development of therapies for Parkinson's disease treatment is the requirement for relevant pre-clinical disease models. A successful cell-based model for drug discovery would facilitate identification of relevant therapeutic targets and compounds to modulate those targets. We propose to develop a new *in vitro* model for Parkinson's disease based on the recently established human induced pluripotent stem cells (hiPSCs)-derived BrainSphere (BS) cell culture system.
Methods: BS were prepared from hiPSCs. After differentiation, BS were treated with alpha-synuclein monomers (20 ng), alpha-synuclein pre-formed fibrills (PFFs) (20 ng) or PBS during 72 h. Medium was removed and fresh medium without alpha-synuclein was added. BS were analysed 14 days after treatment.
Results: Exposure to alpha-synuclein PFF led to a significant increase of total alpha-synuclein, insoluble pSer129 alpha-synuclein and the presence of alpha-synuclein aggregates. The presence of alpha-synuclein aggregates was associated with a decrease in TH dopaminergic neurons. Moreover, LAMP-2A protein level was decreased in BS treated with alpha-synuclein PFF. Treatment with alpha-synuclein monomer did not result in the presence of alpha-synuclein aggregation or dopaminergic cell death.
Conclusions: Our results demonstrate that human BS exposed to alpha-synuclein PFFs mimic pathological mechanisms previously identified in Parkinson's disease human brain samples and animal models, and therefore constitute a new promising and versatile *in vitro* model for this disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1197 / #208

Poster Topic: *Theme C: α-Synucleinopathies / C07.c. Animal Models: Non-mammalian models ,Other*

A NOVEL RAT MODEL OF PARKINSON'S DISEASE INDUCED BY UNILATERAL OR BILATERAL INTRASTRIATAL ADMINISTRATION OF A DIABETOGENIC COMPOUND

POSTERS: C07.C. ANIMAL MODELS: NON-MAMMALIAN MODELS ,OTHER

Jelena Osmanovic Barilar[1,2], Vito Papic[1,2], Vladimir Farkas[3], Robert Bagaric[4], Patrik Meglić[1,2], Ana Babić Perhoč[1,2], Jan Homolak[1,2], Davor Virag[1,2], Melita Salkovic-Petrisic[2], Ana Knezovic[1,2]
[1]School of Medicine University of Zagreb, Pharmacology, Zagreb, Croatia, [2]School of Medicine University of Zagreb, Croatian Institute For Brain Research, Zagreb, Croatia, [3]Rudjer Boskovic Institute, Molecular Medicine, Zagreb, Croatia, [4]Rudjer Boskovic Institute, Experimental Physics, Zagreb, Croatia

Aims: Growing evidence suggest that type 2 diabetes is a risk factor for Parkinson's disease (PD). The aim of this project is to examine whether direct application of streptozotocin (STZ; used for generation of diabetes in animals) to brain region affected in PD (striatum) can induce characteristic PD symptoms.
Methods: Adult male Wistar rats were given intrastriatally STZ unilaterally or bilaterally (0.75 or 1.5 mg/kg per striatum) or vehicle and one month after, cognitive, behavioural, metabolic and motoric functions were tested by RotaRod, Novel Object Recognition, Passive Avoidance, Morris Water Maze, Elevated Plus Maze, CatWalk and PET scan. Levels of tyrosine hydroxylase (TH), insulin receptor (IR), D1, AMPAR and ChAT were measured in hippocampus and striatum.
Results: STZ rats showed deficits in motoric functions, spatial learning and memory, fear conditioned and recognition memory, and anxiety-like behaviour. Deficit was found more pronounced after bilateral administration in comparison to unilateral and with higher bilateral STZ dose. Brain glucose uptake was found increased after lower STZ dose and decreased after higher one in comparison to vehicle. Only higher STZ dose induced acute weight loss in comparison to vehicle. STZ decreased levels of TH and IR in stratum independently on the administration method and a dose, while TH levels remained unchanged in hippocampus.
Conclusions: The results demonstrate the development of PD hallmark symptoms after instrastriatal STZ administration, indicating its possible use as a new PD model. This work was funded by University of Zagreb project (10106-23-2439) and the Scientific Centre of Excellence for Basic, Clinical and Translational Neuroscience (project "Experimental and clinical research of hypoxic-ischemic damage in perinatal and adult brain"; GA KK01.1.1.01.0007 funded by the European Union through the European Regional Development Fund).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1198 / #1352

Poster Topic: *Theme C: α-Synucleinopathies / C07.c. Animal Models: Non-mammalian models ,Other*

GUT MICROBIOTA-MEDIATED MODULATION OF PARKINSON'S DISEASE-LIKE PHENOTYPES IN C. ELEGANS BY ΔHNS E. COLI: INSIGHTS INTO THE ROLE OF MICROBIAL GENES IN NEURODEGENERATION

POSTERS: C07.C. ANIMAL MODELS: NON-MAMMALIAN MODELS ,OTHER

Eun Jeong Lee
Ajou University School of Medicine, Department Of Brain Science, Suwon, Korea, Republic of

Aims: Parkinson's disease (PD) patients often exhibit elevated levels of methylglyoxal (MG), a reactive carbonyl compound linked to the formation of advanced glycation end products and various pathologies, including neurodegenerative diseases. Drawing from prior research that demonstrated the lifespan-extending effects of low MG-producing *Δhns Escherichia coli (E. coli)* on *Caenorhabditis elegans (C. elegans)* (Shin et al., 2020, PNAS), we hypothesized that this *E. coli* strain might alleviate PD-like symptoms, particularly dopaminergic neuron neurodegeneration.
Methods: 1. *Δhns E. coli*-fed *C. elegans* with 6-OHDA treatment 2. Analysis of single cell RNA-seq data from the substantia nigra of PD patients 3. The expression of H-NS in the fecal samples from PD patients 4. The expression of human genes affected by methylglyoxal
Results: *Δhns E. coli* effectively mitigated the degeneration of dopaminergic neurons induced by 6-OHDA (6-hydroxydopamine) in *C. elegans*. Furthermore, we discovered that synapse-related genes, upregulated in *Δhns E. coli*-fed *C. elegans*, continued to exhibit increased expression even under 6-OHDA treatment. Remarkably, the expression levels of these genes were found to be reduced in the substantia nigra of PD patients, based on publicly available single-cell RNA-seq data. What's even more striking, our investigation of fecal samples from PD patients revealed an upregulation of the H-NS protein compared to a healthy control group. Consequently, we explored whether the human genes corresponding to those restored in *Δhns E. coli*-fed *C. elegans* could be influenced by MG levels. Indeed, the expression of these genes was reduced by MG but restored by MG scavengers.
Conclusions: These findings suggest the possibility of utilizing gene modifications in microbiota to reverse neurodegenerative phenotypes in the host, offering a potential therapeutic avenue for intervening in PD by targeting the gut microbiota.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1199 / #1877

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

TOXIC INTERPLAY BETWEEN SMALL DIPEPTIDE PROTEIN REPEATS AND TAU IN TAUOPATHIES

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Nemil Bhatt[1], Nicha Puangmalai[1], Cynthia Jerez[1], Mauro Montalbano[2], Shailee Gandhi[1], Rakez Kayed[2]
[1]University of Texas Medical Branch, Neurology, Galveston, United States of America, [2]The University Of Texas Medical Branch, Neurology, Galveston, United States of America

Aims: Tauopathies, including Alzheimer's Disease and Frontotemporal Dementia, are characterized as intracellular lesions composed of aggregated tau proteins. Soluble tau oligomers are shown to be one of the most toxic species and are responsible for the spread of tau pathology. Recent studies have found that several proteins such as amyloid b, a-synuclein, and TDP-43 can aggregate tau. In this study, we investigated the ability of small metabolites like *C9orf72* associated dipeptide protein repeats (DPRs) to interact with and aggregate tau to form toxic soluble tau oligomers.
Methods: We have developed various models which express dipeptide protein repeats to understand the interaction between short peptides and tau. The dipeptide protein repeat induced tau aggregates were characterized using biophysical, as well as biochemical assays in vitro and in cellular models. Furthermore, we evaluated their toxicity, and seeding potency to understand the biological effects of this interaction.
Results: Our results suggest the propensity for DPRs, especially glycine-arginine and proline-arginine repeats to form oligomeric structures which interact and seed tau in a prion like fashion. This interaction leads to the production of tau oligomers, which trigger subsequent neurodengeration. Tau oligomers also trigger alterations in the microtubule dynamics in cell lines as well as primary neuronal culture systems.
Conclusions: Many studies have investigated the toxicity of small protein repeats, however, the role of DPR oligomers in inducing tau aggregation is still unclear. Thus, the ability to understand the toxic interplay between small peptide repeats and tau oligomers has great potential to further the understanding of tau progression and aid in the development of targeted therapeutics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1200 / #1018

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

THE GUT-BRAIN AXIS IN ALS: A SYSTEMATIC REVIEW AND META-ANALYSIS ASSESSING THE ROLE OF THE GUT AND ITS MICROBIOME IN AMYOTROPHIC LATERAL SCLEROSIS

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Fergal Waldron, Alexander Jackson, Rollo Press, Holly Spence, Jenna Gregory
University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom

Aims: To investigate the role of the gut and it's microbiome in amyotrophic lateral sclerosis by carrying out a systematic review and meta-analysis of relevant studies from the clinical and pre-clinical literature.
Methods: Here we present a systematic review and meta-analysis assessing the role of the gut-brain axis in ALS including preclinical and clinical studies examining both the microbiome, and non-microbial related pathological pathways. Database searches of Medline, PubMed, and Embase were performed using pre-determined search terms, and both qualitative and quantitate data were extracted for systematic literature review and meta-analysis respectively.
Results: Studies examining differences in the microbiome constituents between (i) people with ALS and healthy controls, and (ii) animals of preclinical models of ALS and controls, largely show no significant differences, noting relatively small sample sizes and both inter- and intra-study heterogeneity. However, interventions targeting the gut microenvironment and/or gut-resident pathologies demonstrate a significant improvement in disease outcomes, such as motor function and survival.
Conclusions: Our findings suggest that interventions either targeting the gut microenvironment or alleviating gut pathology offer a promising therapeutic route for treatment of ALS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1201 / #978

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

INVESTIGATING MICROGLIA MEDIATED NEUROINFLAMMATION IN STEM CELL DERIVED MODELS OF C9ORF72 AMYOTROPHIC LATERAL SCLEROSIS

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Yujing Gao[1], Harpreet Saini[2], Greg O'Sullivan[1], Elena Di Daniel[1], Carla F. Bento[1], Lizzie Glennon[1], Daniel Tams[1], Brent Graham[1]
[1]Astex Therapeutics Ltd, Translational Bioscience, Cambridge, United Kingdom, [2]Astex Therapeutics Ltd, Informatics, Cambridge, United Kingdom

Aims: Amyotrophic Lateral Sclerosis (ALS) or Motor Neurone Disease (MND) is a neurodegenerative disorder caused by the progressive loss of motor neurons. The mechanisms underlying ALS are unclear, although neuroinflammation is a major factor contributing to disease pathology. In ALS patients and animal models, brain resident macrophages called microglia demonstrate altered function, which can be detrimental to neuronal health. To investigate changes in microglia in ALS and their impact on motor neurons, we assessed monocultures and cocultures of microglia and motor neurons derived from human induced pluripotent stem cells (iPSC) carrying the hexanucleotide repeat expansion (HRE) in C9ORF72, a common genetic cause of ALS.
Methods: Human iPSCs were differentiated into microglia and motor neurons using established small molecule differentiation protocols. Generation of microglia and motor neurons were verified by expression of established cell lineage markers. The inflammatory profiles of microglia upon lipopolysaccharide (LPS) stimulation were assessed using enzyme-linked immunosorbent assays, dot blots and real time PCR. The transcriptomic profiles of microglia/motor neuron cocultures were assessed using single cell RNA sequencing.
Results: Microglia with loss of function (LOF) of C9ORF72 (HRE or knockout) showed reduced capacity for cytokine production compared to isogenic and non-isogenic controls. Specifically, the LPS-induced expression and secretion of IL-6 were reduced in C9ORF72 LOF microglia. In coculture models, we performed single cell RNA sequencing and investigated the transcriptomes of microglia and motor neuron populations independently, identifying genes of interest.
Conclusions: C9ORF72 LOF attenuated the inflammatory capacity of stimulated microglia by reducing the levels of cytokine secretion and altering gene expression. Microglia mediated neuroinflammation plays an important role in the progression of ALS, and the impact on neuronal health and function is currently under investigation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1202 / #2680

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

INVESTIGATING ALTERATIONS IN THE HNRNP NETWORK IN FRONTOTEMPORAL DEMENTIA.

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Ariana Gatt, Katherine Fodder, Yaz Buhidma, Christina Toomey, Conceicao Bettencourt, Tammaryn Lashley
University College London, Neurodegenerative Disease, LONDON, United Kingdom

Aims: Heterogenous Nuclear Ribonucleoproteins (HnRNPs) are a family of RNA-binding proteins which are widely expressed in the brain. TDP-43, a well known HnRNP is present in pathological inclusions in FTLD (frontotemporal lobar degeneration) and FTLD cases are now classified into subtypes based on the pattern of TDP-43 pathology observed. We hypothesized that other HnRNPs might be playing a role in the pathogenesis of FTLD. We aimed to elucidate how the HnRNP network is altered in the presence of TDP-43 pathology.
Methods: This study encompassed a multi-omic approach to investigate changes occurring in the HnRNP network in FTLD. Different FTLD subtypes (FTLD-TDP A (C9orf72 negative / positive), FTLD-TDP C) and controls were analysed. A semi-quantitative pathological assessment was carried out for TDP-43 pathology and other HnRNPs by immunohistochemistry. Transcriptomic analysis was undertaken on bulk tissue and via single-cell RNA sequencing. DNA methylation data was analysed to observe whether methylation of HnRNPs was up or downregulated in different FTLD subtypes. Lastly, proteomic analysis was carried out to identify changes at the protein level.
Results: Pathological assessment revealed that multiple HnRNPs are mislocalised in FTLD, irrespective of TDP-43 pathological subtype. HnRNPs which showed upregulation at the bulk RNA-sequencing, methylation and proteomics level, did not, however, necessarily show overt changes in terms of pathology (e.g. HnRNP F). Overall, changes in the HnRNP network interactome were observed in the different pathological subtypes of FTLD.
Conclusions: Currently, TDP-43 pathology serves at the hallmark for post-mortem diagnosis of FTLD. We find that other RNA-binding proteins belonging to the same HnRNP family also exhibit pathological changes in FTLD and are also likely to have an effect on neuronal health and should therefore be studied in conjunction with TDP-43 in FTLD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1203 / #1547

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

THE INTERPLAY BETWEEN ELECTROSTATIC AND HYDROPHOBIC FORCES IN TDP-43 PHASE SEPARATION

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Raza Haider[1], Brandon Shipley[2], Krystyna Surewicz[1], Michael Hinczewski[2], Witold Surewicz[1]
[1]Case Western Reserve University, Physiology And Biophysics, Cleveland, United States of America, [2]Case Western Reserve University, Physics, Cleveland, United States of America

Aims: 1. Ascertain the effect of C-terminal phosphomimetic substitution on TDP-43 liquid-liquid phase separation (LLPS) C-terminal phosphorylation of TDP-43 is a biomarker of proteinopathy, but few studies have investigated its effect on LLPS. We purified variants of the low complexity domain (LCD), which drives TDP-43 LLPS, with phosphomimetic substitutions at 2-to-4 pathologically-relevant sites (S403, S404, S409, S410), and explored how LLPS of these variants differed from that of WT protein. 2. Analyze forces driving C-terminal phosphomimetic TDP-43 LLPS via coarse-grained simulations Coarse-grained modeling probed the electrostatic and hydrophobic interactions contributing to TDP-43 LLPS. These simulations quantified total intermolecular electrostatic and hydrophobic forces present during LLPS, as well as pairwise/residue-residue intermolecular electrostatic and hydrophobic forces between different regions of the protein.
Methods: 1. Turbidimetic and microscopic studies Turbidity (optical density at 280 nm) and microscopy were used to ascertain droplet formation. 2. Circular dichroism spectroscopy CD profiles were used to evaluate α-helical content of proteins. 3. Coarse-grained molecular modeling Coarse-grained simulations were used to model LLPS and evaluate the intermolecular hydrophobic and electrostatic forces involved.
Results: While WT protein LLPS is enhanced by increasing salt concentration, phosphomimetic TDP-43 LLPS displayed a bi-phasic salt dependence; NaCl initially inhibited LLPS, until a point beyond which increasing NaCl further increased LLPS propensity. Coarse-grained simulations revealed hydrophobic forces drove LLPS for phosphomimetic proteins, but electrostatic interactions modulated these hydrophobic forces by causing the phosphomimetic proteins to pack differently than WT protein within droplets. The transiently α-helical region was still present in the phosphomimetic variants and remained important for their LLPS.
Conclusions: C-terminal phosphomimetic substitution of TDP-43 LCD at pathologically-relevant sites confers a bi-phasic dependence on NaCl concentration as a result of electrostatic interactions tuning the hydrophobic forces that drive LLPS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1204 / #546

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

CELL CYCLE DYSREGULATION IN NEURONS FROM C9ORF72 CARRIERS

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Rodrigo Lopez Gonzalez, Imran Ali
Cleveland Clinic Lerner research Institute, Neurosciences, Cleveland, United States of America

Aims: The GGGGCC (G4C2) repeat expansion in C9ORF72 is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Previous data shows an increase in DNA damage and the generation of reactive oxygen species (ROS) in iPS derived neurons from C9ORF72 carriers. Dysregulation of cell cycle suppression in post-mitotic neurons caused by DNA instability and chronic insults including oxidative stress, may lead to cell cycle re-entry and neuronal death. Cyclin and CDK over expression have been observed in several neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD), and ALS. Here, we analyzed cell cycle markers in post-mitotic iPSC-derived neurons from C9ORF72 carriers.
Methods: We differentiated induced pluripotent cells (iPSs) from *C9ORF72* carriers and controls into high-yield post-mitotic neurons. All the iPS lines were previuosly fully characterized. We differentiated 3 controls and *3 C9ORF72* iPS-lines and analyzed cell cycle markers by qPCR and western blot at different time points: 1, 1.5 and 2-month-old iPS derived neurons.
Results: We found a significant age dependent increase in Ki67 and Geminin (GMNN), in 2- month-old iPS-derived neurons from *C9ORF72* carriers as compared to controls, but no significant differences on 1-month and 1.5-month-old MN cultures. We further analyzed the expression of several cyclins and CDKs by qPCR. We found that cyclin A2 (CCNA2), cyclin B1 (CCNB1), cyclin B2 (CCNB2), CDK1, CDK2 and CDK4 are significantly upregulated in 1.5-month-old, and 2-month-old *C9ORF72 neurons* as compared to controls. we found a similar increase in the blot cyclin A2 and cyclin B2 proteins by western blot in 2-month-old *C9ORF72 neurons.*
Conclusions: Age-dependent increase in cell division markers, cyclins and CDKs in iPSC derived post-mitotic neurons from C9ORF72 carriers as compared to controls in gene expression and protein levels.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1205 / #974

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

TDP-43 CONDENSATION DYNAMICS BEHAVIOUR INFLUENCES PATHOLOGY-RELATED TDP-43 PHOSPHORYLATION

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Simone Mosna[1,2], Yelyzaveta Zadorozhna[1,2], Dorothee Dormann[1,3]
[1]Johannes Gutenberg University Mainz, Institute Of Molecular Physiology, Mainz, Germany, [2]IPP, International Phd Program, Mainz, Germany, [3]Institute of Molecular Biology gGmbH, Imb, Mainz, Germany

Aims: TDP-43 is the major aggregating protein in ALS and FTD, as well as 50% of AD patients. The deposited TDP-43 aggregates are hyperphosphorylated, and C-terminal S409/S410-phosphorylation is considered to be a pathological hallmark of these disorders. Our previous work showed that C-terminal TDP-43 phosphorylation, as seen in patients, causes a more liquid-like behaviour of TDP-43 condensates and renders TDP-43 less prone to aggregation. Based on these findings, we proposed that C-terminal TDP-43 phosphorylation could be a protective mechanism against TDP-43 aggregation. Therefore, we now aim to understand what triggers C-terminal TDP-43 phosphorylation in cells and how the TDP-43 condensation/aggregation status influences this pathology-related modification.
Methods: We use rationally designed mutations to tune TDP-43 phase separation and aggregation. In a cellular model system with stable expression of the different GFP- or MYC-tagged TDP-43 variants with different condensation properties, we quantify TDP-43 S409/S410-phosphorylation induced by cellular stress. Additionally, we use phosphoproteomics to identify the induced phosphorylation sites. In an in vitro kinase assay with recombinant TDP-43 and CK1d, we determine how the efficiency of TDP-43 phosphorylation is influenced by TDP-43 condensation status.
Results: In the cellular model system, aggregation-prone TDP-43 variants show slightly reduced S409/S410 phosphorylation levels in comparison to TDP-43 wild-type (WT), whereas liquid-like variants show a stronger decrease in S409/S410 phosphorylation. In vitro, CK1d-mediated hyperphosphorylation of TDP-43 is strongly accelerated upon phase separation of TDP-43. In line with the cellular data, aggregation-prone TDP-43 variants showed slower TDP-43 phosphorylation kinetics, and liquid-like or monomeric variants showed little to no hyperphosphorylation.
Conclusions: C-terminal TDP-43 phosphorylation can be induced by specific cellular stressors. TDP-43 hyperphosphorylation is favoured by the formation of physiological TDP-43 condensates, whereas condensates with altered dynamics reduce kinase efficiency.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1206 / #2519

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

DIFFERENTIAL NEURONAL VULNERABILITY TO C9ORF72 REPEAT EXPANSION DRIVEN BY XBP1 TRANSCRIPTION SIGNATURE.

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Dunxin Shen[1], Alec Vincent[1], Evan Udine[2], Yaz Buhidma[3], Carlo Frigerio[4], Marka Van Blitterswijk[5], Tammaryn Lashley[3], Teresa Niccoli[1]
[1]UCL, Iha, London, United Kingdom, [2]Mayo Clinic, Department Of Neuroscience, Jacksonville, United States of America, [3]Queen Square Brain Bank for Neurological Disorders, Department Of Clinical And Movement Neuroscience, London, United Kingdom, [4]UCL, Dri, London, United Kingdom, [5]Mayo Clinic, Neuroscience, Jacksonville, United States of America

Aims: C9orf72 repeat expansion mutation (C9) is the most common genetic cause of sporadic and familial Amyotrophic Lateral Sclerosis(ALS) and Frontotemporal Dementia (FTD). The aim of this study was to determine why cell death is triggered only in specific neuronal populations, while others remain 'protected' or are less susceptible to disease is still an open question. In particular, whether it's the way neurons respond to the accumulation of toxic insults or the initial neuronal transcriptional state that determines their vulnerability is still unknown.
Methods: We have carried out a large scale profiling of single cell transcription signature throughout disease development in a *Drosophila* model of C9 toxicity.
Results: We followed transcriptional changes across the development of disease and tracked cell populations during disease progression. We have identified cell populations which are depleted in response to C9 repeat expression, and therefore vulnerable to toxicity. On the other hand, other populations are resistant to toxicity, and maintain their cell number during disease progression. We find that a major determinant of vulnerability is the transcriptional state of the cell before it's exposed to C9 repeat expression and that this resistant transcriptional state is conserved. We identify Xbp1 as a key transcription factor in regulating the trascriptional state of a resistant population and we show that upregulating Xbp1 can rescue C9 toxicity in our fly models.
Conclusions: We find that a major determinant of vulnerability is the transcriptional state of the cell before it's exposed to C9 repeat expression and that this resistant transcriptional state is conserved, we also show that cells resistant to disease have a higher expression of pathways involved in maintenance of proteostasis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1207 / #1881

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

PROGRANULIN MUTATIONS IN MICROGLIA AND ITS IMPACT IN NEURODEGENERATION

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Paula Polanco Miquel[1,2], Laura Fumagalli[1,2], Jessie Premereur[1], Diede Van Den Biggelaar[1,2], Maxim Van Hoek[1,2], Tim Meese[1,2], Bob Asselbergh[2], Renzo Mancuso[1,2]
[1]VIB Center for Molecular Neurology, Microglia And Inflammation In Neurological Disorders (mind) Lab, Antwerpen, Belgium, [2]University of Antwerp, Biomedical Sciences, Antwerpen, Belgium

Aims: Loss of function mutations in the progranulin gene (GRN), are the second most common genetic cause of frontotemporal lobar degeneration (FTLD), a disorder that accounts for 10-20% of all young-onset dementias. GRN, as other risk genes associated with dementia, is primarily expressed in microglia, the immune cells of the brain. However, the functional consequences of granulin deficiency on human microglia biology remain unknown.
Methods: Using CRISPR/Cas9 genome editing technology, we generated a *GRN* knockout (KO) induced pluripotent stem cell (iPSC) line. We confirmed the knockout using sanger sequencing and immunoblot. We have differentiated the *GRN*-KO line into microglia using our MIGRATE protocol. We have performed a series of *in vitro* experiments exploring whether GRN deficiency leads to functional alterations.
Results: We found that GRN-deficient microglia show altered transcriptomic and functional features associated with phagocytosis and lysosomal dysfunction. To better understand the effect of microglial GRN deficiency *in vivo*, we xenotransplanted the iPSC-derived microglia progenitors into the mice brain and performed histological assessment of the mouse brain.
Conclusions: Overall, our results reveal an essential role of *GRN* in regulating microglial physiology and potentially highlighting disease mechanisms contributing to *GRN*-FTLD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1208 / #1598

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

MODELLING FTLD-FUS USING PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELL MODELS

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Rafaela Policarpo[1,2], Miranda Lastra Osua[1,2], Bavo Heeman[1,2], Linus De Witte[1,2], Dorothee Dormann[3], Saskia Hutten[3], Merel Mol[4], Anne Sieben[5,6,7,8], Bart De Vil[5,6,9], Christine Van Broeckhoven[1,2], Wouter De Coster[1,2], Sebastiaan Engelborghs[6,10,11], Rik Vandenberghe[12,13], Dietmar Thal[14,15,16], Harro Seelaar[4], John Van Swieten[4], Rosa Rademakers[1,2,17]
[1]University of Antwerp, Vib-uantwerp Center For Molecular Neurology (cmn), Antwerpen, Belgium, [2]UAntwerp, Biomedical Sciences, Antwerp, Belgium, [3]Johannes Gutenberg University Mainz, Institute Of Molecular Physiology, Mainz, Germany, [4]Erasmus Medical Center, Department Of Neurology, Rotterdam, Netherlands, [5]University of Antwerp, Laboratory Of Neurology, Translational Neurosciences, Antwerpen, Belgium, [6]University Antwerp, Insitut Born-bunge, Antwerp, Belgium, [7]Ghent University Hospital, Department Of Neurology, Ghent, Belgium, [8]Antwerp University Hospital, Department Of Pathology, Edegem, Belgium, [9]Antwerp University Hospital, Department Of Neurology, Antwerpen, Belgium, [10]Universitair Ziekenhuis Brussel (UZ Brussel), Department Of Neurology, Brussels, Belgium, [11]Vrije Universiteit Brussel (VUB), Center For Neurosciences (c4n), Brussels, Belgium, [12]UZ Leuven, Department Of Neurology, Leuven, Belgium, [13]KU Leuven, Laboratory For Cognitive Neurology, Department Of Neurosciences, Leuven, Belgium, [14]University Hospital Leuven, Department Of Pathology, Leuven, Belgium, [15]KU Leuven, Laboratory For Neuropathology, Department Of Imaging And Pathology, Leuven, Belgium, [16]KU Leuven, Leuven Brain Institute (lbi), Leuven, Belgium, [17]Mayo Clinic, Department Of Neuroscience, Jacksonville, United States of America

Aims: Around 10% of all frontotemporal lobar degeneration patients display neuronal inclusions containing the fused in sarcoma protein (FTLD-FUS). Atypical FTLD-U (aFTLD-U) is the most common FTLD-FUS subgroup and is associated with a uniform presentation of a very early-onset, severe behavioral FTD phenotype, often without a family history. The etiology of FTLD-FUS is still largely unknown, hampering the development of effective therapies. To unravel the molecular mechanisms driving the disease and enable translational studies, we aim to generate and characterize human induced pluripotent stem cell (iPSC)-derived models from patients diagnosed with FTLD-FUS.
Methods: Initially, we reprogrammed four independent lymphoblastic lines (3 aFTLD-U, 1 healthy control) originating from the International Consortium on FTLD-FUS. Subsequently, we guided their differentiation into neuronal progenitor cells and eventually into cortical neurons. One line containing a genetically engineered mutation in FUS (p.Arg495X) that leads to amyotrophic lateral sclerosis (ALS) with FUS pathology and the corresponding isogenic control line were also included to compare and contrast pathological hallmarks in FTLD-FUS with ALS-FUS.
Results: We confirmed the expression of distinct pluripotency markers in all iPSC lines. To validate the success of neural induction and establish the cortical identity of the neural tissue, we characterized these lines using well-established markers. Our next steps will focus on exploring whether cortical neurons derived from aFTLD-U patients manifest pathological features associated with FTLD. Specifically, we will investigate FUS mislocalization or aggregation, as well as the deposition of other proteins known to co-accumulate with FUS in FTLD-FUS patients, including EWS, TAF15 and TNPO1.
Conclusions: By developing a human iPSC model of FTLD-FUS using patient-derived cells, we expect to initiate efforts for targeted therapies to be developed, ultimately leading to clinical trials and new treatment options for patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1209 / #1856

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

UNDERSTANDING THE NEUROPATHOLOGICAL CONSEQUENCES OF NEK1 MUTATIONS IN ALS

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Olivia Rifai[1], Danielle Leighton[2], Judi O'Shaughnessy[1], Fergal Waldron[3], Jenna Gregory[3]
[1]University of Edinburgh, Centre For Clinical Brain Sciences, Edinburgh, United Kingdom, [2]University of Glasgow, School Of Psychology & Neuroscience, Glasgow, United Kingdom, [3]University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom

Aims: NEK1, or (never in mitosis gene-A)-related kinase 1, is a serine/threonine kinase with loss-of-function and missense variants that have recently been associated with an increased risk of ALS. However, the cellular consequences of NEK1 mutation, as well as the clinical and pathological phenotypes related to specific NEK1 variants, remain undescribed, as no study thus far has pathologically examined *post-mortem* tissue from these rare cases. Here we set out to undertake the first characterisation of neuropathological phenotypes associated with NEK1 mutations in ALS, in a case series.
Methods: Our study characterises *post-mortem* tissue from three Scottish patients with a NEK1 mutation who went on to develop ALS. Using immunohistochemistry, we evaluated the expression and distribution of NEK1 as well as phosphorylated TDP-43 (pTDP-43) aggregates, a pathological hallmark of ALS, in the motor cortex and amygdala. We additionally examined the abundance and distribution of *NEK1* mRNA molecules using *BaseScope™ in situ* hybridisation.
Results: For one case with a p.Arg261His missense mutation, we observed increased *NEK1* mRNA expression and abundant NEK1-positive cytoplasmic aggregates, with the same morphology and distribution as the pTDP-43 aggregates. By contrast, the other two NEK1-ALS cases exhibited reduced *NEK1* mRNA expression and an absence of NEK1-positive cytoplasmic aggregates, indicating loss of NEK1 function.
Conclusions: Our findings suggest a spectrum of clinical and neuropathological consequences for NEK1 variants in ALS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1210 / #1575

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

FUNCTIONAL PHENOTYPIC DISEASE MODELS WITH HUMAN IPSC-DERIVED SPINAL MOTOR NEURON CULTURES FOR AMYOTROPHIC LATERAL SCLEROSIS

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Olaf Schroeder
NeuroProof Systems GmbH, R&d, Rostock, Germany

Aims: Amyotrophic lateral sclerosis, ALS, is a fatal disease with not fully understood disease mechanisms. Therefore, phenotypic disease models are needed for the development of new therapies. The disease occurs in familial and sporadic forms, fALS and sALS. Although only about 10% of cases are familial with a known hereditary origin, they are important for disease modeling. Known fALS forms have mutations in the SOD1, C9orf72, TDP-43, FUS, and other genes.
Methods: Human induced pluripotent stem cells with fALS mutations can be differentiated toward spinal motor neurons. They are canonical disease models that reflect phenotypic disease symptoms. In our hands, iPSC-derived spinal motor neurons with SOD1 D90A, SOD1 A4V, three C9orf72 mutations, TDP43 G298S, and TDP43 A384V mutation could be cultivated on microelectrode array plates for 14 to 28 days.
Results: First electrophysiological activity can be observed after 7 days and lasts more than 5 weeks. After 14 days in vitro, a reliable hyperexcitation of the disease motor neurons compared to the wild-type neurons can be observed for C9orf72 and SOD1 mutated forms but not for the TDP43 mutated forms. Measurement of NF-L and an MTT assay delivered complementary results. We tested riluzole, TUDCA, and spermidine in these assays. Riluzole demonstrated in all assays a robust effect.
Conclusions: Observation of cells from 14 to 28 div delivers significant information on compound action profiles.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1211 / #1165

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

DECIPHERING THE HYPE OF EIF5A: MECHANISMS THAT DRIVE TDP-43 NEUROPATHOGENESIS IN ALZHEIMER DISEASE AND RELATED DEMENTIA.

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Christopher Saunders[1,2], Patricia Rocha-Rangel[2], Jerry Hunt[2,3], Peter Nelson[4], Ramon Sun[5], Mathew Gentry[5], Daniel Lee[2,3], Maj-Linda Selenica[1,2]
[1]University of Kentucky, Molecular And Cellular Biochemistry, Lexington, United States of America, [2]University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America, [3]University of Kentucky, Neuroscience, Lexington, United States of America, [4]University of Kentucky, Department Of Pathology & Laboratory Medicine, Lexington, United States of America, [5]University of Florida, Biochemistry And Molecular Biology, Gainsville, United States of America

Aims: TAR DNA-binding protein 43 (TDP-43) pathology is associated with clinical dementia in Alzheimer's disease (AD) patients and limbic-predominant TDP-43 encephalopathy (LATE). Regional decline in glucose metabolic rate linked to tau and amyloid-beta pathologies suggest that impaired brain metabolism is one of the earliest and most consistent features of AD. Despite decade-long efforts, the impact of TDP-43 pathology on neurometabolic dysregulation remain poorly understood. eIF5A is the only protein undergoing hypusination (eIF5A^{Hyp}) via deoxyhypusine synthase (DHS) and deoxyhypusine hydroxylase (DOHH) activity converting a single lysine to a *hypusine moiety*. Considering the role of eIF5A^{Hyp} in mitochondrial function, we investigated how exacerbated hypusination affects brain metabolic profile in a TDP-43 animal model.
Methods: Heterozygous wtTDP-43 mice (TAR^{het}) expressed rAAV-DHS/DOHH or rAAV-eIF5A for 2 months. We applied biochemical and immunohistochemical analysis to assess cerebral TDP-43 pathology and neuronal loss. Comprehensive metabolome coverage via GCMS was performed to measure cerebral metabolite levels. RNAseq and NanoString analysis were applied to identify transcriptomic profiles.
Results: Biochemical analysis demonstrated increased phosphorylated TDP-43 levels following DHS/DOHH expression. Interestingly, metabolome analysis revealed significant reduction of cortical pyruvate, lactate and several other metabolite levels following induced neuronal eIF5A^{Hyp}. In agreement, bulk RNAseq and the NanoString analyses identified upregulation of genes in mitochondrial OXPHOS pathway, carbohydrate metabolism, and oxidative stress uniquely pertinent to DHS/DOHH. Notably, DHS and hypusine levels are increased in AD and AD+LATE-NC brain, also corroborated in TDP-43 brain tissue.
Conclusions: Our study suggests that hypusination drives the cerebral metabolic dysregulation observed in rAAV-DHS/DOHH expressing mice, suggesting eIF5A^{Hyp} as a metabolic switch in controling pyruvate supply and ATP production. Our findings provide pioneering evidence for eIF5A^{Hyp} regulation of brain glucose hemostasis and mitochondrial impairment under energy-demanding TDP-43 proteinopathy state in ADRD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1212 / #1566

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

RECOGNITION OF CYTOSOLIC TDP-43 CONDENSATES BY THE SELECTIVE AUTOPHAGY MACHINERY

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Yongwon Suk[1,2], Simone Mosna[1,2], Dorothee Dormann[1,3]
[1]JGU Mainz, Institute Of Molecular Physiology, Mainz, Germany, [2]IPP, International Phd Program, Mainz, Germany, [3]Institute of Molecular Biology gGmbH, Imb, Mainz, Germany

Aims: Cytoplasmic TDP-43 inclusions are a hallmark of ALS/FTD pathology. Here, we aim to investigate the molecular mechanisms underlying the recognition of aberrant TDP-43 condensates/aggregates by the cellular degradation machinery. A further aim is to check whether the biophysical state of TDP-43 condensates influences TDP-43 degradation and recognition by the degradation machinery.
Methods: In doxycycline-inducible stable cell lines expressing GFP-tagged C-terminal fragments (CTFs) of 25 kDa (TDP-43$_{220-414}$) or mutant variants (more liquid-like or more aggregation-prone), we examine TDP-43 CTF condensates upon inhibition of the proteasome or autophagy. Using an unbiased proteomics approach, we identify differential interactors of more liquid-like versus more solid-like TDP-43 CTF condensates. Furthermore, we examine colocalization of autophagy-related factors with TDP-43 CTF condensates.
Results: We demonstrate that TDP-43 CTFs form large cytosolic condensates upon inhibition of the proteasome, e.g. with MG132 or Bortezomib. TDP-43 CTF condensates do not colocalize with stress granule marker proteins, e.g. G3BP1 or ATXN2, demonstrating that they are distinct from stress granules. TDP-43 CTF condensates exhibit distinct dynamic behavior at different timepoints after inhibitor treatment and show distinct degradation kinetics. TDP-43 CTF condensates colocalize with autophagy-related factors, such as p62/SQSTM1, UBQLN2, and NBR1. These and other factors were also found to associate with TDP-43 CTF condensates in an unbiased proteomics experiment.
Conclusions: Our study suggests that TDP-43 CTFs are degraded by the proteasome, but upon proteasome inhibition accumulate to high levels and then form cytosolic condensates that are distinct from stress granules. The formed TDP-43 CTF condensates co-localize with autophagy-related factors, suggesting that they are recognized by specific autophagy receptors and cleared by autophagy. Future studies will test the hypothesis that the biophysical state of TDP-43 condensates governs their degradation mechanism.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1213 / #1272

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

METHYLOME ANALYSIS OF FRONTOTEMPORAL LOBAR DEGENERATION PATIENTS WITH TDP-43 PATHOLOGY

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Cristina T. Vicente[1,2], Tejasvi Niranjan[1,2], Claudia Schrauwen[1,2], Billie Matchett[3,4], Matthew Baker[4], Mariely Dejesus-Hernandez[4], Nicole Finch[4], Cyril Pottier[1,2,4], Marka Van Blitterswijk[4], Joanna Biernacka[5], Yan Asmann[6], Melissa Murray[4], Leonard Petrucelli[4], Sarah Weckhuysen[1,2,7], Björn Oskarsson[8], Keith Josephs[9], Ronald Petersen[9], Nilüfer Ertekin-Taner[4,8], Bradley Boeve[9], Neill Graff-Radford[8], Dennis Dickson[4], Rosa Rademakers[1,2,4]
[1]VIB-UAntwerp, Center For Molecular Neurology, Antwerp, Belgium, [2]University of Antwerp, Department Of Biomedical Sciences, Antwerp, Belgium, [3]University of Manchester, Division Of Neuroscience & Experimental Psychology, Manchester, United Kingdom, [4]Mayo Clinic, Department Of Neuroscience, Jacksonville, United States of America, [5]Mayo Clinic, Department Of Quantitative Health Sciences, Rochester, United States of America, [6]Mayo Clinic, Department Of Quantitative Health Sciences, Jacksonville, United States of America, [7]Antwerp University Hospital, Department Of Neurology, Antwerp, Belgium, [8]Mayo Clinic, Department Of Neurology, Jacksonville, United States of America, [9]Mayo Clinic, Department Of Neurology, Rochester, United States of America

Aims: In the last decade, numerous studies have highlighted the importance of DNA methylation in the functioning of the central nervous system, yet the genome-wide contribution of epigenetic changes to the development of FTLD remains largely unexplored and constitutes the aim of the present study.
Methods: We performed the largest FTLD methylation study to date, focused on patients with TDP-43 pathology (FTLD-TDP), where we included 192 matched pairs of frozen post-mortem tissue samples from frontal cortex (FCX) and cerebellum (CER) regions (N=394; Mayo Clinic Brain Bank). Samples were divided into 6 groups: FTLD-TDP types A, B and C, *GRN* mutation carriers, *C9ORF72* repeat expansion carriers (N=25 per group); and neurologically normal controls (N=42). For each sample, DNA methylation was profiled using reduced representation bisulfite sequencing. MethylKit, DMRFinder and EdgeR tools were employed to compare patient groups *versus* controls at the CpG level as well as differentially methylated regions, either including all genomic locations or focusing specifically on promoters.
Results: We identified differentially methylated CpGs both unique and shared between patient groups and/or brain regions. Importantly, we found multiple CpGs within *NFATC1* across all patients, possibly impacting gene transcription and neuroinflammation. At the DMR level, we identified 93 loci in FCX (FDR<0.05; 53 hypomethylated; 40 hypermethylated *versus* controls) and 138 loci in CER (79 hypomethylated; 59 hypermethylated *versus* controls). Results were prioritized for functional follow-up using an in-house built scoring system, which highlighted an important role for the hexosamine biosynthetic pathway in FTLD-TDP. Integration of the methylome data with already existing genome, transcriptome and proteome data is currently ongoing.
Conclusions: Overall, our results suggest that epigenetics plays a role in FTLD-TDP pathophysiology and highlights the need for further studies to profile additional epigenetic layers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1214 / #2851

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D02. Therapeutic Targets, Mechanisms for Treatment*

UNC13A TARGETING SPLICE SWITCHING ASOS AMELIORATE TDP-43 DEPENDENT MIS-SPLICING PHENOTYPES IN FTD AND ALS

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Marisa Kamelgarn, Nicholas Fiore, Jayce Brown-Culbertson, Yasmin Hamwi, Maria Banuelos, James Chow, Sandy Hinckley
QurAlis, Discovery, Cambridge, United States of America

Aims: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the loss of neurons in the spinal cord, brainstem, and brain. A defining feature of both sporadic and familial disease is the cytoplasmic mis-localization of TAR DNA Binding Protein- 43 (TDP-43), resulting in defects in numerous cellular processes, including splicing of pre-mRNA transcripts. One of these transcripts is *UNC13A/MUNC13-1*, which encodes a synaptic protein required for normal priming and release of excitatory neurotransmitter containing synaptic vesicles. At QurAlis, we hypothesize that ameliorating *UNC13A* mis-splicing using a splice-switching ASO can alleviate symptoms of ALS, FTD, and ALS/FTD spectrum disorder associated with synaptic dysfunction that underlies clinical manifestation and disease progression.
Methods: We have developed an in-house iPSC motor and cortical neuron model to screen ASOs for mRNA and protein potency. Selected ASOs were assessed for restoration of synaptic function using biochemical and live-cell imaging methods.
Results: Splice-switching ASOs targeting *UNC13A* were screened via qPCR and a small subset demonstrating correction of splicing moved onto protein rescue validation studies. From those rescue experiments, ASOs were selected for functional assay testing. To assess synaptic vesicle priming and fusion, we optimized a SNAP-25/ VAMP-2 co-immunoprecipitation assay and synaptopHluorin, respectively. These assays demonstrated a restoration of UNC13A function after ASO treatment.
Conclusions: Using in-house models of iPSC motor and cortical neurons, we have established a phenotype to demonstrate the cellular consequences of *UNC13A* mis-splicing due to TDP-43 loss of function. Using these models, we were able to establish that restoring *UNC13A* splicing through treatment with a splice-switching ASOs lead to the amelioration of defects in synaptic activity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1215 / #639

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D02. Therapeutic Targets, Mechanisms for Treatment*

OVEREXPRESSION OF HEAT SHOCK PROTEIN 27 MODULATES HIPPOCAMPAL APOLIPOPROTEIN E AND REDUCES AGGREGATION OF TRANSACTIVE RESPONSE DNA BINDING PROTEIN 43

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Muhammad Abeer[1], Amina Gauff[2], Justin Sherad[2], Isaiah Brooks[2], Michael Gitcho[2]
[1]Delaware State University, Biological Sciences, Dover, United States of America, [2]Delaware State university, Biological Sciences, Dover, United States of America

Aims: Aggregation of transactive response DNA binding protein 43 (TDP-43) has been recently discovered in up to 50% of Alzheimer's disease (AD) cases. Several studies reported that TDP-43 binds to heat shock protein family B (small) member 1 (HSPB1 or HSP27) but no functional evaluation of this interaction has been explored. Inducing expression of HSP27 has been shown to reduce aggregation of amyloid in AD. In general, the goal is to utilize both primary neuronal cultures and mice that are selectively expressing pathogenic TDP-43, HSP27, and apolipoprotein E (APOE) in the brain to characterize the effect of HSP27 overexpression on TDP-43 and APOE. In the present study, we hypothesize that increased expression of HSP27 may reduce TDP-43 aggregation and alter mitochondrial morphology.
Methods: A new transgenic mouse model was developed to selectively drive human HSP27 and pathological TDP-43 with a defective nuclear localization signal (DNLS) in the hippocampus and neocortex using the Ca^{2+}/calmodulin protein kinase (Camk2a) tetracycline-inducible system. The following genotypes have been evaluated for immunohistochemistry, biochemistry (solubility fractionation), and Western blot: wild-type, Camk2a/DNLS, Camk2a/HSP27 and Camk2a/HSP27/TDP43DNLS at 4 months of age. Immunohistochemical and bioenergetic experiments are currently being carried out to evaluate the brain and mitochondrial morphology upon HSP27 overexpression.
Results: Preliminary *in vitro* results show that cells overexpressing HSP27 reduce aggregation and protein levels of TDP43. However, mice overexpressing HSP27 in a TDP43DNLS background in the hippocampus and cortex does not show any reduction in the soluble fraction. Interestingly, increased expression of HSP27 in the hippocampus of Camk2a/HSP27 mice showed a significant reduction of endogenous APOE expression.
Conclusions: Our initial data suggests that modifying HSP27 expression modulates endogenous hippocampal APOE levels and may reduce TDP-43 aggregation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1216 / #713

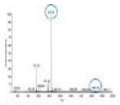
Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D02. Therapeutic Targets, Mechanisms for Treatment*

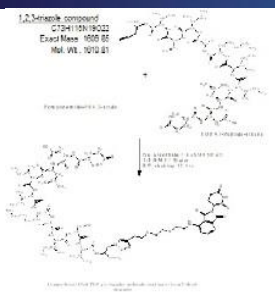
CLICK-BASED PROTEIN DEGRADERS FOR TDP 43 DEGRADATION IN NEURONAL CELL LINE

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Krishna Bhavsar, Sharad Gupta
Indian Institute of Technology Gandhinagar, Department Of Biological Science And Engineering, Gandhinagar, India

Aims: Neurodegenerative diseases such as AD, ALS, etc., are among the incurable diseases for which pertinent causes and appropriate treatments are lacking. The newly developed field of targeted protein degradation rapidly expands with significant potential for treating undruggable protein targets. We have developed the Hybrid degrader molecule CLiPD (click-based protein degrader) library targeting TDP 43 with the following objectives: Objective 1: Development of CLiPD library against cytoplasmic TDP 43. Objective 2: Establishment of mammalian and recombinant expression of full-length TDP 43. Objective 3: Neuronal cell-based TDP 43 degradation assays. CLiPD is a hybrid bi-functional molecule that hijacks the UPS and delivers the target protein to the degradation. It has three components: The E3 ubiquitin ligase sequence binds to the E3 ubiquitin ligase enzyme. Target protein sequence: binds the target protein; A linker sequence that provides flexibility to the molecule and allows the target protein to be in proximity to the E3 ligase.
Methods: CLiPD synthesis: Fmoc-based solid-phase peptide synthesis, Cu-click chemistry, RP-HPLC, UPLC-MS, and MALDI-TOF/TOF. Recombinant protein: Plasmid containing TDP 43 (pJ4M) was used for expression in *E. Coli* BL21 (DE3) —purification using Ni-NTA and characterized by MALDI-TOF. Mammalian cell culture, cellular permeability: HEK293t and SH-SY5Y were grown per ATCC's protocol. Addgene WT plasmid (wtTDP43tdTOMATOHA) and Mutant (EGFP construct 3). Viability using MTT. UPS-dependent Degradation cell-based assay using MG 132 proteasome inhibitor.
Results: The cell-permeable and non-toxic CLiPD molecules were synthesized using fmoc-SPPS and ligated by Cu-click chemistry, characterized using
LCMS.





Conclusions: The designed CLiPD molecule can potentially degrade the cytoplasmic TDP 43 involved in neurodegeneration. The CLiPD library will provide the targeted protein degradation therapy with minimized toxicity and high specificity with different targets against various mutations and isoforms of the TDP 43.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1217 / #2379

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D02. Therapeutic Targets, Mechanisms for Treatment*

EZEPROGIND (AZP2006) IS ABLE TO PROTECT MOTONEURONS AND NEUROMUSCULAR JUNCTIONS FROM GLUTAMATE INJURY. IN VITRO EVIDENCES

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Noëlle Callizot[1], Cécilia Estrella[2], Alexandre Henriques[3], Philippe Verwaerde[2]
[1]Neuro-sys SAS, Neuropharmacology Dpt, Gardanne, France, [2]Alzprotect, Clinical Research, Loos, France, [3]Neuro-Sys, -, Gardanne, France

Aims: Amyotrophic lateral sclerosis (ALS) is a fatal disorder characterized by subtle onset of focal weakness, typically in the limbs but sometimes in bulbar muscles, which progresses to paralysis of almost all skeletal muscles. Death of motoneurons (MN) occurs in conjunction with deposition of aggregated proteins in motoneurons and oligodendrocytes, and neuroinflammation. Progranulin (PGRN), is a secreted protein that plays key roles in the brain and spinal cord regulating anti-inflammatory responses and neuron survival. PGRN reduced levels of insoluble TDP-43 and axon fibers loss in the lateral horn. PGRN overexpression significantly slowed down disease progression in TDP-43(A315T) mice. AZP2006 is a small molecule displaying neuroprotective properties currently under clinical development for Progressive Supranuclear Palsy. Its effect was shown to involve PGRN/PSAP complex and was able to help lysosomal function and homeostasis.
Methods: In this study, we investigated AZP2006 in *in vitro* ALS models. Using primary cultures of transgenic SOD1 motoneurons or spinal cord-muscle cocultures injured both with glutamate, AZP2006 effects of on MN survival and neuromuscular junctions (NMJ) integrity were studied.
Results: After Glutamate stress, AZP2006 was shown to reduce SOD1 MN death and cytoplasmic TDP43 accumulation. In nerve muscle coculture AZP2006 was able to protect loss of NMJs after glutamate injury. AZP2006 was associated with an increase of NMJ subunits clustering associated with an increased area of innervation. AZP2006 neuroprotective effect were associated with PGRN release and lysosomal stress reduction. AZP2006 displayed protective effects at nanomolar range and on a dose-dependent manner
Conclusions: AZP2006 is under clinical development (Phase2a in PSP completed) and under preclinical development for the treatment of AD and related disorders, in light of our last results, AZP2006 seems to be serious candidate for ALS indication.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1218 / #2789

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D01. Disease Mechanisms, Pathophysiology*

NEURONAL VULNERABILITY TO HNRNP K MISLOCALISATION: MAPPING DIFFERENT BRAIN REGIONS

POSTERS: D01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Xinwa Jiang[1], Ariana Gatt[2], Tammaryn Lashley[3]
[1]Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, London, UK, Ucl Institute Of Neurology - Neurodegenerative Diseases, London, United Kingdom, [2]University College London, Neurodegenerative Disease, LONDON, United Kingdom, [3]UCL Queen Square Institute of Neurology, Department Of Neurodegenerative Disease, London, United Kingdom

Aims: Heterogeneous nuclear ribonucleoprotein K (hnRNP K) is an RNA-binding protein. It is abundant and widely expressed in the brain, playing a crucial role in transcriptional regulation. HnRNP K predominantly resides in the nucleus. However, our group discovered that in pyramidal cells from patients with frontotemporal lobar degeneration (FTLD), hnRNP K is abnormally localized and aggregated into the cytoplasm, resulting in aberrant downstream splicing events. We investigated whether other neuronal cells in other brain regions were also vulnerable to mislocalisation, and whether it correlated with disease pathology.
Methods: We examined 13 different brain regions across different neurodegenerative diseases. HnRNP K immunohistochemistry (IHC) and hematoxylin & eosin (HE) and cresyl violet staining were performed. Staining was analysed by QuPath and ImageJ.
Results: The map reveals that mislocalisation of hnRNP K is prevalent in multiple brain regions. These regions include the cerebral cortex, CA4 neurons in the hippocampus, red nucleus in the midbrain, dorsal accessory olivary nucleus (DAO) in the medulla, thalamus, and other subregions of the brainstem. Particularly, high mislocalisation was observed in the thalamus, putamen and medulla. Moreover, we also observed that hnRNP K distribution varies among different brain regions and neuronal cell types depending on the disease context.
Conclusions: We have created a comprehensive brain map illustrating the mislocalisation of hnRNP K in different neuronal populations. The brain map serves as a valuable tool for future studies on hnRNP K mislocalisation to investigate the association between the neuronal variability of hnRNP K localisation and the clinical manifestations of the different neurodegenerative diseases. Furthermore, determining whether hnRNP K plays a causative role in the pathogenesis of neurodegenerative diseases is a question that warrants further exploration.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1219 / #1286

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D02. Therapeutic Targets, Mechanisms for Treatment*

IDENTIFICATION OF HUMAN GENETIC MODIFIERS OF TDP-43-MEDIATED TOXICITY AND AGGREGATION

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Matisse Jacobs, Rebecca San Gil, Adam Walker
University of Queensland, Queensland Brain Institute, Brisbane, Australia

Aims: To identify potential therapeutic strategies for motor neuron disease (MND) by identifying human genes that modulate TAR DNA-binding protein 43 (TDP-43) -mediated aggregation and toxicity.
Methods: We conducted a pooled human genome-wide CRISPR activation screen in HEK293T cells expressing cytoplasmic-targeted TDP-43 protein mimicking pathology found in disease. This assessed the capability of over 18,000 genes to, when activated, modulate protein aggregation and confer cytoprotection in HEK293T cells with TDP-43 pathology. The established ranking system Model-based Analysis of Genome-wide CRISPR/Cas9 Knockout pipeline was employed, assigning a rank to genes by assessing their effect on toxicity and TDP-43 aggregation. Gene ontology (Metascape) analysis of the top 200 ranked genes from each category assessed enriched biological pathways. To identify genes involved in proteostasis pathways, these top ranked genes were also compared to a curated library of 3541 human proteostasis genes.
Results: Subsets of genes were identified that when activated significantly protected from, or sensitised cells to, toxicity (601 'Protect' genes; 733 'Sensitise' genes. LFC > 1) and inhibited or enhanced TDP-43 aggregation (832 'Inhibit' genes; 37 'Enhance' genes. LFC > 1). A subset of genes significantly influenced both toxicity and aggregation. Gene ontology analysis revealed that the top ranked genes that protected cells from toxicity when activated are involved in protein degradation pathways, and top ranked genes that inhibited TDP-43 aggregation were associated with regulation of apoptotic signalling. Many of the top 200 ranked genes in each category appeared in a library of proteostasis genes (87 'Protect' genes; 88 'Sensitise' genes; 114 'Inhibit' genes; 3 'Enhance' genes).
Conclusions: This CRISPR activation screen identified targets that may promote clearance or refolding of pathological TDP-43, supporting development of therapies for those living with MND.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1220 / #465

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D02. Therapeutic Targets, Mechanisms for Treatment*

SORTILIN INHIBITION WITH VES001 AND ELEVATION OF PROGRANULIN AS A NOVEL THERAPEUTIC APPROACH IN FTD-GRN AND OTHER NEURODEGENERATIVE DISEASES

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Louise Klem, Ove Pedersen, Paul Little, Anders Nykjaer, Mads Kjolby
Vesper Bio, Research And Development, Copenhagen, Denmark

Aims: Progranulin deficiency is associated with different neurodegenerative diseases, including GRN-related frontotemporal dementia (FTD-GRN). Heterozygote carriers of null GRN mutations have 50% progranulin levels relative to healthy controls. Reduced progranulin levels are associated with distinct and overlapping pathological processes, including gliosis, complement activation, TDP-43 accumulation, and neurodegeneration. Sortilin inhibition elevates extracellular progranulin and reduces the apoptotic signalling stemming from the sortilin-$P75^{NTR}$ complex. Vesper Bio has developed novel small molecule sortilin inhibitors for oral administration and is investigating the therapeutic potential within different neurodegenerative diseases. Vesper Bio aims to develop the first sortilin inhibitor for oral administration to treat FTD-GRN, and lead candidate, VES001, will enter Phase 1 clinical trials Q4 of 2023.
Methods: Characterization of VES001 included quantification of target affinity by Grating-Coupled Interferometry, competition binding with progranulin by flow cytometry, and PK/PD studies in different species. The PK/PD studies included multiple rodent studies that quantified the levels of compound and progranulin in a) plasma following a VES001 dose range, and b) in plasma, CSF, and brain interstitial fluid following repeated administration of VES001 in a microdialysis experiment. Pharmacodynamic changes in progranulin were quantified in both absolute terms and relative to baseline levels.
Results: VES001 shows a high affinity for sortilin across multiple species and inhibits progranulin binding. VES001 was measured in all compartments. Single-dose VES001 administration increased plasma progranulin up to ~1.5-fold, and repeated dosing increased progranulin in plasma, CSF, and brain ~2-fold with the selected dose-range. The vehicle groups did not show changes in progranulin.
Conclusions: Sortilin inhibition with oral small molecule VES001 increases progranulin in different compartments and holds promise as a novel therapeutic approach to attenuate neuroinflammation and neurodegeneration for different neurodegenerative diseases, including FTD-GRN.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1221 / #1553

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D02. Therapeutic Targets, Mechanisms for Treatment*

SHIFTING THE PARADIGM - A BIOMARKER DRIVEN APPROACH FOR STUDYING AMYOTROPHIC LATERAL SCLEROSIS (ALS) THERAPY ACTIVITY

POSTERS: D02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Shiran Salomon-Zimri[1], Nitai Kerem[1], Tiziana Petrozziello[2], Gabriel Linares[3], Niva Russek-Blum[1], Andrew Thompson[4], Jacob Harris[4], Jin Xu[4], Nicole Wong[4], Craig Lawless[4], Martin Bachman[4], Ernestas Sirka[4], Meitar Grad[5], Guy Shapira[5], Noam Shomron[5], Justin Ichida[3], Ghazaleh Sadri-Vakili[2], Ferenc Tracik[1]
[1]NeuroSense Therapeutics, Research And Development, Herzliya, Israel, [2]Mass General Hospital, Sean M. Healey & Amg Center For Als, Boston, United States of America, [3]University of Southern California, Eli And Edythe Broad Cirm Center For Regenerative Medicine And Stem Cell Research, Los Angeles, United States of America, [4]Inoviv, Research And Development, London, United Kingdom, [5]Tel Aviv University, Faculty Of Medicine, Tel Aviv, Israel

Aims: ALS's complex pathophysiology necessitates a multifactorial therapeutic strategy targeting various pathways. PrimeC, a novel formulation combining ciprofloxacin and celecoxib, synergistically targets key pathologies to impede ALS progression. The synergistic effect between ciprofloxacin, a Dicer gene regulator, and celecoxib, a neuroinflammation regulator was demonstrated preclinically. Rodent studies demonstrated improved pharmacokinetics when the two were combined, with significant beneficial effects for the combination utilizing synaptoneurosomes and iPSC ALS models. PrimeC was evaluated clinically in a 12-month, open-label, Phase 2a study. 15 patients with ALS treated with PrimeC were compared to propensity-matched, untreated ALS patients. Significant changes in ALS-related biomarkers following treatment (TDP43 p=0.002, PGJ2 p<0.001, CATD p=0.015, LC3 p=0.05) indicated PrimeC's biological activity. Clinical outcomes demonstrated an 18% and 30% improvement, as measured by ALSFRS-R and FVC, respectively. NeuroSense's PARADIGM trial reflects a pioneering approach to spotlighting blood-based biomarkers. Primary outcomes include analyzing TDP-43 and PGJ2. Exploratory endpoints include additional biomarker-driven assays, potentially elucidating PrimeC's biological activity and target engagement.
Methods: PARADIGM is a prospective, randomized, double-blind, placebo-controlled Phase 2b study evaluating PrimeC. A multicenter trial on 69 patients was commenced. A large battery of biomarkers will be screened using mass spectrometry-based Proteomics Discovery and validated via Targeted Proteomics Assay. Additionally, miRNA profiling in PrimeC-treated patients' blood will map differentially expressed miRNAs. PrimeC's ability to alter NfL elevation, a promising biomarker for neuronal degeneration and death, and its correlation to key clinical outcomes, will also be assessed.
Results: would elucidate PrimeC's effects on target biomarkers and miRNAs, and their correlation with clinical outcomes and efficacy.
Conclusions: Consolidating this battery of biomarkers will enhance our understanding of PrimeC's MoA and biological activity, setting the stage for a more sophisticated and precisely tailored pivotal study.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1222 / #1518

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D03. Imaging, Biomarkers, Diagnostics*

NUCLEAR TDP-43 PATHOLOGY DETECTED BY AN RNA APTAMER IS AN EARLY AGGREGATION EVENT THAT CORRELATES WITH STMN-2 CRYPTIC SPLICING AND PRECEDES CLINICAL MANIFESTATION IN ALS

POSTERS: D03. IMAGING, BIOMARKERS, DIAGNOSTICS

Fergal Waldron, Holly Spence, Mathew Horrocks, Jenna Gregory
Institute of Medical Sciences, University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom

Aims: The presence of phosphorylated, cytoplasmic TDP-43 (pTDP-43) aggregation is a specific, but not sensitive, marker of regional phenotypic presentation in amyotrophic lateral sclerosis and frontotemporal dementia spectrum disorders (ALSFTSD). The recent identification of cryptic splicing events such as the detection of *Stathmin-2* (*STMN-2*) cryptic exons, are thought to be a sensitive molecular surrogate of TDP-43 pathology and clinical phenotype. Therefore, we set out to assess if alternative methods for the detection of TDP-43 pathology can improve diagnostic sensitivity, rather than relying on molecular surrogates that might lack stability in the clinical setting.
Methods: To do this we use an RNA aptamer that we have previously designed to bind to the RNA-binding domains of TDP-43 (TDP-43^{APT}).
Results: We demonstrate that using an adapted immunostaining protocol, TDP-43^{APT} identifies pathological TDP-43 with high sensitivity and specificity and can detect aggregation events that cannot be detected by classical antibody stains. Furthermore, we show that TDP-43^{APT} detects TDP-43 pathology in distinct cell compartments, and that the protein sub-cellular distribution correlates with both (i) molecular phenotype (*STMN-2* cryptic splicing events) and (ii) clinical phenotype (cognition). In addition, we show that nuclear TDP-43^{APT} pathology, in the form of nuclear membrane accumulation and nuclear puncta, is an early aggregation event that precedes clinical manifestation.
Conclusions: Taken together, our data show that TDP-43^{APT} enables the detection of a wider range of aggregation events, with implications for early diagnostics and improved accuracy in detecting disease phenotypes for future biomarker development.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1223 / #447

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D03. Imaging, Biomarkers, Diagnostics*

DEVELOPMENT AND CHARACTERIZATION OF ALPHA-INTERNEXIN ANTIBODIES FOR IMMUNOASSAY DEVELOPMENT

POSTERS: D03. IMAGING, BIOMARKERS, DIAGNOSTICS

Francisco Meda[1], Camilla Johansson[2], Karin Palm[2], Gunnar Brinkmalm[1], Ulf Andreasson[1,2], Kaj Blennow[1,2], Hlin Kvartsberg[1,2], Henrik Zetterberg[1,2,3,4,5,6]
[1]Department of Psychiatry and Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy, University Of Gothenburg, Mölndal, Sweden, [2]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [3]Clear Water Bay, Hong Kong Center For Neurodegenerative Diseases, Hong Kong, Denmark, [4]Department of Neurodegenerative Disease, Ucl Institute Of Neurology, London, United Kingdom, [5]UK Dementia Research Institute, Ucl Institute Of Neurology, London, United Kingdom, [6]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America

Aims: Alpha-internexin (AINX) is a type IV intermediate filament alongside the neurofilament triplet proteins. Although AINX is mostly expressed during the developing brain, it is still present in mature neurons and said to be involved in axonal outgrowth. Previous work recognized it as a major component aggregating in neuronal intermediate filament inclusion disease (NIFID), a subtype of frontotemporal lobar degeneration with fused in sarcoma aggregates. Based on this, the objective of this project was to produce and characterize antibodies against AINX, in addition to combining them with commercially available antibodies to develop a novel AINX immunoassay.
Methods: In-house monoclonal antibodies originated from mice immunization with two recombinant AINX peptides (Ina1; B15) and posterior fusion of B-cells with a myeloma cell line. Commercial antibodies selected: anti-AINX PA5-95368, anti-AINX NBP2-75407 and anti-AINX NB300-140. Standard ELISA was performed with different combinations of antibodies using in-house produced recombinant AINX89-499 as calibrator. Immunoprecipitation followed by mass spectrometry (IP-MS), using both in-house and commercial PA5-95368 was performed to assess antibody binding and specificity.
Results: The in-house antibodies were successfully raised, purified, and tested on a direct ELISA setup, where the recombinant protein was detected with high affinity. When tested against biological samples (CSF and brain extracts) all antibody combinations detected AINX in sodium dodecyl sulphate (SDS) brain fractions, however in CSF, it was only detected by one combination (B15_PA5-95368). To further assess antibody binding, IP-MS using the in-house antibodies and PA5-95368 revealed that, in SDS brain fractions, PA5-95368 had AINX sequence coverage of 90%, B15 of 56% and Ina1 of 85%.
Conclusions: The antibodies raised in-house alongside PA5-95368 are a promising base for immunoassay development, although further optimization is needed to specifically detect AINX in body fluids.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1224 / #2440

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D03. Imaging, Biomarkers, Diagnostics*

FRONTOTEMPORAL LOBAR DEGENERATION TYPE C: DIFFERENTIAL DETECTION OF TDP-43 IMMUNOPOSITIVE NEURITES USING ANTIBODIES TARGETING TDP-43 PHOSPHOSERINES 305, 369, 375, AND 409/410

POSTERS: D03. IMAGING, BIOMARKERS, DIAGNOSTICS

Kathy Newell[1], Max Jacobsen[1], Emanuele Buratti[2], Holly Garringer[1], Martin Farlow[3], Benjamin Ryskeldi-Falcon[4], Bernardino Ghetti[1], Laura Cracco[1]
[1]Indiana University, Pathology And Laboratory Medicine, Indianapolis, United States of America, [2]International Centre for Genetic Engineering and Biotechnology (ICGEB), Molecular Pathology Group, Trieste, Italy, [3]Indiana University School of Medicine, Department Of Neurology, Indianapolis, United States of America, [4]Medical Research Council, Laboratory Of Molecular Biology, Cambridge, United Kingdom

Aims: The aim of this study was to determine whether antibodies to epitopes of TDP-43 containing phosphoserines differentially detect neurites in the neocortex of an individual affected by primary progressive aphasia (PPA).
Methods: Neuropathologic studies revealed cerebral atrophy with a brain weight of 876.6 grams. Immunohistochemistry was carried out using antibodies targeting TDP-43 phosphoserines 305, 369, 375, and 409/410. Whole slide images were taken using Huron Tissuescope LE120. Images were analyzed using Indica Labs' Halo object colocalization module. Five ROIs were selected across the superior frontal gyrus with each ROI expanding from layer I to layer VI. Statistical test used was students t-test, two tailed. Using Western blot analysis and immunoelectron microscopy, each antibody's immunoreactivity to sarkosyl- insoluble TDP-43 will be determined.
Results: The number of neurites immunolabeled by antibody recognizing phosphoserine 375 matched that obtained using antibody recognizing phosphoserines 409/410. Antibodies recognizing phosphoserines 305 and 369 immunolabeled a statistically significant higher number of neurites as compared to those detected by the antibody recognizing phosphoserines 409/410. When analyzing the density per mm^2 the results were consistent with those of absolute counts.
Conclusions: Previous studies carried out by mass spectrometry have revealed the post translational phosphorylation at S305, S369 and S375 in TDP-43 from FTLD human brain tissue. Such data have revealed the significance of these phosphorylation sites and the necessity of producing and validating new antibodies for characterizing FTLD types. The current results show that antibodies to S305 and S369 immunolabel a significantly higher number of neurites as compared to the currently used antibody to phosphoserines 409/410. Whether these differences between antibodies are related to specific misfolded species of TDP-43 in the aggregates present in neurites needs further investigation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1225 / #2231

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D03. Imaging, Biomarkers, Diagnostics*

ASSOCIATIONS BETWEEN CEREBRAL PERFUSION AND COGNITIVE PERFORMANCE IN GENETIC FTD: A GENFI STUDY

POSTERS: D03. IMAGING, BIOMARKERS, DIAGNOSTICS

Maurice Pasternak[1], Saira Mirza[2], Nicholas Luciw[2], Henk Mutsaerts[3], Jan Petr[4], David Thomas[5], David Cash[6], Martina Bocchetta[6], Maria Tartaglia[7], Sara Mitchell[8], Sandra Black[9,10], Morris Freedman[11], David Tang-Wai[12,13], Ekaterina Rogaeva[14], Lucy Russell[6], Arabella Bouzigues[5], John Van Swieten[15], Lize Jiskoot[15], Harro Seelaar[15], Robert Laforce Jr[16], Pietro Tiraboschi[17], Barbara Borroni[18], Daniela Galimberti[19], James Rowe[20], Caroline Graff[21], Elizabeth Finger[22], Sandro Sorbi[23], Alexandre Mendonca[24], Chris Butler[25], Alexander Gerhard[26], Raquel Sánchez-Valle[27], Fermin Moreno[28], Matthis Synofzik[29], Rik Vandenberghe[30], Simone Ducharme[31], Johannes Levin[32], Markus Otto[33], Isabel Santana[34], Antonio Strafella[35], Bradley Macintosh[9], Jonathan Rohrer[36], Mario Masellis[1]
[1]University of Toronto, Institute Of Medical Science, Toronto, Canada, [2]Sunnybrook Research Institute, Medicine, Toronto, Canada, [3]Amsterdam UMC, Radiology And Nuclear Medicine, Amsterdam, Netherlands, [4]Institute of Radiopharmaceutical Cancer Research, Helmholtz-zentrum Dresden-rossendorf, Dresden, Germany, [5]UCL Queen Square Institute of Neurology, Brain Repair And Rehabilitation, London, United Kingdom, [6]UCL Queen Square Institute of Neurology, Neurodegenerative Disease, London, United Kingdom, [7]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [8]Sunnybrook Health Sciences Centre, Neurology, Toronto, Canada, [9]Sunnybrook Research Institute, Hurvitz Brain Sciences Program, Toronto, Canada, [10]University of Toronto, Department Of Medicine (neurology), Toronto, Canada, [11]Baycrest Health Sciences, Rotman Research Institute, Toronto, Canada, [12]Universitry of Toronto, Neurology, Toronto, Canada, [13]University Health Network, Krembil Brain Institute, Toronto, Canada, [14]University of Toronto, Tanz Centre For Research In Neurodegenerative Disease, Toronto, Canada, [15]Erasmus MC, Neurology, Rotterdam, Netherlands, [16]Clinique Interdisciplinaire de Mémoire, CHU de Québec, Département des Sciences Neurologiques, Université Laval, Neurology, Quebec, Canada, [17]Fondazione IRCCS Istituto Neurologico Carlo Besta, Neurology, Milan, Italy, [18]University of Brescia, Brescia, Italy, Clinical And Experimental Sciences, Brescia, Italy, [19]University of Milan, Neurology, Milan, Italy, [20]University of Cambridge, Clinical Neurosciences, Cambridge, United Kingdom, [21]Karolinska Institute, Neurology, Solna, Sweden, [22]Lawson Health Research Institute, Department Of Clinical Neurological Sciences, London, Canada, [23]Neurophysiopathology, Irccs Fondazione Don Carlo Gnocchi, Florence, Italy, [24]University of Lisboa, Medicine, Lisbon, Portugal, [25]Nuffield department of Primary Care Health Sciences, Medicine, Oxford, United Kingdom, [26]Manchester University, Neurology, Manchester, United Kingdom, [27]Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Alzheimer's Disease And Other Cognitive Disorders Unit, Neurology Service, Barcelona, Spain, [28]Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, Neurology, San Sebastian, Gipuzkoa, Spain, Spain, [29]Hertie-Institute for Clinical Brain Research & Center for Neurology, Neurology, Tubingen, Germany, [30]KU Leuven, Laboratory For Cognitive Neurology, Department Of Neurosciences, Leuven, Belgium, [31]University of McGill, Neurology, Montreal, Canada, [32]Ludwig-Maximilians-University Munich, Neurology, München, Germany, [33]University of Ulm, Neurology, Ulm, Germany, [34]Coimbra University Hospital, Neurology, Coimbra, Portugal, [35]Centre for Addiction and Mental Health, Campbell Family Mental Health Research Institute, Toronto, Canada, [36]University College London, Dementia Research Centre, Department Of Neurodegenerative Disease, Ucl Queen Square Institute Of Neurology, London, United Kingdom

Aims: Presymptomatic genetic FTD features decreases in cerebral blood flow (CBF) involving frontotemporal and subcortical regions. We investigated whether associations between regional cerebral


hypoperfusion and cognition manifest during the presymptomatic and prodromal stages.
Methods: This study includes individuals from the Genetic FTD Initiative (GENFI). Individuals were classified into groups based on mutation +/- with or without early symptoms as follows: presymptomatic carriers who scored zero on the Clinical Dementia Rating plus NACC FTLD Behavior & Language Domains (CDR+NACC FTLD; n = 196), prodromal carriers who scored a 0.5 on the CDR+NACC FTLD (n = 36), and non-carrier relatives (n = 202). Participants completed a neuropsychological battery covering attention & processing speed, executive function, language, memory recall, visuospatial ability, and social cognition domains, calculated as mean composite z-scores of individual tests. Linear mixed effects models tested the association of regional CBF measured by arterial spin labeling MRI with these domain scores across groups. Models adjusted for the effects of age, sex, and years of education. A random intercept clustered over families was included.
Results: After Bonferroni correction, the interaction between regional CBF and group membership was significantly positive for the attention & processing speed domains in the CDR 0.5 group relative to non-carrier controls within several left hemisphere regions: the superior, medial, and inferior frontal gyri, the inferior & medial temporal gyri, and the medial orbitofrontal cortex. The right thalamus and right temporal pole were also significant for this interaction.
Conclusions: Regional cerebral hypoperfusion may represent an early biomarker of the prodromal stages of genetic FTD and could be considered as a neurophysiological outcome measure in clinical trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1226 / #451

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D03. Imaging, Biomarkers, Diagnostics*

PLASMA LYSOSPHINGOLIPIDS ARE DISEASE-TRACKING BIOMARKERS IN FRONTOTEMPORAL DEMENTIA ASSOCIATED WITH GRN MUTATIONS

POSTERS: D03. IMAGING, BIOMARKERS, DIAGNOSTICS

Dario Saracino[1], Walid Khrouf[2], Marion Houot[3], Fabienne Clot[4], Foudil Lamari[2], Isabelle Le Ber[1]
[1]Sorbonne Université / Paris Brain Institute / Hôpital Pitié-Salpêtrière, Department Of Neurology, Paris, France, [2]AP-HP.Sorbonne Université, Dmu Biogem-metabolic Biochemistry Department, Neurometabolic And Neurodegenerative Unit - Hôpital Pitié-salpêtrière, Paris, France, [3]Sorbonne Université / Paris Brain Institute / Hôpital Pitié-Salpêtrière, Centre Of Excellence Of Neurodegenerative Disease (coen), Paris, France, [4]Hôpital Pitié-Salpêtrière, AP-HP.Sorbonne Université, Department Of Genetics, Paris, France

Aims: *GRN* mutations are one of the most frequent causes of frontotemporal lobar degeneration with TDP-43 pathology. As progranulin is involved in lysosomal pathways, we aimed to study whether plasma lysosphingolipids, byproducts of lysosomal metabolism, are increased in *GRN* mutation carriers, and to evaluate their possible use as fluid-based biomarkers in frontotemporal dementia (FTD) associated with *GRN* mutations.
Methods: We analyzed plasma levels of four lysosphingolipids (glucosylsphingosin d18:1 [LGL1], lysosphingomyelins d18:1 and isoform 509 [LSM18:1, LSM509] and lysoglobotriaosylceramide [LGB3]) in 128 *GRN* carriers and 142 non-carriers. *GRN* carriers consisted of 102 patients with *GRN*-associated FTD (FTD-*GRN*), and 26 presymptomatic carriers (PS-*GRN*), and we performed longitudinal assessments in the latter. Non-carriers included healthy controls, patients with *C9orf72*-associated FTD, and sporadic FTD. Plasma lysosphingolipids were measured by electrospray ionization-tandem mass spectrometry coupled to ultraperformance liquid chromatography, and neurofilament light chain (NfL) with SIMOA.
Results: *GRN* carriers had higher levels of LGL1, LSM18:1 and LSM509 compared to non-carriers (p<0.0001). Sporadic and *C9orf72*-associated FTD patients had no lysosphingolipid increases. In FTD-*GRN*, LGL1 and LSM18:1 increased along with the age at sampling, and LGL1 with the disease duration. In PS-*GRN* carriers, there was a significant increase of the same two lysosphingolipids over 3.4-year follow-up; notably, LGL1 levels were associated with NfL changes.
Conclusions: This study evidences an age-dependent increase of β-glucocerebrosidase and acid sphingomyelinase substrates in *GRN* patients, with progressive changes along disease course since the presymptomatic phase. Among FTD patients, plasma lysosphingolipids appear to be uniquely elevated in *GRN* carriers, which suggests their use as non-invasive disease-tracking biomarkers of progression, specific to the pathophysiological process. This could be particularly relevant in the context of disease-modifying approaches based on lysosomal function rescue in *GRN* disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1227 / #2940

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D04. Genetics, Epidemiology*

NASU-HAKOLA DISEASE ASSOCIATED WITH EARLY ONSET DEMENTIA OF FRONTAL LOBE TYPE

POSTERS: D04. GENETICS, EPIDEMIOLOGY

Stanislav Sutovsky[1], Ivana Paucinova[2], Peter Turcani[1]
[1]Comenius University, Faculty of Medicine, First Department Of Neurology, Bratislava, Slovak Republic, [2]University Hospital, Department Of Genetics, Zilina, Slovak Republic

Aims: Nasu-Hakola disease (NHD) is a rare autosomal recessive disorder, pathologically characterized by leukoencephalopathy, astrogliosis, axonal spheroids, and accumulation of microglia. Clinically, it is characterized by cognitive decline, skeletal pain and polycystic osteodysplasia. NHD is caused by a mutation in the TYROBP gene in a homozygous state.
Methods: In this case report we describe a 40 years old patient with progressive cognitive deterioration within four years.
Results: At the forefront of the clinical picture were the symptoms of prefrontal syndrome, memory and concentration disorders and the overall breakdown of personality. Brain MRI showed severe diffuse atrophy and increased white matter signal predominantly periventricular, which was milder than seen in leukodystrophies and ALD. CSF examination showed increased total proteins, increased IgG and absent oligoclonal synthesis of gamma globulins. 14-3-3 protein was negative, and screening for PrP mutations was also negative. WES revealed the mutation c.94G→A in TYROBP gene in the homozygous state confirmed the Nasu-Hakola disease. The patient did not report any skeletal pain, nor did we detect any bone abnormalities. In the genealogical analysis, we did not confirm the consanguinity of the parents, but we found that the parents came from neighbouring villages in a sparsely populated area in the north of Slovakia.
Conclusions: Early onset dementia is always a big diagnostic challenge. In the case of a negative family history, rare autosomal recessive diseases, including Nasu-Hakola disease, should be considered. WES is a reliable method for detecting such rare diseases and a logical step when diagnostic options are exhausted.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1228 / #681

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D04. Genetics, Epidemiology*

ROLE OF OPTINEURIN IN THE FTD-ALS SPECTRUM. NEW MUTATION WITH EXCEPTIONAL PHENOTYPIC EXPRESSIVITY IN A FIVE-PATIENT CASE REPORTS.

POSTERS: D04. GENETICS, EPIDEMIOLOGY

Anxo Manuel Minguillón Pereiro[1], Juan Manuel Pías Peleteiro[1], Beatriz Quintáns Castro[2], José Manuel Aldrey Vázquez[1], Carmen Gómez Lado[3], Tomás Sobrino Moreiras[4], Alberto Ouro Villasante[4], Marta Aramburu Núñez[4], Julia Cortés Hernández[5], Julio Pardo Fernández[6]
[1]Complejo Hospitalario Universitario de Santiago de Compostela, Servicio De Neurología, Rúa da Choupana s/n, Spain, [2]Fundación Pública Galega de Medicina Xenómica, Fundación Pública Galega De Medicina Xenómica, Rúa da Choupana s/n, Spain, [3]Complejo Hospitalario Universitario de Santiago de Compostela, Servicio De Pediatría, Rúa da Choupana s/n, Spain, [4]NeuroAging Laboratory (NEURAL) Group, Health Research Institute (IDIS), Neuroaging Laboratory, Rúa da Choupana s/n, Spain, [5]Complejo Hospitalario Universitario de Santiago de Compostela, Servicio De Medicina Nuclear. Sección De Sistema Nervioso Central., Rúa da Choupana s/n, Spain, [6]Complejo Hospitalario Universitario de Santiago de Compostela, Servicio De Neurología. Unidad De Patología Neuromuscular, Rúa da Choupana s/n, Spain

Aims: Frontotemporal dementia (FTD) is the most prevalent cause of dementia under 45 years of age and the third in global rates. Although very infrequently, mutations in the optineurin gene have been associated with cases of FTD and, likewise, with amyotrophic lateral sclerosis (ALS).
Methods: We report a five-patient cohort, two of them with clinical features that suggest FTD (one behavioral variant and one primary progressive nonfluent aphasia), two with motor neuron disease (a Mills' hemiplegic variant) and one pediatric patient with a dystonic-myoclonic clinical picture.
Results: Complementary tests support the clinical diagnosis in all cases. Despite obvious phenotypic differences, genetic study reveals in all five cases the same variant in OPTN [NM_021980.4:c.1552C>T (p.Gln518*)] in heterozygosis. A systematic review is performed ratifying the association of OPTN with ALS, but also with the ALS/DFT spectrum. No previous descriptions were found of a dystonia-myoclonus phenotype, neither on paediatric age nor in adults. The main pathophysiological scenarios are explained with pathogenic variants affecting OPTN gene domains involved in the mechanism of autophagy, causing accumulation of protein aggregates and mitochondrial dysfunction.
Conclusions: We present a new likely pathogenic mutation with a high clinical expressivity. Its pathophysiological consequences at the molecular level could provide valuable information not only on the cellular basis of genetic neurodegenerative pathologies, but especially on the role that optineurin may play in the FTD-ALS spectrum.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1229 / #762

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D04. Genetics, Epidemiology*

RHEUMATOID ARTHRITIS, SEX DIFFERENCES, COGNITIVE DECLINE AND DEATH IN DEMENTIA: A POPULATION-BASED SWEDISH STUDY

POSTERS: D04. GENETICS, EPIDEMIOLOGY

Minjia Mo[1], Maria Eriksdotter[1], Sumonto Mitra[1], Sofia Ajeganova[2], Sara Garcia-Ptacek[1], Hong Xu[1]
[1]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, STOCKHOLM, Sweden, [2]Department of Medicine Huddinge, Department Of Medicine Huddinge, Karolinska Institutet, STOCKHOLM, Sweden

Aims: To determine whether rheumatoid arthritis (RA) is associated with cognitive decline in dementia patients and to explore how sex modifies the association.
Methods: We conducted a population-based cohort study including dementia patients aged 40 years or older identified from the Swedish Registry for Cognitive/Dementia Disorders-SveDem during 2007-2018. We used mixed-effects models to examine the interactive associations of RA and sex on cognitive decline and Cox proportional hazards models to investigate the risk of all-cause mortality.
Results: The final cohort included 24 727 patients with dementia, among them 10 527[42.6%] were men (mean[SD] age, 77.1[7.5] years) and 14 200[57.4%] were women (78.3[7.6] years). The median follow-up was 3.9 years (interquartile range, 2.5-5.6 years) for men and 4.2 years (2.7-5.9 years) for women. In all, 521 persons were diagnosed with RA, of them 147[1.4%] were men and 374[2.6%] women. After adjusted for age, comorbidities, cholinesterase inhibiters, memantine, disease modifying antirheumatic drugs, cognitive trajectories did not differ between RA and non-RA patients. However, compared to non-RA patients, patients with RA had slower cognitive decline in women (0.37 points/y; 95%CI, 0.02 to 0.72 points/y) but not men (0.11 points/y; 95%CI, −0.50 to 0.72 points/y). Compared to non-RA, RA patients with dementia had a higher risk of all-cause mortality (HR[95%CI], 1.22[1.03-1.44]), especially men (HR[95%CI], 1.74[1.28-2.36]). We observed similar results across specific dementia types of Alzheimer's disease and mixed dementia.
Conclusions: In this cohort study, we found that compared to non-RA patients, cognitive decline to a lower extent in female than in male dementia patients with RA, but a higher risk of mortality was found in men, which might be related to the sex differences in comorbidities and comedications.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1230 / #1184

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D04. Genetics, Epidemiology*

UNRAVELING THE MOLECULAR CONSEQUENCES OF THE FUSION BETWEEN YAF2 AND RYBP IN AMYOTROPHIC LATERAL SCLEROSIS.

POSTERS: D04. GENETICS, EPIDEMIOLOGY

Tiziana Petrozziello, Sommer Huntress, John Lemanski, Maheswaran Kesavan, Ayleen Castillo-Torres, Celine De Esch, Dadi Gao, Merit Cudkowicz, James Berry, Ricardo Mouro Pinto, Micheal Talkowski, Ghazaleh Sadri-Vakili
Mass General Brigham, Neurology, Boston, United States of America

Aims: Recently, we demonstrated an enrichment in gene fusion events in ALS post-mortem brain and spinal cord using STAR-Fusion to assess publicly available RNA-Seq datasets. Here, we began to assess the consequences of these fusion events with a focus on one of the most recurrent gene fusions identified in ALS: the inter-chromosomal fusion between YY1 Associated Factor 2 (YAF2) and RING1 and YY1 Binding Protein (RYBP). Both genes are involved in chromatin remodeling and transcriptional regulation through ubiquitination of histone H2 ($H2AK119ub_1$) and interaction with polycomb (PcG) proteins.
Methods: Human neuroblastoma SH-SY5Y cells were transfected with plasmids coding for either YAF2, RYBP or YAF2-RYBP fusion. Immunocytochemistry followed by immunofluorescence was performed to assess $H2AK119ub_1$ levels as well as interactions with PcG proteins. Western blots were performed to assess PcG proteins and $H2AK119ub_1$ levels in human control and ALS post-mortem motor cortex (mCTX).
Results: Our results indicated that YAF2 and RYBP interact with three PcG proteins in SH-SY5Y cells: EZH2, RING1A and histone H3 tri-methylated at lysine 27 ($H3K27me_3$). While YAF2-RYBP fusion did not alter EZH2, and $H3K27me_3$ levels, there was a significant increase in RING1A levels in YAF2-RYBP fusion-transfected cells compared to EGFP- and RYBP-transfected cells. Consistently, YAF2-RYBP fusion significantly decreased $H2AK119ub_1$ levels in SH-SY5Y cells. Lastly, our results did not reveal any changes in EZH2, RING1A, $H3K27me_3$, and $H2AK119ub_1$ levels in ALS mCTX compared to controls, thus supporting a role for YAF2-RYBP fusion in modulating these proteins.
Conclusions: Altogether, our results demonstrate that YAF2 fusion to RYBP regulates interaction with RING1A in ALS. Ongoing RNA-Seq and transposase-accessible chromatin with sequencing (ATAC-Seq) studies will determine whether YAF2-RYBP fusion alters chromatin accessibility and thereby gene expression in ALS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1231 / #1101

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D03. Imaging, Biomarkers, Diagnostics*

AMYGDALA TDP-43 PATHOLOGY IS ASSOCIATED WITH FERRITIN ACCUMULATION AND BEHAVIOURAL DYSFUNCTION IN AMYOTROPHIC LATERAL SCLEROSIS

POSTERS: D03. IMAGING, BIOMARKERS, DIAGNOSTICS

Olivia Rifai[1], Fergal Waldron[2], Judi O'Shaughnessy[1], Fiona Read[2], Martina Gilodi[3], Neil Shneider[4], Gian Tartaglia[3], Elsa Zacco[3], Mathew Horrocks[5], Holly Spence[6], Jenna Gregory[6]
[1]Centre for Discovery Brain Sciences, University of Edinburgh, UK, Centre For Discovery Brain Sciences, Edinburgh, United Kingdom, [2]University of Aberdeen, The Institute Of Medical Sciences,, Aberdeen, United Kingdom, [3]RNA system Biology Lab, Istituto Italiano di Tecnologia, Rna System Biology Lab, Genoa, Italy, [4]Department of Neurology, Center for Motor Neuron Biology and Disease, Columbia University, Department Of Neurology, New York, United States of America, [5]EaStCHEM, School Of Chemistry, Edinburgh, United Kingdom, [6]Institute of Medical Sciences, University of Aberdeen, Institute Of Medical Sciences, Aberdeen, United Kingdom

Aims: Cognitive and behavioural deficits are observed in around 50% of ALS patients. While it is thought that cognitive deficits are largely driven by TDP-43 pathology, there is currently no sensitive pathological correlate of behavioural deficits.
Methods: The current cohort consisted of 30 sporadic ALS patients who underwent neuropsychological behavioural assessment as part of the Edinburgh Cognitive ALS Screen (ECAS). In these patients we examined post-mortem brain tissue from 6 brain regions (i) amygdala, (ii) orbitofrontal cortex (BA11/12), (iii) ventral anterior cingulate (BA24), (iv) medial prefrontal cortex (BA6), (v) prefrontal cortex (BA9) and (vi) the dorsolateral prefrontal cortex (BA46).
Results: ECAS behavioural screen predicted pTDP-43 pathology with 100% specificity and 86% sensitivity with amygdala showing best sensitivity and specificity. In the amygdala we show that presence and severity of intra-neuronal pTDP-43 pathology but not astroglial or Tau pathology is associated with clinically detectable behavioural deficit. Severity of TDP-43 aptamer staining was also associated with clinically detectable behavioural deficit and exhibited a positive correlation with ferritin immunoreactivity (regardless of phenotype).
Conclusions: This suggests that TDP-43 pathology in the amygdala is associated with ECAS determined behavioural deficit and that ferritin increases occur upstream of behavioural deficit.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1232 / #2567

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D05. Cell, Molecular and Systems Biology*

APEX2-BIOTINYLATION PROTEOMICS DISCOVERED THAT POLY (A)-BINDING PROTEIN MEDIATES THE DEGRADATION OF C9ORF72-GGGGCC REPEAT RNA

POSTERS: D05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Ryota Uozumi[1], Kohji Mori[1], Shiho Gotoh[1], Tesshin Miyamoto[1], Shizuko Kondo[1], Tomoko Yamashita[1], Yuya Kawabe[1,2], Shinji Tagami[2,3], Shoshin Akamine[1], Manabu Ikeda[1]
[1]Osaka University, Department Of Psychiatry, Osaka, Japan, [2]Minoh Neuropsychiatric Hospital, Psychiatry, Osaka, Japan, [3]Osaka University, Health And Counseling Center, Osaka, Japan

Aims: Neurodegeneration in *C9orf72*-linked frontotemporal lobar degeneration (FTLD)/amyotrophic lateral sclerosis (ALS) is known to be caused by the toxicities of transcribed GGGGCC repeat RNA (repeat RNA) itself and/or its repeat-associated non-AUG (RAN) translation products, dipeptide repeat protein (DPR). We previously reported that hnRNPA3, through binding to repeat RNA, suppressed the accumulation of repeat RNA and DPR. It indicates that hnRNPA3 promotes the degradation of the repeat RNA; however, hnRNPA3 itself is not structurally expected to function as an RNase. Here, we aimed to identify RNA degradation-associated proteins that interact with hnRNPA3.
Methods: In the presence or absence of (GGGGCC)80 repeat RNA, we performed proximity biotin-phenol labeling assays, known as APEX2 proteomics, to biotinylate and purify the proximate interactors of fused hnRNPA3-APEX2 in HeLa cells. Biotinylated interactors were then identified by LC-MS/MS. To test their effects on repeat RNA accumulation, siRNA-mediated knockdown screenings were performed. Further validation was conducted on endogenous repeat RNA using fibroblasts derived from *C9orf72* GGGGCC expansion mutation carriers.
Results: hnRNPA3-APEX2 proteomics identified 190 proteins whose biotinylation state changes in the presence or absence of the repeat RNA; however, no apparent RNases were included. Accordingly, we performed a stringent filtering of the 190 proteins and selected nine RNA-binding proteins (GO: 0003723) as candidate interactors that might be involved in repeat RNA degradation. The following siRNA-screening identified reduction of PABPC1 (a cytoplasmic isoform of poly adenylate-binding protein) increased the repeat RNA accumulation in HeLa cells, as well as hnRNPA3. In addition, *In Situ* Hybridization revealed that the siRNA-mediated PABPC1 reduction also promoted the accumulation of repeat RNA foci in (GGGGCC)80 repeat expression HeLa cells and in *C9orf72* mutation carrier-derived fibroblasts.
Conclusions: With APEX2 proteomics, we identified that PABPC1 interacts with hnRNPA3 and mediates the degradation of the pathogenic *C9orf72* repeat RNA. Our results have the potential for the development of novel therapies targeting repeat RNA for *C9orf72*-FTLD/ALS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1233 / #926

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D05. Cell, Molecular and Systems Biology*

EXTRACELLULAR MATRIX IMPAIRMENT IN SPINAL CORD ORGANOIDS OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS

POSTERS: D05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Matteo Bordoni[1], Eveljn Scarian[1], Letizia Messa[2], Maria Garofalo[3], Emanuela Jacchetti[4], Manuela Raimondi[4], Luca Diamanti[5], Stella Gagliardi[3], Stephana Carelli[6], Cristina Cereda[2], Orietta Pansarasa[1]
[1]IRCCS Mondino Foundation, Cellular Model And Neuroepigenetics Unit, Pavia, Italy, [2]Buzzi Hospital, Department Of Pediatrics, Milan, Italy, [3]IRCCS Mondino Foundation, Molecula Biology And Transcriptomics Unit, Pavia, Italy, [4]Politecnico of Milan, Department Of Electronics, Information And Bioengineering, Milan, Italy, [5]IRCCS Mondino Foundation, Neuroncology Unit, Pavia, Italy, [6]University of Milan, Department Of Biomedical And Clinical Sciences, Milan, Italy

Aims: Amyotrophic lateral sclerosis (ALS) is a non-cell autonomous disorder as many cell types contribute to motor neurons death. The lack of effective treatments is due to the absence of a realistic model.Organoids are stem cell-derived self-organizing structures that allow in vitro generation of tissues. Thus, aim of the work was to develop and characterize a 3D organoid model for the study of ALS pathogenesis.
Methods: We started from iPSCs obtained from healthy controls and sporadic ALS (sALS) patients. We differentiated iPSCs into neural stem cells (NSCs). We dissociated NCSs using StemPro Accutase and a cell strainer. Then, we plated NSCs on low-attachment plates and we cultured them in floating conditions using an orbital shaker. We differentiated NSCs to generate SCOs. We then characterized SCOs by phase-contrast microscope, confocal microscopy and transcriptomics analysis.
Results: We found that SCOs derived from sALS patients were smaller and with irregular morphology compared to controls. Using the GFAP marker, we found that sALS SCOs have a thicker glial layer. We also found that sALS SCOs show shorter neurites. By RNAseq, we found a ten-fold increase of deregulated gene in SCOs respect to 2D cell models. Moreover, in ALS SCOs we found an extensive deregulation of genes involved in extracellular matrix organization when compared to control. Finally, we compared transcriptomic profile of both sALS SCOs and human spinal cord tissue, finding many similarities.
Conclusions: Our data suggest that brain organoids represent a promising tool for the investigation of pathogenic mechanisms of ALS. Indeed, we found typical pathological hallmarks of the pathology, such as the presence of gliosis, the smaller length of neurites, and decreased level of mature MNs. Moreovers sALS SCOs transciptomics signature shares many similarities with the spinal cord tissue.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1234 / #544

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D05. Cell, Molecular and Systems Biology*

SHORT- AND LONG-READ TRANSCRIPTOMICS IN FTLD-TDP TO IDENTIFY DISEASE-ASSOCIATED TRANSCRIPTS GENERATED BY ABERRANT SPLICING

POSTERS: D05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Júlia Faura[1,2], Bavo Heeman[1,2], Cyril Pottier[1,2,3], Matthew Baker[4], Mariely Dejesus-Hernandez[4], Laura Heiß[1,2], Sarah Wynants[1,2], Marleen Van Den Broeck[1,2], Tim De Pooter[1,2], Geert Joris[1,2], Peter De Rijk[1,2], Nicole Finch[4], Marka Van Blitterswijk[4], Joanna Biernacka[5], Yan Asmann[6], Mojca Strazisar[1,2], Melissa Murray[4], Leonard Petrucelli[4], Keith Josephs[7], Ronald Petersen[8], Bradley Boeve[7], Neill Graff-Radford[9], Dennis Dickson[4], Rosa Rademakers[1,2]
[1]VIB, Vib Center For Molecular Neurology, Antwerp, Belgium, [2]University of Antwerp, Biomedical Sciences, Antwerp, Belgium, [3]Mayo Clinic Florida, Neuroscience, Jacksonville, United States of America, [4]Mayo Clinic, Neuroscience, Jacksonville, United States of America, [5]Mayo Clinic, Quantitative Health Sciences, Jacksonville, United States of America, [6]Mayo Clinic, Quantitative Health Sciences, Rochester, United States of America, [7]Mayo Clinic, Neurology, Rochester, United States of America, [8]Mayo Clinic, Department Of Neurology, Rochester, United States of America, [9]Mayo Clinic, Neurology, Jacksonville, United States of America

Aims: Dysregulation of TDP-43 as seen in TDP-43 proteinopathies leads to specific RNA splicing dysfunction. While short-read RNA-sequencing (SR-RNA-seq) has been widely used for transcriptomics profiling, long-read (LR) RNAseq is emerging as a powerful alternative. We hypothesize that the combination of SR- and LR-RNAseq data can highlight novel disease-associated transcripts with relevance to the identification of disease pathways and biomarkers.
Methods: We performed the largest differential splicing analysis to date in FTLD-TDP patients using SR-RNA-seq data from frontal-cortex (FCX) tissue of 127 patients and 22 control subjects (Mayo Clinic Brain Bank; Illumina), using LeafCutter. In addition, we generated LR-RNAseq data from (1) TDP-43 knockdown (KD) iPSC-derived neurons at different levels of TARDBP KD and (2) FCX brain tissue, using the Oxford Nanopore Technology. Reads were aligned with minimap2 and isoform quantification was performed with IsoQuant.
Results: In human brain, we identified 4234 differentially spliced events (FDR<0.05, |dPSI|>0.05) between FTLD-TDP patients and controls in 1644 unique genes. To prioritize events driven by TDP-43 loss-of-function rather than cellular composition, we created a second dataset of TARDBP targets by correlating the expression of TARDBP in the different KD neurons with the expression of each detected transcript. We identified 1377 isoforms negatively correlated (R<-0.8) and 1937 positively correlated (R>0.8) with TARDBP expression. When overlapping both datasets, 25 genes showed extensive evidence for regulation by TARDBP in neurons and a significant differential splicing of transcripts in FTLD-TDP brains.
Conclusions: Twenty-five potential TDP-43-driven splicing events have been identified by combining SR- and LR-RNAseq data. They will be further explored in the LR-RNAseq data from FTLD-TDP and control brain and their proteoform expression will be explored in already generated cerebrospinal fluid and plasma proteomics data to study their potential as biomarkers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1235 / #2328

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D05. Cell, Molecular and Systems Biology*

EIF5 REGULATES POLY-GA RAN TRANSLATION IN A CELLULAR MODEL OF C9ORF72 FTLD/ALS.

POSTERS: D05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Shiho Gotoh[1], Kohji Mori[1], Yoshitaka Nagai[2], Manabu Ikeda[1]
[1]Osaka University, Department Of Psychiatry, Osaka, Japan, [2]Kindai University, Department Of Neurology, Osaka, Japan

Aims: *C9orf72* related frontotemporal lobar degeneration and amyotrophic lateral sclerosis (C9-FTLD/ALS) patients have unusually expanded GGGGCC (G_4C_2) repeat sequence in intron 1 of *C9orf72* gene. G_4C_2 repeat sequence is transcribed and then translated into di-peptide repeat proteins (DPR) via repeat associated non-AUG (RAN) translation. DPR accumulates in the C9-FTLD/ALS patient's brain. DPR toxicity has revealed in multiple models. Suppression of DPR expression levels via inhibition of RAN translation would have a therapeutic potential for C9-FTLD/ALS. In this study we propose eukaryotic initiation factor 5 (eIF5) as a novel regulator of RAN translation.
Methods: We used cellular model expressing $(G_4C_2)_{80}$ repeats. Western blotting was performed for detect poly-GA DPR expression. Puromycin incorporation assay was performed for quantify the global translation.
Results: siRNA-mediated knockdown of eIF5 decreased the expression level of poly-GA DPR. Conversely, overexpression of eIF5 increased poly-GA expression level. Moreover, inactivation of eIF5 by site directed mutagenesis reduced poly-GA expression. Puromycin incorporation assay revealed that eIF5 preferentially upregulates poly-GA DPR through RAN translation over global translation.
Conclusions: In conclusion, we revealed that eIF5 stimulates poly-GA DPR translation through its intrinsic activity. Further investigation of the mechanism by which eIF5 regulates RAN translation could lead to the development of a new treatment for C9-FTLD/ALS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1236 / #1918

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D05. Cell, Molecular and Systems Biology*

CHARACTERIZING THE EFFECTS OF TMEM106B PROTEIN LEVELS IN THE ENDOLYSOSOMAL PATHWAY

POSTERS: D05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Miranda Lastra Osua, Bavo Heeman, Rafaela Policarpo, Paula Miquel, Maxim Van Hoek, Simona Manzella, Bob Asselbergh, Renzo Mancuso, Rosa Rademakers
University of Antwerp, Vib-uantwerp Center For Molecular Neurology (cmn), Antwerpen, Belgium

Aims: *TMEM106B* haplotypes have been found to modulate the risk for several neurodegenerative diseases such as Frontotemporal lobar degeneration with TDP-43 aggregates and Alzheimer's disease and were shown to impact healthy aging and neuronal reserve, suggesting that they determine neuronal vulnerability to external stressors. These haplotypes are thought to regulate expression of TMEM106B, a lysosomal type-II transmembrane protein, with a slight increase in expression associated with the risk haplotype. In this project we assessed how subtle changes in TMEM106B protein levels condition neuronal fitness by dysregulating lysosomal physiology.
Methods: We generated isogenic pluripotent stem cell (PSC)-derived cortical neurons with different TMEM106B expression levels: a full knockout (*TMEM106B*$^{-/-}$) and an inducible-reversible overexpression (*TMEM106B*^{OE}) model. In depth characterization of the endolysosomal pathway of these neurons *in vitro* is currently performed by analyzing their proteome with lysosomal immunoprecipitation and mass spectrometry, whereas lysosomal trafficking with live cell imaging, lysosomal enzymatic activity, as well as lysosomal size and localization with expansion microscopy were already analyzed.
Results: Both *TMEM106B*$^{-/-}$ and *TMEM106B*^{OE} human mature cortical neurons show a dysfunctional endolysosomal pathway. These cells show enlarged lysosomes by expansion microscopy, in which large Cathepsin D and LAMP1 positive structures cluster perinuclearly in the somas of these cells. *TMEM106B*$^{-/-}$ and *TMEM106B*^{OE} neurons also show an increased intensity of Lysotracker in the somas together with a dysregulated lysosomal transport and enzymatic activity, potentially due to changes in lysosomal pH.
Conclusions: Our results show that dysregulations of TMEM106B protein levels, both an increase and a decrease, lead to dysregulations of the endolysosomal pathway. Further understanding of the mechanisms that link this lysosomal dysfunction to neuronal resilience will be essential for the development of drugs that improve the survival of neurons in neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1237 / #2320

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D05. Cell, Molecular and Systems Biology*

KNOCKDOWN SCREENING FOR POTENTIAL RAN TRANSLATION MODULATORS IN CELLULAR MODELS OF C9ORF72 FTLD/ALS

POSTERS: D05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Kohji Mori[1], Shiho Gotoh[1], Ryota Uozumi[1], Tesshin Miyamoto[1], Shizuko Kondo[1], Yuya Kawabe[1], Shoshin Akamine[1], Yoshitaka Nagai[2], Manabu Ikeda[1]
[1]Osaka University, Department Of Psychiatry, Osaka, Japan, [2]Kindai University, Department Of Neurology, Osaka, Japan

Aims: A hexanucleotide expansion in the intron of C9orf72 is the most frequent cause of genetic form of FTLD/ALS. The expanded DNA repeat suffers transcription and produces repeat RNA. The repeat RNA further undergoes repeat associated non-AUG (RAN) translation. In the expanded C9orf72 repeat, RAN translation produces five distinct dipeptide repeat proteins (DPR) that are considered to be highly neurotoxic. Therefore, selective inhibition of RAN translation could have therapeutic potential. Although several factors have been proposed as potential RAN translation modulators, detailed mechanism of RAN translation remains obscure.
Methods: Here we have utilized nano-luciferase based RAN translation reporters that can monitor either poly-GA or poly-GR expressions. Conventional AUG dependent translation was monitored with firefly luciferase reporter activity.
Results: With 22 different siRNA-mediated knockdowns of translation-related factors, we have identified several factors that significantly inhibit/stimulate relative signals of RAN translation reporter over conventional AUG dependent reporter.
Conclusions: These results implicate that C9orf72 RAN translation could be modulated via multiple endogenous factors. Further experimental work will clarify how these factors contribute to RAN translation, thereby elucidating an important aspect of the pathogenesis of C9orf72 FTLD/ALS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1238 / #2123

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D04. Genetics, Epidemiology*

AN ALUYB8 RETROTRANSPOSON CHARACTERISES A RISK HAPLOTYPE OF TMEM106B ASSOCIATED IN NEURODEGENERATION

POSTERS: D04. GENETICS, EPIDEMIOLOGY

Alex Salazar[1], Niccolo Tesi[1], Lydian Knoop[1], Yolande Pijnenburg[2], Sven Van Der Lee[1], Sanduni Wijesekera[1], Jana Krizova[1], Mikko Hiltunen[3], Markus Damme[4], Leonard Petrucelli[5], Marcel Reinders[6], Marc Hulsman[1], Henne Holstege[1]
[1]Vrije Universiteit Amsterdam, Amsterdam UMC, Section Genomics Of Neurodegenerative Diseases And Aging, Department Of Clinical Genetics, Amsterdam, Netherlands, [2]Amsterdam UMC, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [3]University of Eastern Finland, Institute Of Biomedicine, Kuopio, Finland, [4]Christian-Albrechts-University Kiel, 6. Institute Of Biochemistry, Kiel, Germany, [5]Mayo Clinic, Neuroscience, Jacksonville, United States of America, [6]TU Delft, Delft Bioinformatics Lab, CB, Netherlands

Aims: GWASs have identified a common haplotype in *TMEM106B* associated with increased risk for neurodegeneration. This risk haplotype reportedly increases TMEM106B aggregation in human brains, and is sensitive to decreased activity of TDP-43. Here, we investigated if structural variants (SVs) in the *TMEM106B* risk haplotype mediate these interactions.
Methods: We performed long-read whole-genome sequencing of 209 individuals: 92 AD patients and 117 cognitively healthy centenarians. SVs in *TMEM106B* were identified using *sniffles2*, and further characterised through haplotype-phased *de novo* assembly. We performed linkage disequilibrium (LD) of SVs and previously reported GWAS-SNPs in the risk haplotype. We used *pg-CpG-tools* to evaluate methylation status across the *TMEM106B* haplotypes, as well as *TARDBP*. Finally, we compared *TMEM106B* haplotype sequences of AD and centenarian genomes with 47 genomes from the Human Pangenome Research consortium.
Results: We identified an AluYb8 retrotransposon in the 3' UTR of the *TMEM106B* in complete LD with the risk haplotype. Alu-elements can mediate (post-)transcriptional interference of nearby genes. When transcriptionally, active, Alu-elements can further propagate throughout the genome. We found that the risk haplotype is more methylated than the protective haplotype, likely a consequence of an evolutionary selection to suppress AluYb8 activation and propagation. Similarly, we observed age-related demethylation of *TARDBP*, which may dysregulate TDP-43 and enable further dysregulation of *TMEM106B* via the AluYb8. Additionally, we observe convergent evolution for retaining SINE-retrotransposon insertions in the 3' UTR of *TMEM106B* orthologs across species, suggesting evolutionary significance, such as immune-related benefit in lung-tissues. Finally, we found that African genomes harbour two unique haplotype sequences of *TMEM106B*, explaining why LD is reduced in *TMEM106B* in non-European genomes.
Conclusions: An AluYb8 retrotransposon is a candidate causal variant driving association of *TMEM106B* with different neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1239 / #1546

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D06. Animal Models*

LONGITUDINAL CHARACTERIZATION OF B6.SOD1G93A TRANSGENIC MICE

POSTERS: D06. ANIMAL MODELS

Roland Rabl, Aaron Fantina-Woblistin, Tina Loeffler, Livia Breznik, Magdalena Daurer, Stefanie Flunkert, Manuela Prokesch
QPS Austria GmbH, Neuropharmacology, Grambach, Austria

Aims: A range of human mutant SOD1 transgenic mouse models has been developed that is shown to mimic amyotrophic lateral sclerosis (ALS). Of these models, the most widely used is the SOD1(*G93A)1Gur mouse (Gurney et al., 1995) that is bred on a mixed C57BL/6 x SJL background. Although the SOD1G93A mouse has been a bedrock for ALS research and is a well-used model for over a decade, there are some concerns about its strong and early phenotype. The SOD1 mouse model bred on a pure C57BL/6 background might thus be a suitable alternative since it presents with a delayed ALS phenotype onset compared to the original strain and therefore can provide a longer treatment window for interventions. The aim of this study was to longitudinally evaluate the behavioral phenotype as well as electromyography (EMG) and neurofilament-light chain (NF-L) pathology of B6.SOD1G93A mice.
Methods: B6.SOD1G93A mice (JAX mouse #004435) of mixed sex were longitudinally analyzed for motor deficits using Vercelli score, wire suspension test, beam walk test, grip strength test, and pasta gnawing test at an age of 8, 14, and 20 weeks. Additionally, Compound Muscle Action Potential (CMAP) and Motor Unit Number Estimation (MUNE) was measured. In vivo blood of these mice was evaluated for NF-L levels.
Results: Behavioral tests are completed and are currently statistically analyzed. Animals do show a progressive motor phenotype which correlates with a reduction in CMAP and MUNE. NF-L level analyses are currently ongoing.
Conclusions: The progressive pathology observed in B6.SOD1G93A mice could provide a more appropriate model for studying early-stage pathological processes in ALS and provide a longer treatment window for the development of new therapies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1240 / #2042

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D06. Animal Models*

TMEM106B C-TERMINAL FRAGMENTS DRIVE A DISTINCT NEURODEGENERATIVE PROTEINOPATHY IN C. ELEGANS.

POSTERS: D06. ANIMAL MODELS

Ruben Riordan[1], Brian Kraemer[2,3]
[1]University of Washington, Gerontology, SEATTLE, United States of America, [2]VA Puget Sound Health Care System, Grecc, Seattle, United States of America, [3]University of Washington, Medicine, Seattle, United States of America

Aims: Genetic variation of lysosomal protein, transmembrane protein 106B (TMEM106B) has long been known as a risk factor for a diverse range of neurodegenerative disorders, especially FTLD with progranulin (GRN) haplo-insufficiency, though the mechanisms involved are not yet understood. Recently, through advances in cryo-electron microscopy (cryo-EM), aggregates of the C-Terminal domain of TMEM106B (TMEM CT) were shown to make up previously unidentifiable protein aggregates in the brains of human FTLD, AD, progressive supranuclear palsy (PSP), and dementia with Lewy Bodies (DLB) patients.
Methods: To determine the TMEM CT aggregation propensity and neurodegenerative potential, we generated a new transgenic C. *elegans* proteinopathy model pan-neuronally expressing the TMEM CT fragment constituting the fibrillar core in FTLD cases.
Results: We found that C. *elegans* pan-neuronal expression of TMEM CT causes neuronal dysfunction as evidenced by behavioral analysis. TMEM c-terminal fragments accumulate as detergent insoluble material. Behavioral dysfunction was accompanied by neurodegeneration as illustrated by loss of GABAergic neurons. To investigate the mechanisms driving TMEM106B proteinopathy, we aimed to explore the impact of GRN loss on the neurodegenerative effect of TMEM CT expression. To this end, we generated TMEM CT expressing C. *elegans* with PRGN loss of function. We found that loss of PGRN did not alter TMEM phenotypes confirming PGRN loss of function is upstream of TMEM aggregation. We also observed TMEM neurodegenerative phenotypes exhibit a distinct set of genetic modifiers as strong suppressors of tauopathy such as spop-1, sut-2 sut-6 show only modest modification of TMEM proteinopathy.
Conclusions: Taken together, our data suggest expression of TMEM CT in C. *elegans* neurons provides a useful model for the functional characterization of TMEM106B proteinopathy in neurodegenerative disease. Comparison with other proteinopathy models will inform potential disease mechanisms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1241 / #1926

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D06. Animal Models*

GENERATION AND SCREENING OF MOUSE MODELS OF ADRD WITH MULTIPLE GENETIC MANIPULATIONS TO MODEL DEMENTIA WITH MIXED BRAIN PATHOLOGIES.

POSTERS: D06. ANIMAL MODELS

Bethany Macdonald[1], Harpreet Kaur[1], Andrew Tooley[2], Aamir Zuberi[2], Cathleen Lutz[2], Kristen O'Connell[2], Amy Dunn[2], Catherine Kaczorowski[3]
[1]University of Michigan, Neurology, Ann Arbor, United States of America, [2]The Jackson Laboratory, Research, Bar Harbor, United States of America, [3]The University of Michigan, Neurology, Ann Arbor, United States of America

Aims: Alzheimer's disease-related dementias (ADRD) encompass a wide range of neurodegenerative diseases including Alzheimer's disease, vascular dementia, frontotemporal dementia (FTD), Lewy body dementia (LBD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and mixed dementia. The heterogeneity of ADRDs presents challenges for animal modeling of disease mechanisms to recapitulate the full spectrum of human disease.
Methods: Mouse strains carrying disease associated alleles in the Psen, App, Apoe, Tardbp, Mapt and Scna on the C57BL/6J genetic background were breed to homozygosity and then crossed to either B6, DBA/2J, FVB/NJ or WSB/EiJ to generate a set of 36 unique ADRD models. The generated models were assessed using a high-capacity multi-domain screening to prioritize future ADRD modeling of drug discovery, preclinical testing, and disease pathology.
Results: We found that the genetic background of strain significantly influenced the onset of behavioral deficits. Male and female App/Psen1/Mapt/Tardbp mice on an FVB or WSB background met our "no-go" criteria by showing elevated body temperature, reduced activity or increased frailty at 6 months of age. However, the same 4xKI mutations on a B6 (heterozygous and homozygous KI) or D2 (heterozygous KI) background are our top candidates as they show a late-onset trajectory of decline suggestive of a translatable ADRD model.
Conclusions: Our results demonstrate that combining ADRD mutations across genetically distinct backgrounds is a promising strategy to generate new mouse models that better model the human mid and late-life onset of deficits associated with ADRD. We identified several promising models of ADRD that exhibited late-onset frailty and motor deficits as function of mutation burden. The resulting model(s) will be translationally relevant and provide important insight into disease mechanisms for the future of ADRD research and drug discoveries.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1242 / #1045

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D05. Cell, Molecular and Systems Biology*

EPIGENETIC CHARACTERIZATION OF CONTROL AND SALS MOTOR NEURON ORGANOIDS

POSTERS: D05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Eveljn Scarian[1], Matteo Bordoni[1], Camilla Viola[2], Francesca Dragoni[2], Rosalinda Di Gerlando[2], Luca Diamanti[3], Stella Gagliardi[4], Orietta Pansarasa[1]
[1]IRCCS Mondino Foundation, Cellular Model And Neuroepigenetics Unit, Pavia, Italy, [2]University of Pavia, Dep. Of Biology And Biotechnology, Pavia, Italy, [3]IRCCS Mondino Foundation, Neuroncology Unit, Pavia, Italy, [4]IRCCS Mondino Foundation, Molecular Biology And Transcriptomics Unit, Pavia, Italy

Aims: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease (NDD) with a progressive clinical course that affects upper and lower motor neurons (MNs). There are two typical forms of ALS, the sporadic (sALS) and the familial one. Until now, only symptomatic treatments are available, for the lack of realistic models. Organoids are pluripotent stem cell-derived self-organizing structures which can recapitulate the tissue of origin in vitro. Aim of this project was the investigation of the epigenetic characteristics of motor neuron organoids (MNOs) at each differentiation step, neural stem cells organoids (NSCO), motor neuron progenitor organoids (MNOPs) and MNOs and the comparison of these characteristics which the ones of 2D cultured cells.
Methods: We performed an ELISA assay for DNA methylation status on 5-methylcytosine (5-mC) and a western blot analysis to test the expression of two key methylating enzymes, the DNA methyltransferase 1 (Dnmt1) and the DNA methyltransferase 3a (Dnmt3a). The gene expression of Dnmt1 and Dnmt3a was tested by Real-Time qPCR. Finally, we performed a western blot analysis to test the methylation status of two sites involved in ALS pathology, lysine 9 and lysine 27, both on histone 3.
Results: By ELISA assay we found a decreased methylation in sALS MNOs, which was due to the decrease in the protein expression of Dnmt1 in sALS MNOs when compared to the corresponding 2D MNs. By RT-qPCR we observed some differences both between organoids and 2D cultured cells and between CTRL and sALS cultures. Finally, we found an increasing trend of the trimethylation of lysine 9 and 27 during the differentiation protocol.
Conclusions: In conclusion, we confirmed the major deregulation of MNOs when compared to 2D cultured cells, already seen by our group through RNA-seq.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1243 / #961

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

MOYAMOYA DISEASE EMERGING AS AN IMMUNE-RELATED ANGIOPATHY

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Caroline Asselman[1,2,3], Dimitri Hemelsvoet[2,3,4], Denzel Eggermont[1], Evelien Van Hamme[1], Elke Bogaert[2,3], Jo Van Dorpe[5], Francis Impens[1,2,3], Bart Dermaut[2,3]
[1]VIB, Vib-ugent Center For Medical Biotechnology, Ghent, Belgium, [2]Ghent University Hospital, Center For Medical Genetics, Ghent, Belgium, [3]Faculty of Medicine and Health Sciences, Ghent University, Department Of Biomolecular Medicine, Gent, Belgium, [4]Ghent University Hospital, Department Of Neurology, Ghent, Belgium, [5]Ghent University Hospital, Department Of Pathology, Ghent, Belgium

Aims: Moyamoya disease is a rare cerebrovascular disorder with unknown etiology characterized by progressive narrowing of arteries of the brain and the formation of a compensatory network of fragile vessels. Genetic studies have identified RNF213, also known as mysterin, as a susceptibility gene for MMD. Given the low penetrance of RNF213 variants in genetically susceptible individuals, a second still unidentified hit is necessary to trigger disease onset. Recently, several molecular studies uncovered RNF213 as a key antimicrobial protein with important functions in the immune system. Furthermore, an increasing number of clinical reports describe the development of moyamoya angiopathy in association with infection or autoimmune disorders. Together, providing a growing body of molecular and clinical evidence pointing towards immune-related responses as second hits to trigger MMD onset. We hypothesize that the disease originates from an aberrant immune response to infection in patients carrying RNF213 mutations.
Methods: To address this, we compiled a Moyamoya cohort of 12 patients with age-matched healthy controls. Blood and tissue samples were collected and transmitted to our multi-omics pipeline including genomic and plasma proteomics.
Results: In 10 patients we were able to identify genetic variations in MMD susceptibility genes. In plasma, several proteins are differentially expressed. Further data analysis is ongoing to identify disease-relevant pathways. Data integration of these data with our clinical data will be the next step. In addition to this study, we applied a spatial proteomics technique (MACsima) on affected brain tissue of one MMD patient to characterize the immune environment of Moyamoya vessels.
Conclusions: These experiments have the potential to further elucidate the etiology of Moyamoya disease, and potentially lead to novel insights into cellular processes that link cellular immunity with vascular remodeling.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1244 / #2983

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

IATROGENIC CEREBRAL AMYLOID ANGIOPATHY AFTER NEUROSURGICAL PROCEDURE: A CASE REPORT

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Lidia Bojtos[1], Aida Fernández-Lebrero[2,3], Albert Puig-Pijoan[2,3], Ana Rodríguez-Campello[4,5], Irene Navalpotro-Gómez[2,6], Elisa Cuadrado-Godia[4,5]
[1]Hospital del Mar, Neurology, Barcelona, Spain, [2]Hospital del Mar Research Institute, Systems Neurology And Neurotherapies. Neurosciences Research Program, Barcelona, Spain, [3]Hospital del Mar, Neurology. Cognition And Behaviour Unit, Barcelona, Spain, [4]Hospital del Mar, Neurology. Neurovascular Unit, Barcelona, Spain, [5]Hospital del Mar Research Institute, Neurovascular. Neurosciences Research Programme, Barcelona, Spain, [6]Hospital del Mar, Neurology. Movement Disorders Unit, Barcelona, Spain

Aims: Cerebral amyloid angiopathy (CAA) is a condition characterized by the accumulation of beta-amyloid within the walls of cortical and leptomeningeal blood vessels. This deposition leads to various vascular issues, including rupture, fibrinoid necrosis, and obstruction. Recently, a novel condition known as iatrogenic CAA (iCAA) has emerged. iCAA is believed to arise from the inadvertent transmission of beta-amyloid between individuals through the use of cadaveric materials or neurosurgical instruments. This unique variant of CAA tends to manifest at an earlier age, typically presenting with symptoms such as lobar hemorrhages, seizures, and cognitive impairment. The introduction of diagnostic criteria for iCAA has resulted in greater awareness and recognition of cases. Our aim is to describe the clinical, radiological and biomarker features in a case of iCAA.
Methods: Presentation of a case report.
Results: A 48-year-old woman, with a history of childhood encephalocele repair, initiated follow-up at the age of 37 due to the presence of multiple lobar hematomas. A cranial MRI revealed chronic bilateral cortico-subcortical microbleeds, superficial siderosis, and leukoaraiosis. Additionally, PET-amyloid imaging displayed a positive result, while the analysis of cerebrospinal fluid biomarkers indicated low beta-amyloid levels, slightly elevated t-tau, and normal p-tau. ApoE genotyping confirmed E2/E3 genotype. Furthermore, genetic evaluations for Fabry, CADASIL, COL4A1, PSEN1, PSEN2, APP, CST3, and exome capture all returned negative results.
Conclusions: While the reported cases od iCAA remain limited, it is crucial to maintain a high level of suspicion for this condition in patients experiencing early-onset CAA, with a specific focus on scrutinizing their medical history for prior procedures. Our case aligns with the diagnostic criteria set forth for this emerging entity and supports the potential transmission of amyloid through a neurosurgical intervention.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1245 / #2097

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

REPORTED COGNITIVE AND DEPRESSIVE SYMPTOMS IN RELATION TO HISTORY OF TIA/STROKE IN CADASIL PATIENTS IN SWEDEN

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Pia Andersen[1], Helena Karlström[2], Matti Viitanen[1], Anne Börjesson-Hanson[1]
[1]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, Huddinge /Stockholm, Sweden, [2]Karolinska Institutet, Neurobiology, Care Sciences And Society Division Of Neurogeriatrics, Stockholm, Sweden

Aims: Cognitive impairment and mood disorders are common after stroke, even if the underlying mechanisms aren't fully understood. In this study we evaluated associations between reported cognitive and psychiatric symptoms and a history of TIA/stroke in a subsample of the Swedish CADASIL-cohort.
Methods: Forty-two individuals with clinical or preclinical CADASIL (*NOTCH3*-mutations confirmed) were evaluated by semi-structured systematic interviews covering medical and social history, lifestyle, symptoms, and course of disease. Medical records were evaluated. Crosstabulation was applied for analyzing relationships between groups and Chi-square test for the test of associations. When the sample size was small, the Fisher's exact test was applied instead.
Results: We evaluated 16 men and 26 women, aged 25-77 years. Twenty-four had a history of ischemic events with a mean age of 50 for the first event. Both cognitive and psychiatric problems were commonly reported. There was a trend for the association between the history of an ischemic event and reported cognitive problems (concentration difficulties, stress sensitivity, difficulty finding words, lack of initiative or memory problems), but not between the ischemic event and psychiatric symptoms. None of the results were clinically significant. No significant differences were observed between men and women in any of the parameters explored.
Conclusions: We found a trend for a higher frequency of cognitive problems in patients with the history of ischemic events but this was not statistically significant. No trend, nor associations were found between psychiatric symtoms and the history of ischemic events. Both the small sample size and the self-reported data are limitations in this study. Cognitive testing of patients, MRI analysis and potential biomarkers and are planned on our project and can hopefully give a better perspective for analyzing the background of these clinical manifestations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1246 / #2928

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

UNRAVELLING DISEASE PATHOLOGY FOR A NOVEL APP INTRACELLULAR DOMAIN VARIANT USING HIPSC-BASED 2D AND 3D MODELS

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Bas Voesenek[1], Elena Daoutsali[1], Julie Rutten[2], Saskia Lesnik Oberstein[2], Willeke Van Roon-Mom[1], Ronald Buijsen[1]
[1]LUMC, Human Genetics, Leiden, Netherlands, [2]LUMC, Clinical Genetics, Leiden, Netherlands

Aims: The Amyloid Precursor Protein (APP) has gained great interest in biomedical research due to its causal involvement in Alzheimer's Disease (AD) and Cerebral Amyloid Angiopathy (CAA). The vast majority of pathogenic variants causing AD or CAA are located inside or around the Amyloid-Beta (Aβ) domain of APP. To date, only one pathogenic variant (associated with AD) has been found in the APP intracellular domain (AICD). We report a novel AICD variant in the VTPEER motif in a patient with recurring strokes and aim to unravel pathomechanisms.
Methods: We obtained a skin biopsy from this patient and measured APP expression levels and its subcellular localization in fibroblasts. We will generate isogenic induced pluripotent stem cells (iPSCs) from these fibroblasts, which will be used to generate 2D neuronal cultures where we will measure APP expression and its subcellular localization. We will apply mass-spectrometry to identify changes in AICD interactors. In 3D cerebral organoids and neuro-mesodermal assembloids (to better capture the neurovascular phenotype) we will use single-cell RNA sequencing to investigate changes in gene expression and employ the recently published SCOUT pipeline to extensively characterize multiscale features of 3D fluorescence imaging datasets.
Results: Experiments in patient fibroblasts have shown no differences in APP RNA and protein levels compared to controls. However, presence of APP C-terminus in lysosomes was increased in the patient line. Moreover, we successfully reprogrammed patient fibroblasts into iPSCs and have implemented the SCOUT pipeline on our control cerebral and striatal organoids.
Conclusions: We identified a novel *APP* variant associated with stroke in the AICD. This variant may increase APP abundance in lysosomes. Using iPSC-based models, we will further investigate disease mechanisms in more relevant cell types.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1247 / #2462

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

DECREASED EXPRESSION OF CLAUDIN-5 IN CEREBRAL AMYLOID ANGIOPATHY-ASSOCIATED INTRACEREBRAL HAEMORRHAGE

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Lieke Jäkel[1], Kiki Claassen[1], Anna De Kort[1], Benno Küsters[2], Floris Schreuder[1], Catharina Klijn[1], H. Bea Kuiperij[1], Marcel Verbeek[1]
[1]Radboud University Medical Center, Neurology, Nijmegen, Netherlands, [2]Radboudumc, Pathology, Nijmegen, Netherlands

Aims: Cerebral amyloid angiopathy (CAA) is characterized by the deposition of the amyloid β (Aβ) protein in the cerebral vasculature which poses a major risk factor for the development of intracerebral haemorrhages (ICH). However, only a minority of patients with CAA develops ICH (CAA-ICH), and to date it is unclear which mechanisms determine why some patients with CAA are more susceptible to haemorrhage than others. Claudin-5 is a tight junction protein critical for functioning of the blood-brain barrier (BBB). We hypothesized that the expression of claudin-5 is altered in CAA-ICH cases compared to non-hemorrhagic CAA (CAA-NH) cases.
Methods: Using immunohistochemistry, we assessed the expression of claudin-5 in the microvasculature of occipital lobe and temporal lobe tissue from cases with CAA-associated ICH (CAA-ICH; n=20) and non-haemorrhagic CAA (CAA-NH; n=40). Also 42 control cases free of stroke and neurodegenerative pathologies were included. Group differences were assessed using linear regression with correction for potential confounders (age, sex, and biobank).
Results: We found lower levels of claudin-5 expression in the microvasculature of CAA-ICH cases compared to CAA-NH cases in both occipital (p=0.027) and temporal (p=0.035) grey matter, and in these patients, claudin-5 expression did not correlate to CAA severity. Claudin-5 expression was also reduced in the overlying white matter of the occipital (p=0.018) and temporal (p=0.015) lobe tissue of CAA-ICH cases compared to CAA-NH cases.
Conclusions: We provide evidence that decreased levels of claudin-5, potentially reflecting impaired BBB integrity, might be associated with the development of CAA-associated ICH. Future studies in larger cohorts with more biomarkers of BBB function are needed to substantiate these findings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1248 / #330

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

LINKING CEREBRAL DEMYELINATION TO VASCULAR RISK FACTORS USING ADVANCED QUANTITATIVE MAGNETIC RESONANCE IMAGING

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Mustapha Bouhrara, John Laporte, Mary Faulkner, Zhaoyuan Gong
National Institutes of Health, National Institute On Aging, Baltimore, United States of America

Aims: It is increasingly established that vascular risk factors (VRF), especially hypertension, obesity and arterial stiffness, represent contributing factors to Alzheimer's and Parkinson's diseases (AD, PD). Further, vascular dysregulation due to potential synergetic effects of arterial remodeling and blood pressure may lead to transient reductions in cerebral blood flow (CBF) resulting in hypoglycemia, hypoxia and lack of essential nutrients and concomitant cerebral tissue damage. However, the implication of these VRF on myelin degeneration has received little attention. Yet, myelin breakdown is associated with decline in cognition, and has been demonstrated to represent a potential major hallmark of AD and PD.
Methods: Our studies were conducted on participants drawn from the BLSA, GESTALT and CARDIA cohorts. For each participant, myelin content was measured using our advanced MRI method of myelin water fraction (MWF), a direct measure of myelin content, or fractional anisotropy (FA) and mean diffusivity (MD) DTI metrics. CBF was measured using our implementation of NESMA-ASL MRI. Finally, Hypertension, obesity, and arterial stiffness were also measured within a few hours from the MRI scans.
Results: Our results revealed lower myelin content in subjects with hypertension despite use of blood control medication. Further, higher arterial stiffness and obesity were also linked to lower myelin content. Finally, participants with lower CBF exhibited steeper longitudinal decline in myelin content and white matter integrity.
Conclusions: Our original findings revealed strong and significant relationships between various vascular risk factors and white matter degeneration, especially of myelin content. These results identify potential modifiable targets to prevent neurodegeneration, and highlight the need for a life course approach which can be combined with remyelination to restore normal axonal function and protects against neuro-axonal loss.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1249 / #1252

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

IN SITU TRANSCRIPTOMIC AND PROTEOMIC PROFILING OF THE SAME CELLS IN WNV INFECTED MOUSE BRAIN SECTIONS WITH SPATIAL MOLECULAR IMAGING

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Katrina Van Raay[1], Alyssa Rosenbloom[1], Brian Birditt[1], Ashley Heck[1], Kimberly Young[1], Tien Phan-Everson[1], Zachary Lewis[1], Giang Ong[1], Shilah Bonnett[1], Tushar Rane[1], Megan Vandenberg[1], Mithra Korukonda[1], Aster Wardhani[1], Patrick Danaher[1], Carl Brown[1], Rustem Khafizov[1], David Ruff[1], Margaret Hoang[1], Gary Geiss[1], Caleb Stokes[2], Joseph Beechem[1]
[1]NanoString(R) Technologies, Inc, R&d, Seattle, United States of America, [2]University of Washington, Immunology, Seattle, United States of America

Aims: We develop a proteogenomic workflow on the CosMx™ Spatial Molecular Imager (SMI), a single-cell spatial biology platform that leverages cyclic *in situ* hybridization chemistry to enable high-plex detection of proteins and RNAs at subcellular resolution. To validate the proteogenomic workflow, we profiled uninfected and infected mouse brain with West Nile Virus (WNV) encephalitis.
Methods: We measure 68 proteins (CosMx Mouse Neural Cell Typing and Alzheimer's Pathology Panel) and 1,000 RNA targets (CosMx Mouse Neuroscience Panel) on the same 5 µm thick FFPE section of mouse brain.
Results: As expected from WNV encephalitis, we observed persistent neuroinflammation that includes the recruitment and activation of CD8+ T cells and microglia. We captured the major cell types that comprise inflammatory nodules in post-WNV mouse brain (neurons, microglia, and astrocytes) and identified the signaling pathways that underlie persistent microglial-driven neuroinflammation after WNV encephalitis, and illuminates key aspects of neurodegeneration, neurodevelopment, cell state and signaling, including numerous ligands and receptors involved in neuron-glia communication. Our analysis identified pathways related to inflammation and cellular damage in neurons, astrocytes, microglia and T cells.
Conclusions: We use the CosMx SMI platform to show, for the first time, that large numbers of mouse neuronal cells can be profiled with both protein and RNA at single-cell resolution in a spatial context. This integrated system maximizes the information content per single cell to enable mechanistic understanding into infectious disease pathology and inflammatory response in the brain.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1250 / #1040

Poster Topic: *Theme D: TDP43, TMEM106B and C9orf72-Related Diseases / D06. Animal Models*

INCREASED LEVELS OF TMEM106B LEAD TO LYSOSOMAL DYSFUNCTION AND ABERRANT NEUROTROPHIN SIGNALING IN A TMEM106B OVEREXPRESSION MOUSE MODEL

POSTERS: D06. ANIMAL MODELS

Jolien Perneel[1,2], Sara Alidadiani[1,2], Nele Peeters[1,2], Linus De Witte[1,2], Bavo Heeman[1,2], Reindert Jehoul[3], Elke Calus[4], Debby Van Dam[4], Mieu Brooks[5], Ralph Perkerson[5], Xiaolai Zhou[5,6], Rosa Rademakers[1,2,5]
[1]University of Antwerp, Biomedical Sciences, Antwerp, Belgium, [2]VIB, Vib Center For Molecular Neurology, Antwerp, Belgium, [3]University of Hasselt, Biomedical Sciences, Hasselt, Belgium, [4]University of Antwerp, Neurochemistry And Behaviour Group, Experimental Neurobiology Unit, Department Of Biomedical Sciences, Antwerp, Belgium, [5]Mayo Clinic, Department Of Neuroscience, Jacksonville, United States of America, [6]Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, State Key Laboratory Of Ophthalmology, Guangzhou, China

Aims: Genetic variation in Transmembrane protein 106B (TMEM106B) is known to influence the risk and presentation in several neurodegenerative diseases and modifies healthy aging. Current evidence suggests that the risk allele is associated with higher levels of TMEM106B. However, the precise function of TMEM106B is undetermined and it remains unclear how TMEM106B modulates disease risk.
Methods: To study the effect of increased TMEM106B levels, we generated Cre-inducible transgenic mice expressing human wild-type TMEM106B. Our model stably expresses the transgene resulting in increased TMEM106B RNA and protein levels, unlike a previous model that failed to induce overexpression due to the tight regulation of Tmem106b levels. Detailed biochemical and neuropathological characterizations as well as behavioral analyses of this model are ongoing.
Results: We show that embryonic fibroblasts derived from this model are filled with large vacuoles, which are not acidic, and show increased levels of Lamp1 and Progranulin. This indicates that the increase in TMEM106B levels leads to severe lysosomal dysfunction. We performed bulk RNA sequencing on brain tissue from 15-month-old animals and identified the downregulation of genes associated with neuronal plasticity, learning, and memory. Pathway enrichment analysis confirmed the dysregulation of neurotrophin signaling, which was validated in primary cortical neurons.
Conclusions: We created a novel TMEM106B overexpression model and show that overexpression of TMEM106B induces severe lysosomal dysfunction. We show that increased levels of TMEM106B lead to dysregulation of neurotrophin signaling which may underly the disease-modifying effect and may contribute to neurodegeneration *in vivo*. Together, our data further supports the hypothesis that TMEM106B modulates the resilience or vulnerability of the brain to neurodegeneration and aging.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1251 / #1920

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

CLINICAL AND DIAGNOSTIC CHARACTERISTICS OF HEADACHE IN PATIENTS WITH SMALL VESSEL DISEASE.

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Victoria Vershuta
Sechenov First State Medical University, Neurology, Moscow, Russian Federation

Aims: Small vessel disease(SVD) is one of the most pressing problems of modern medicine.The leading complaint in SVD is headache(HA). **Aim:**Determination of clinical and diagnostic characteristics of HA in SVD.
Methods: The study included 72 patients suffering from SVD. The patients were divided into two groups: group 1 - 44 patients suffering from HA, control group -28 patients without HA.Patients underwent the questionnaire survey: MOCA test, HADS, sleep questionnaire, MRI of the brain
Results: Tension-type headache(TTH) was detected in 27(37.5%)patients, migraine -11(15.3%), migraine and TTH - 6(8.3%). Cognitive impairment in migraine occurred in 8(72.7%) people, in TTH in 17(62.9%), in migraine and TTH in 5(83,3%). In patients with TTH, sleep was disturbed in 18 (66.7%)cases, with migraine in 9(81.8%), with migraine and TTH in 6(100%). Anxiety in TTH patients was diagnosed in 21(77.8%) patients, migraine - 6(54.5%), depression in patients with TTH - 10(37%), with migraine - 7(63.6%). With migraine and TTH, anxiety was diagnosed in 4 (66.7%)cases, depression in 5(83.3%). According to MRI of the brain, white matter pathology corresponding to grade 3 Fazekas was diagnosed in 6(54.5%) patients with migraine, with TTH in 6(22.2%), with TTH and migraine -4(66, 7%)
Conclusions: 44(61.1%) people suffering from SVD complained of HA,while the diagnosis of HA was previously established in 11(15.3%). TTH was the most common among patients with SVD(37.2%). Among patients with migraine cognitive impairment was 9.8% more common than in TTH, as well as more pronounced white matter changes according to MRI of the brain. Anxiety(77.8%) and sleep disorders(66.7%) prevailed among patients with TTH, depression(66.7%) among patients with migraine and TTH. Thus, the majority of patients with SVD suffered from primary HA, the course of which was aggravated by emotional and sleep disturbance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1252 / #9

Poster Topic: *Theme E : Vascular Diseases / E01. Disease Mechanisms, Pathophysiology*

ACTIVATION OF WNT/B-CATENIN PATHWAY IN THE BRAIN ENDOTHELIUM MITIGATES AB-INDUCED BLOOD-BRAIN BARRIER DYSFUNCTION IN ALZHEIMER'S DISEASE

POSTERS: E01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Chenju Yi
SEVENTH AFFILIATED HOSPITAL OF SUN YAT-SEN UNIVERSITY, Research Center, SHENZHEN, China

Aims: Alzheimer's disease (AD) is the leading cause of age-related neurological and cognitive decline. As the mechanisms of this disease are yet to be fully understood, the treatments for AD pose a significant challenge. Dysfunction of the blood-brain barrier (BBB) is increasingly recognized as a major contributor to the pathophysiology of AD, especially at the early stages of the disease. However, underlying mechanisms remain poorly characterized, while few molecules can directly target and improve BBB function in the context of AD.
Methods: Here using both AD patients and APPswe/PS1dE9 (APP/PS1) mouse model of AD, BBB damage and the underlying molecular mechanism were examined.
Results: We showed dysfunctional BBB in AD patients indicated by perivascular accumulation of blood-derived fibrinogen in the hippocampus and cortex, accompanied by decreased tight junction proteins Claudin- 5 and glucose transporter Glut-1 in the brain endothelial cells (BECs). In the APP/PS1 mice, BBB dysfunction started at 4 months and became severe at 9 months. In the cerebral microvessels of APP/PS1 mice and Aβ- treated BECs, we found suppressed Wnt/β-catenin pathway triggered by an increase of GSK3β activation, but not an inhibition of the AKT pathway or switch to the Wnt/planar cell polarity pathway. Furthermore, using our newly developed optogenetic tool for controlled regulation of LRP6 (upstream regulator of the Wnt signaling) to activate Wnt/β-catenin pathway, Aβ-inhibited BBB function was restored by promoting the barrier repair and preventing Aβ-induced BEC impairments.
Conclusions: Targeting LRP6 in the Wnt/β-catenin pathway in the brain endothelium can alleviate BBB dysfunction induced by Aβ, which may be a potential treatment strategy for AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1253 / #1733

Poster Topic: *Theme E : Vascular Diseases / E02. Therapeutic Targets, Mechanisms for Treatment*

COMPARISON OF DIFFERENT APPROACHES FOR COGNITIVE REHABILITATION AFTER STROKE

POSTERS: E02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Anna Bezdenezhnykh, Semen Prokopenko
FSBEI HE Prof. V.F. Voino-Yasenetsky KrasSMU MOH Russia, Department Of Nervous Diseases With A Pe-course, Krasnoyarsk, Russian Federation

Aims: The aim of the study is to compare the effectiveness of different methods for cognitive rehabilitation after stroke.
Methods: 111 patients after hemispheric stroke in the recovery period with cognitive impairments without dementia (age 40-70) were randomized into four groups. All patients received conventional rehabilitation. Patients in the computer intervention group had 10 daily training sessions with a special neuropsychological software of 40 min duration. The participants in the active control group played entertaining computer games keeping the identical regimen. The patients in the classic intervention group were individually trained by a neuropsychologist using the Luria's approach. The passive control group patients received conventional physical rehabilitation only.
Results: After the treatment period there were improvements in both intervention groups and the active control group on MoCA, MMSE, FAB. In the passive control group only the increase of attention was observed on the Shulte's table test. The increase of IADL was found in the classic and computer intervention groups. Improvements of cognitive functions in the computer intervention group were significantly better than in the control groups and there were some advantages compared with the classic intervention group. In the classic intervention group significant improvements were observed compared to the passive control (ΔMMSE 8 %, ΔFAB 14 %, ΔMoCA 17 %). Effectiveness of cognitive functions restoration in the active control was statistically insignificant compared to the passive control ($p>0,05$). Considering functional status, meaningful advantages of the classic intervention group were found in comparison to other groups (IADL 28%).
Conclusions: The computer cognitive training and the classic neuropsychological approach are both effective methods for post stroke cognitive rehabilitation. Entertaining computer games probably increase the attention but their effectiveness is insignificant compared to the passive control.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1254 / #1205

Poster Topic: *Theme E : Vascular Diseases / E02. Therapeutic Targets, Mechanisms for Treatment*

ALLEVIATING ALZHEIMER'S PATHOLOGY IN A RAT MODEL THROUGH ORAL SOLUBLE EPOXIDE HYDROLASE INHIBITION

POSTERS: E02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Fan Fan[1], Jane Border[2], Chengyun Tang[1], Huawei Zhang[2], Xing Fang[2], Seung Min Shin[3], Hongwei Yu[3], Bruce Hammock[4], Richard Roman[2]
[1]Augusta University, Physiology, Augusta, United States of America, [2]University of Mississippi Medical Center, Pharmacology, MS, United States of America, [3]Medical College of Wisconsin, Anesthesiology, Milwaukee, United States of America, [4]University of California - Davis, Entomology & Ucd Comprehensive Cancer Center, Davis, United States of America

Aims: Objectives. Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) pose a global healthcare crisis with complex mechanisms. Genome-wide studies reveal AD-associated SNPs in soluble epoxide hydrolase (sEH). Elevated sEH levels occur in AD/ADRD humans and animal models. sEH inhibition enhances cognition and neuroprotection in AD mice. This study investigates the impact of sEH inhibition on cerebral vascular function and AD pathology in a rat model.
Methods: Methods. The translational potential of sEH inhibition was evaluated using TgF344-AD rats. These rats were administered orally TPPU, a sEH inhibitor, at 1 mg/kg/day via their drinking water for three months. Various parameters were assessed, including cognitive function using an eight-arm water maze, cerebral vascular function through myogenic response of the middle cerebral artery using a pressure myography, cerebral blood flow autoregulation using laser-Doppler flowmetry, amyloid plaques examined via MOAB antibody and Congo Red staining, and neurodegeneration assessed through Nissl staining.
Results: Results. TPPU treatment rescued impaired learning and memory in AD rats. The myogenic responses of the middle cerebral artery and cerebral blood flow autoregulation were impaired in AD rats and were normalized with TPPU. TPPU significantly reduced amyloid plaques in the cortex and hippocampus. Neuronal counts in the hippocampus increased in TPPU-treated AD rats (86.91 ± 3.71 vs. 64.57 ± 3.92).
Conclusions: Conclusions. These results underscore the potential of chronic sEH inhibition as a multifaceted therapeutic approach for AD/ADRD. By enhancing cognition, restoring cerebrovascular functions, reducing neurodegeneration, and mitigating amyloid plaque formation in AD rats, sEH inhibition emerges as a promising avenue for addressing the challenges posed by AD/ADRD. Further research and clinical exploration of sEH inhibition promises to advance our understanding and treatment of this pressing healthcare concern.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1255 / #1573

Poster Topic: *Theme E : Vascular Diseases / E02. Therapeutic Targets, Mechanisms for Treatment*

LIPIDIZED PRRP ANALOG EXHIBITS A NEUROPROTECTIVE EFFECT IN SHRSP RATS

POSTERS: E02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Silvie Hojna[1], Jaroslav Kuneš[2], Lenka Maletínská[3], Lucia Mrazikova[3]
[1]Czech Academy of Sciences, Institute Of Fhysiology, Prague, Czech Republic, [2]Institute of Physiology, Experimental Hypertension, Prague, Czech Republic, [3]IOCB CAS Prague, Biochemistry And Molecular Biology, Prague, Czech Republic

Aims: Stroke-prone spontaneously hypertensive rats (SHRSP) are an animal model of essential hypertension with a high incidence of brain stroke and other marks of microbleeding which appear also in patients and lead to dementia. Incidence and sizes of brain lesions are known to relate to the age and neuroinflammation. Recently, neuropeptides regulating food intake were proposed for treatment of neurodegenerative disorders. One of them, palmitoylated analog of prolactin-releasing peptide (Palm^{11}-PrRP31), is a novel modified anorexigenic neuropeptide with a potential neuroprotective effect.
Methods: Six months old SHRSP rats were treated with Palm^{11}-PrRP31 (5 mg/kg ip.) for 8 weeks. Age-matched, not treated Wistar-Kyoto (WKY) rats were used as controls. Acute phase and late phase of peripheral inflammation were tested using CRP ELISA kit, MCP-1 ELISA kit respectively. The level of astrogliosis was determined by immunohistochemical (IHC) analysis using astrocyte marker glial fibrillary acidic protein (GFAP).
Results: Hypertophic heart and kidney of both groups of SHRSP rat confirmed developed hypertension. Neither experimental group showed any marks of peripheral inflammation as well as brain microbleeding. On the other hand, we were able to prove, that SHRSP rats at the age of 8 months have significantly increased positive GFAP labelling in the cerebral cortex and even more in the hippocampus compared to WKY rats. This astrogliosis was improved by treatment with Palm^{11}-PrRP31. The intervention also significantly decreased the body weight gain of SHRSP rats compared to not treated animals.
Conclusions: Even though 8 months old SHRSP animals did not developed any brain lesions, astrogliosis in the brain cortex and in the hippocampus was set up. Our study indicate that Palm^{11}-PrRP31 can improve the neuroinflammation. Exact mechanism must be elucidated.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1256 / #1576

Poster Topic: *Theme E : Vascular Diseases / E02. Therapeutic Targets, Mechanisms for Treatment*

BIOMARKER AND EDEMA ATTENUATION IN INTRACEREBRAL HEMORRHAGE (BEACH): A PHASE 2A PROOF-OF-CONCEPT STUDY OF AN ANTI-NEUROINFLAMMATORY SMALL MOLECULE DRUG CANDIDATE

POSTERS: E02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Linda Van Eldik[1], Wendy Ziai[2], Lauren Sansing[3], Daniel Hanley[2]
[1]University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America, [2]Johns Hopkins University, Bios Clinical Trials Coordinating Center, Baltimore, United States of America, [3]Yale University, Neurology, New Haven, United States of America

Aims: Patients with acute spontaneous intracerebral hemorrhage (ICH) develop secondary neuroinflammation and cerebral edema that can further damage the brain. Preclinical studies in acute brain injury models have shown that the investigational drug candidate, MW01-6-189WH (MW189), decreases neuroinflammation and cerebral edema and improves functional outcomes. MW189 was also safe and well tolerated in phase 1 clinical trials in healthy adults. Therefore, we designed the first-in-patient exploratory trial to determine safety and tolerability of MW189 in acute ICH patients, identify trends in potential mitigation of neuroinflammation and cerebral edema, and assess effects on functional outcomes.
Methods: The **B**iomarker and **E**dema **A**ttenuation in Intra**C**erebral **H**emorrhage (BEACH) trial is a first-in-patient phase 2a, proof-of-concept study of MW189 in patients with ICH. This multicenter, prospective, randomized, double-blind study will enroll 120 non-traumatic ICH participants, with an anticipated average age in their mid-60s and substantial numbers of individuals with cerebral small vessel disease and cerebral amyloid angiopathy. Patients will be randomly assigned 1:1 to receive intravenous MW189 (0.25 mg/kg) or placebo (saline) within 24 hours of symptom onset and every 12 hours for up to 5 days or until hospital discharge.
Results: The trial is actively enrolling participants. The primary outcome is all cause-mortality within 7 days post-randomization between treatment arms. Secondary endpoints include all-cause mortality at 30 days, perihematomal edema volume after symptom onset, adverse events, vital signs, pharmacokinetics of MW189, and inflammatory cytokine concentrations in plasma (and cerebrospinal fluid if available). Other exploratory endpoints are functional outcomes collected on days 30, 90, and 180.
Conclusions: BEACH will provide important information about the utility of targeting neuroinflammation in ICH and will inform the design of future larger trials of acute CNS injury.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1257 / #2213

Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

QUANTITATIVE ANALYSIS OF WHITE MATTER NEUROIMAGING BIOMARKERS IN A US CADASIL CONSORTIUM

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

H. Bockholt[1], Bradley Baker[1], Nicholas Pasley[1], Jordan Clemsen[1], Laura Eisenmenger[2], David Liebeskind[3], Michael Geschwind[4], Vince Calhoun[1], Jane Paulsen[5]
[1]Tri-Institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, and Emory University, Neuroinformatics, Atlanta, United States of America, [2]University of Wisconsin-Madison, Radiology, Madison, United States of America, [3]University of California, Los Angeles, Neurology, Los Angeles, United States of America, [4]University of California, San Francisco, Neurology, San Francisco, United States of America, [5]University of Wisconsin-Madison, Neurology, Madison, WI, United States of America

Aims: This study seeks to identify white matter neuroimaging biomarkers within a US-based CADASIL consortium. CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a notable genetic small vessel disease. Accurately delineating its neuroimaging biomarkers proves critical for early diagnosis, progression assessment, and targeted intervention strategies.
Methods: The investigation encompasses a cohort of 120 NOTCH3 positive patients: 50 non-symptomatic and 70 symptomatic. For comparative analysis, 5 family controls are also included. The study employs a range of neuroimaging modalities to assess white matter lesions, lacunes, enlarged perivascular spaces, microbleeds, and altered diffusion characterized by the peak width of skeletonized mean diffusivity (PSMD). Additionally, it examines alterations in both functional and structural connectivity, emphasizing changes within the basal ganglia circuits.
Results: Preliminary data reveal distinct white matter pathology patterns between symptomatic and non-symptomatic groups. Through this technical exploration, a set of definitive neuroimaging markers is being established.
Conclusions: These findings aim to advance the understanding of CADASIL, potentially refining diagnostic criteria and guiding effective clinical management.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1258 / #2393

Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

PLASMA VEGF-A AND PLGF IMPACT LONGITUDINAL TAU AND COGNITION IN PRECLINICAL ALZHEIMER'S DISEASE

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

Hyun-Sik Yang[1], Wai-Ying Wendy Yau[1], Becky Carlyle[2], Bianca Trombetta[2], Zahra Shirzadi[2], Aaron Schultz[2], Jennifer Rabin[2], Jeremy Pruzin[2], Rudolph Tanzi[2], Keith Johnson[3], Reisa Sperling[1], Steven Arnold[2], Jasmeer Chhatwal[2]
[1]Brigham and Women's Hospital, Neurology, Cambridge, United States of America, [2]Massachusetts General Hospital, Neurology, Boston, United States of America, [3]Massachusetts General Hospital, Harvard Medical School, Department Of Radiology, Boston, United States of America

Aims: Vascular dysfunction is increasingly recognized as an important contributor to the pathogenesis of Alzheimer's disease. Alterations in vascular endothelial growth factor (VEGF) signaling have been implicated as potential mechanisms, though the specific impacts of VEGF pathway dysregulation in preclinical Alzheimer's disease remain to be elucidated.
Methods: We examined VEGF family protein levels (VEGF-A, VEGF-C, VEGF-D, PlGF, and FLT1) in plasma from 320 older adults participating in the Harvard Aging Brain Study, a cohort of individuals who were cognitively unimpaired at baseline and followed longitudinally for up to 12 years. Using linear mixed effects models, we examined the interactive effects of baseline plasma VEGF proteins and amyloid PET burden (C11-Pittsburgh Compound-B PET) on longitudinal cognition (Preclinical Alzheimer Cognitive Composite-5) and neocortical tau accumulation (F18-Flortaucipir PET).
Results: Lower VEGF-A and higher PlGF were associated with greater prospective cognitive decline in individuals with elevated amyloid, i.e. those on the Alzheimer's disease continuum. Similarly, lower VEGF-A and higher PlGF were associated with accelerated longitudinal tau accumulation in this population. The effects of VEGF-A and PlGF on tau and cognition remained similar after adjusting for cardiovascular risk score or white matter hyperintensity volume.
Conclusions: Our findings implicate low VEGF-A and high PlGF in accelerating early neocortical tau pathology and cognitive decline in preclinical Alzheimer's disease. Additionally, our results underscore the potential of these minimally-invasive plasma biomarkers to inform the risk of Alzheimer's disease progression in the preclinical population. Lastly, these results highlight the VEGF pathway as a potential therapeutic target to delay or prevent the onset of cognitive decline, either alone or in combination with anti-amyloid or traditional vascular risk reduction therapies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1259 / #528

Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

SUBCLINICAL CORONARY ATHEROSCLEROSIS AND ITS EFFECTS ON COGNITIVE, BLOOD, AND NEUROIMAGING MARKERS IN COGNITIVELY HEALTHY ADULTS

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

Sofia Marcolini, Ingeborg Frentz, Jaime Mondragon, Peter De Deyn
University Medical Center Groningen, Neurology, Groningen, Netherlands

Aims: Atherosclerosis is related to a higher risk of dementia and cognitive decline. We aim to individuate individuals at high risk of cognitive decline using different biomarkers.
Methods: 280 cognitively healthy individuals of mean age 68.05 (SD=8.57), education 13.58 (SD=3.80) years, 42% females, were recruited through the Lifelines study. All participants underwent nonenhanced cardiac computed tomography scanning to obtain a coronary artery calcium score, a proxy of low (scores of 0) or high (scores >300) subclinical coronary atherosclerosis. Participants were administered cognitive and behavioural tests; serum blood biomarkers for inflammation (IL-1beta, IL-6, TNF-alpha, CRP) and Alzheimer's disease (amyloid-β40, amyloid-β42, NfL, p-tau181, GFAP) were collected. Finally, extensive brain magnetic resonance imaging (MRI) data was acquired to assess cerebrovascular function. Analysis of covariance was used to compare the groups; MRI data is currently being analyzed.
Results: After correcting for age and sex, groups differed only in GFAP serum levels (p=0.02) with the high coronary artery calcium score group having lower GFAP values compared to the low coronary artery calcium score. The group with high coronary artery calcium also showed worse quality of life (p=0.03) and worse verbal fluency (p=0.04) compared to the low coronary artery calcium group. Cerebral blood flow data, assessed with multiple post-labeling delayed vessel-encoded arterial spin labeling imaging, has been pre-processed, group comparisons are currently being run, together with white matter lesion quantifications.
Conclusions: These preliminary results suggest that subclinical coronary atherosclerosis might affect some cognitive functioning domains and an Alzheimer's disease marker. How these variables relate to each other is being further studied. The ongoing analysis of cerebral blood flow and other small vessel disease markers will help us further understand the relationship between these variables and the underlying mechanisms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1260 / #2318

Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

THE IMPACT OF CEREBRAL WHITE MATTER LESIONS ON COGNITIVE FUNCTION IS ASSOCIATED WITH BRAIN VOLUME AND ALZHEIMER'S DISEASE BIOMARKER STATUS

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

Sho Miki[1], Shuko Takeda[2,3], Tsuneo Nakajima[1], Sho Yamamoto[1], Naoki Hayakawa[1], Yoshinobu Kisino[1], Shin Teshirogi[1], Momoko Ookawara[1], Yuki Ito[2,3], Nanami Sugihara[2], Kunihiro Miki[2], Yoichi Takami[1], Yasushi Takeya[1,4], Koichi Yamamoto[1], Hiromi Rakugi[1], Ryuichi Morishita[2]
[1]Graduate school of medicine, Osaka University, Geriatric And General Medicine, Suita, Osaka, Japan, [2]Graduate school of medicine, Osaka University, Department Of Clinical Gene Therapy, Suita, Osaka, Japan, [3]Osaka Psychiatric Research Center, Osaka Psychiatric Medical Center, Hirakata, Osaka, Japan, [4]Graduate School of Medicine, Osaka University, Division Of Health Sciences, Suita, Osaka, Japan

Aims: Cerebral white matter lesions (WML) are known to affect the severity of cognitive impairment in patients with dementia. Recent studies have suggested that there is a diversity in the impact of WML on cognitive function depending on patients' brain volume or neuropathological background. In this study, we investigated the correlations between WML and cognitive scores in subgroups stratified based on brain volume and Alzheimer's disease (AD) biomarker status.
Methods: Elderly patients with dementia and MCI at Osaka University Hospital (n = 441) underwent brain MRI, a neuropsychological assessment (MMSE), and cerebrospinal fluid (CSF) biomarker testing. BAAD (Brain Anatomical Analysis using Diffeomorphic deformation) software was used to quantitatively determine the brain volume and WML. Then, patients were divided into one of three subgroups based on the severity of brain atrophy; minimal atrophy ($z < 1$, n = 164), mild atrophy ($1 \leq z < 2$, n = 147), and moderate atrophy ($2 \leq z$, n = 130). CSF p-tau/Aβ42 ≥ 0.087 was regarded as a positive biomarker for AD.
Results: In the subgroup with minimal atrophy, WML volumes were negatively correlated with MMSE scores in both AD biomarker-positive ($r = -0.17$) and -negative ($r = -0.27$) patients with statistical significance ($p < 0.01$, Spearman). In the mild atrophy subgroup, no significant correlations were observed in either AD biomarker population. In the moderate atrophy subgroup, a significant correlation was observed in the AD biomarker-negative patients ($r = -0.32$, $p < 0.05$, Spearman).
Conclusions: The impact of WML on cognitive function can be affected by the severity of brain atrophy and a patient's AD biomarker status.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1261 / #964

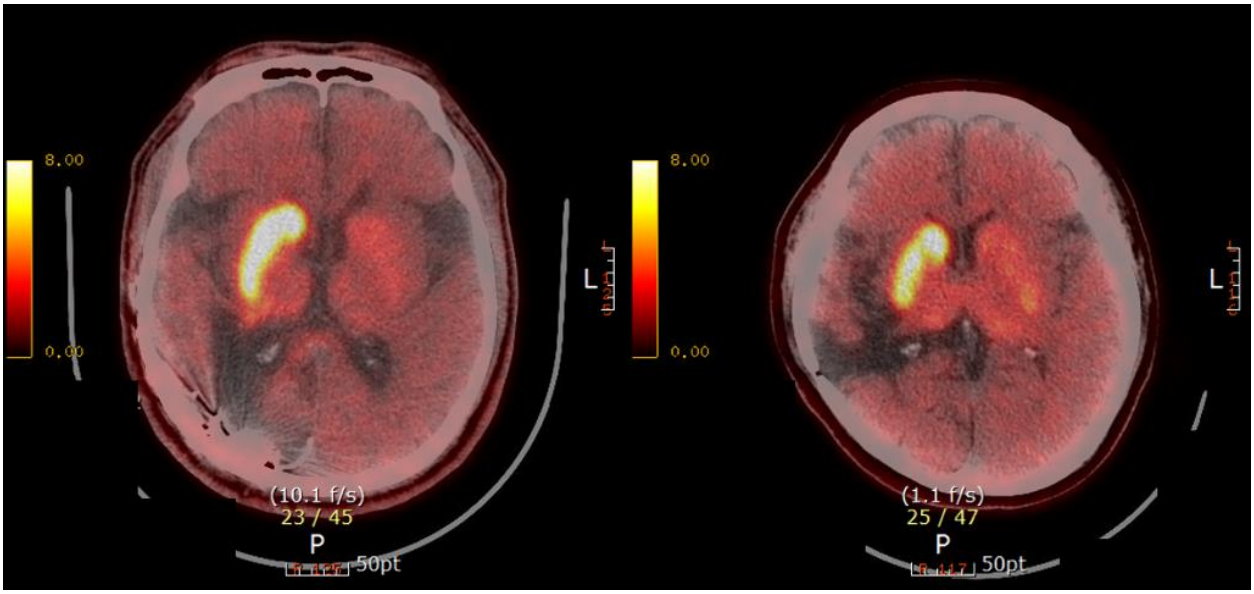
Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

2 CASES OF KERNOHAN'S NOTCH HEMIPARKINSONISM AND HOLME'S TREMOR

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

Eungseok Oh
Chungnam National University Hospital, Neurology, Daejeon, Korea, Republic of

Aims: We experienced the two patients who showed hemiparkinsonism and Holme's tremor after intracerebral hemorrhage (ICH) due to spontaneous rupture of arteriovenous malformation (AVM). Dopamine transporter images of them were nearly non-visible at the unilateral ICH area. Therefore, we report the Kernohan's notch injury and pathomechanism of unilateral dopamine damage.
Methods: We retrospectively review the dopamine transporter images of hemiparkinsonism and Holms' tremor patients to evaluate the relationship between dopamine depletion and parkinsonism and tremor. Among them, two patients showed severe unilateral dopaminergic deficit (nearly not showing any dopamine uptake) and contralateral Holme's tremor and parkinsonism. Their symptoms elicited after large ICH due to AVM.
Results: One patient showed hemiparkinsonism on his right arm and leg and Holme's tremor on his right arm. This symptom occurred after 11 months of large lobar ICH on Rt parietal occipital area and he operated craniectomy and hematoma evacuation, and then AVM embolization was done. He complained of dizziness and clumsiness of his right arm and leg moreover, an uncontrolled tremor that was wax and wane. His symptoms were not well controlled with levodopa, beta-blocker, primidone, levetiracetam, and rivotril. He showed only right-side dopamine uptake on FP-CIT PET (image 1). Another patient showed Holme's tremor without parkinsonism on her right arm and leg. She also injured spontaneous ICH on the right temporoparietal area due to AVM, and a craniotomy was done. She showed only right-side dopamine uptake on FP-CIT PET (image 1). Her symptoms were very well controlled with low-dose levodopa and
levetiracetam.



Conclusions: Kernohan notch injury caused by acute large hemorrhage such as midline shifted lesions. It caused damage to the contralateral dopaminergic tract and then caused contralateral Holme's tremor or hemiparkinsonism.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1262 / #1800

Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

A MODERN APPROACH TO THE DIAGNOSIS AND TREATMENT OF COGNITIVE DISORDERS IN HYPERTENSIVE DISEASES.

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

Raykhon Rasulova[1], Satima Kuranbaeva[2]
[1]Termiz branch of Tashkent Medical Academy, Neurology, Tashkent, Uzbekistan, [2]Tashkent Medical Academy, Neurology, Tashkent, Uzbekistan

Aims: to determine the level of cognitive impairment in hypertension and determine the modern treatment measure.
Methods: The research is based on the examination data of 48 hypertensive patients (12 men 25%, 36 women 75%) of different age, gender, education, profession. The patients in the study underwent a clinical and neurological examination taking into account the level of cognitive impairment using outpatient questionnaires, brain MRI and scales MMSE, clock drawing test, MOCA. Choline alfoscerate was recommended for patients with moderate cognitive impairment.
Results: Before treatment, the level of cognitive impairment in patients was 22±1.8 points on the MMSE scale. According to the examination of the clock drawing test, patients scored 6±1.0 points, nodement cognitive impairment, i.e. "forehead-subcortical" type of cognitive impairment was detected in 32 patients (66.7%). According to the MOCA scale, the indicators of cognitive impairment were 22±2.2 points. According to the results of the examination and observation, patients with hypertension were treated with choline alfoscerate in 38 of the patients in the examination, in addition to slowing down the process of cognitive impairment and increasing work ability.
Conclusions: Long-term therapy of patients with hypertension with choline significantly improved cognitive functions and improved the quality of life of patients of all age groups, increased work ability.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1263 / #494

Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

EFFECT OF THE MIND+SOUL DIET INTERVENTION ON CARDIOMETABOLIC BIOMARKERS RELATED TO ALZHEIMER'S DISEASE AMONG OLDER AFRICAN AMERICANS

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

Ashley Shaw[1,2], Eric Vidoni[2], Janette Berkley-Patton[3], Debra Sullivan[4], Jill Morris[2], Jeff Burns[2]
[1]University of Kansas Medical Center, 2. university Of Kansas Alzheimer's Disease Research Center, Fairway, United States of America, [2]University of Kansas Medical Center, Department Of Neurology, Kansas City, United States of America, [3]University of Missouri-Kansas City, 4. Department Of Biomedical And Health Informatics, Kansas City, United States of America, [4]University of Kansas Medical Center, Dietetics And Nutrition, Kansas City, United States of America

Aims: Objective: Cardiovascular and metabolic disease are associated with an increased risk of Alzheimer's disease (AD), which disproportionately affect African Americans (AA) who are 2 to 3 times more likely to develop AD. Emerging evidence indicates that up to 50% of AD cases are a result of modifiable cardiovascular and metabolic risk factors, therefore prevention strategies may play a critical role in reducing AD risk for AAs. The overall objective of the study was to examine the effect of an adapted brain healthy diet (MIND+SOUL) on cardiometabolic risk among older AAs at risk for AD. The primary aim was to assess the response of cardiometabolic biomarkers (body composition, lipid profile, glucose metabolism, and inflammation) for AD to the MIND+SOUL diet intervention.
Methods: Methods: We conducted a single arm 12-week culturally tailored dietary intervention (MIND+SOUL) in 3 waves that consisted of a total of 30 cognitively normal older AAs, aged 55 years and older who had one or more cardiovascular risk factor. The MIND+SOUL intervention encompassed dietary education classes, health coaching sessions, and weekly groceries. Cardiometabolic risk profile assessments were collected at baseline and at the 12-week mark.
Results: Results: A total of 28 AAs completed the intervention with a retention rate of 93%. From baseline to 12 weeks, improvements in cardiometabolic risk were observed in body mass index (p=0.249) and glucose (p=0.456).
Conclusions: Conclusion: Results from this study indicate the MIND+SOUL intervention is feasible for older AA and changes in cardiometabolic risk from baseline to 12 weeks differ, but are not significant. Also, results from this study will inform the development of a R01-scale randomized control trial that will test the efficacy of the MIND+SOUL intervention among older AA across a larger geographical area.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1264 / #1317

Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

CHARACTERIZING SMALL VESSEL DISEASE IN NATIVE HAWAIIAN AND OTHER PACIFIC ISLANDERS WITH DEMENTIA: A RETROSPECTIVE PILOT STUDY

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

Michelle Trinh[1,2], Sarah Song[1], Elise Wong[1], Megan Baldemor[1], Tyson Wu[1], Julia Jahansooz[1,2], Edward Weldon Iv[1,2], Anson Lee[1,2], Chathura Siriwardhana[2], Yone-Kawe Lin[2], Jason Viereck[1], Kore Liow[1,3], Enrique Carrazana[1]
[1]Hawaii Pacific Neuroscience, Memory Discovery Center Alzheimer's Disease Research Unit, Honolulu, United States of America, [2]University of Hawaii, John A. Burns School Of Medicine, Honolulu, United States of America, [3]John A. Burns School of Medicine, University of Hawaii, Department Of Quantitative Health Science, Honolulu, United States of America

Aims: Small vessel disease (SVD), a major cause of age-related cognitive decline, affects small cerebral blood vessels, leading to cerebral hypoperfusion. Native Hawaiians and other Pacific Islanders (NHOPI) are reported to have higher rates of vascular risk factors of SVD, such as hypertension. This study aims to characterize the prevalence and severity of SVD in NHOPI dementia patients compared to their Caucasian and Asian counterparts.
Methods: This retrospective chart review analyzed data from dementia patients ≥ 18 years old with a brain MRI and MMSE score between 23-27. Each NHOPI patient was matched with a Caucasian and Asian patient based on age, sex, and MMSE score. Patient charts were reviewed for demographics, comorbidities, medications, and SVD MRI findings at time of presentation of memory concerns.
Results: Overall, 108 patients were included, with 36 patients in each racial group, a mean patient age of 72.1 years, and 72 (66.7%) females. NHOPI patients had a higher BMI ($p<0.001$) and higher rates of hypertension ($p=0.024$), diabetes mellitus ($p=0.020$), and coronary artery disease ($p=0.026$). NHOPI had higher rates of reporting attention deficits as a symptom of dementia ($p=0.015$). However, there were no significant differences in prevalence or severity of white matter lesions, subcortical infarcts, or brain atrophy among the racial groups.
Conclusions: NHOPI patients were significantly associated with higher rates of vascular risk factors and showed differences in presentation of dementia. Further investigation is needed to identify potential preventative targets and improve risk predictions for individuals with SVD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1265 / #175

Poster Topic: *Theme E : Vascular Diseases / E03. Imaging, Biomarkers, Diagnostics*

DIETARY INTERVENTION WITH CALORIC RESTRICTION OR ITS MIMETIC RESVERATROL ALTERS RELATIVE CEREBRAL BLOOD FLOW IN WILD TYPE AND TGF344-AD RATS

POSTERS: E03. IMAGING, BIOMARKERS, DIAGNOSTICS

Judith Van Rooij[1,2], Tamara Vasilkosvka[1,2], Johan Van Audekerke[1,2], Ignace Van Spilbeeck[1,2], Monica Van Den Berg[1,2], Lauren Kosten[2], Daniele Bertoglio[1,2], Marleen Verhoye[1,2]
[1]uNeuro Research Centre of Excellence, University of Antwerp, Faculty Of Pharmaceutical, Biomedical And Veterinary Sciences, Antwerpen, Belgium, [2]Bio-Imaging lab, University of Antwerp, Pharmaceutical, Biomedical And Veterinary Sciences, Wilrijk, Belgium

Aims: Alzheimer's disease (AD) is a neurodegenerative disorder hallmarked by amyloid-beta and cerebral amyloid angiopathy, which influences vascular reactivity and neurovascular coupling. Caloric restriction (CR) or its mimetic resveratrol (Rsv) have shown to improve vascular health and could therefore possibly delay neurodegeneration in AD. To address their potential vascular effects, we assessed relative cerebral blood flow (rCBF) in healthy (WT) and TgF344-AD (Tg) rats under normal and hypercapnic conditions, using pseudo-continuous Arterial Spin Labeling (pCASL) MRI. Our aim was to establish whether dietary intervention 1) alters rCBF and 2) could possibly preserve healthy vascular physiology in a rat model of AD.
Methods: Graphical abstract of study design and data acquisition:

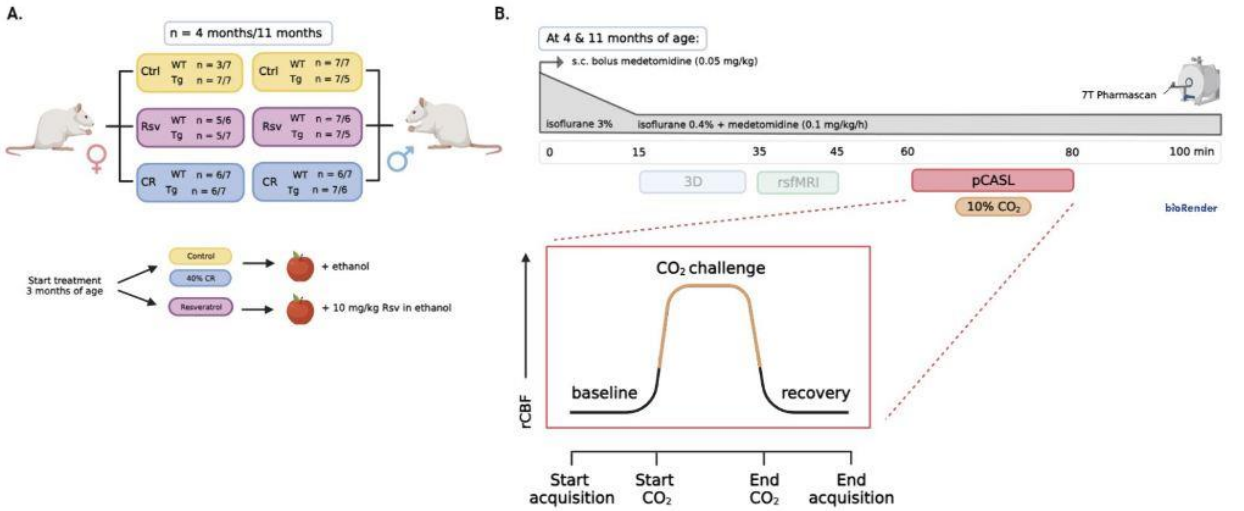


Fig. 1: (A.) TgF344-AD rats and wild-type littermates were randomly divided in 3 treatment groups, with dietary intervention starting at 3 months of age. Resveratrol was supplemented using dried apple chips, with control and CR groups recieving apple chips with vehicle (ethanol) only (B.) Animals were subjected to perfusion MRI scans at 4 and 11 months of age after which data were processed to extract rCBF at baseline (b) hypercapnic (ch) and recovery (r) conditions.

Results: Whole brain analysis revealed differences in rCBF in males, while none of these differences were observed in females (Fig.2A). At baseline conditions, CR lowered rCBF compared to control and Rsv treated male rats (Fig.2B). In addition, we observed a lowered rCBF in aged Tg male rats, different from their age matched WT controls (Fig.2C). The observed lowering of rCBF due to aging or CR treatment, persisted during the CO2 challenge (Fig.2D), where additionally, Rsv Tg males showed higher rCBF, compared to their age matched Tg controls. During the recovery phase, CR lowered rCBF compared to Rsv treated male rats (Fig.2E), similar to the effect observed at baseline.

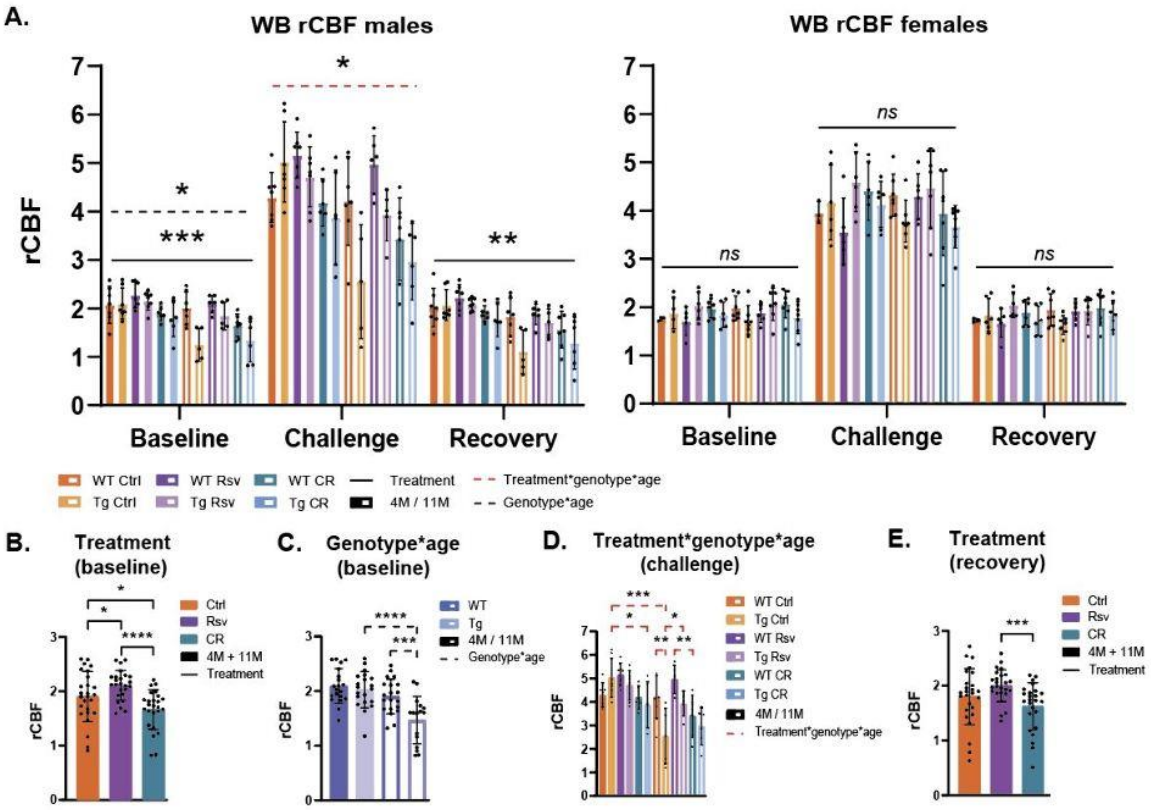


Fig. 2: Whole-brain (WB) rCBF (A.) for both male and female rats, wildtype (WT) and TgF344-AD (Tg) at both 4 (filled bars) and 11 months (open bars) of age for the three conditions. Post-hoc results of the main and interaction effects in the males are shown in B.- E. Groups means ± SD are presented together with the individual subjects data (dots). The asterisks indicate significant differences based on analyses after linear mixed model analysis with corresponding post-hoc testing: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Conclusions: In this MRI study, we provide evidence of differences in blood flow between sexes as well as a contrasting change of rCBF in response to dietary intervention using CR or Rsv in WT- and TgF344-AD rats. To further unravel the difference between these treatments in this model of AD, ongoing work is focusing on the molecular underpinning of mechanisms resulting in the observed rCBF responses.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1266 / #161

Poster Topic: *Theme E : Vascular Diseases / E04. Genetics, Epidemiology*

MAPPING OF PARKINSON'S DISEASE AND PARKINSONIAN SYNDROMES IN THE TROPICS: 94 CASES OBSERVED AT CONAKRY UNIVERSITY HOSPITAL

POSTERS: E04. GENETICS, EPIDEMIOLOGY

Souleymane M'Bara Diallo[1], Mariama Boubacar Diallo[2], Mohamed Lamine Toure[1], Amara Cisse[1]
[1]Hopital National Igance Deen, Neurology Department, Conakry, Guinea, [2]Hopital National Igance Deen, Neurology, Conakry, Guinea

Aims: In tropical environments, the diagnostic criteria for Parkinson's disease established by MDS remain an essential tool in the clinical approach despite the fact that family forms remain difficult to establish. We report 94 cases of the Guinean geographic distribution of Parkinson's disease and Parkinsonian syndromes over a 2-year period for epidemiological, clinical and prognostic re-evaluation.
Methods: This was a 2-year prospective descriptive study from November 1, 2020, to October 30, 2022, conducted at the Conakry Neurology Department, which is the country's only centre for the management of neurological diseases and Parkinsonian syndromes. The diagnosis of Parkinson's disease was based on the use of the UPDRS scale from the first consultation. Parkinsonian syndromes were identified by clinical semiology and MRI data.
Results: The survey involved 94 patients, including 12 cases of Parkinson's disease with a male predominance of 56.26% with a sex ratio of 1.29. Clinical symptomatology was dominated by tremors, followed by hypertonia and akinesia at 95.74%, 94.68% and 34.04, respectively.We noted an improvement in the quality of life of our patients with a frequency of 45% during our study. The impact of the environment was assessed because more than 62% was identified in Lower Guinea in the region where bauxite mining is open-cast by mining companies suggesting an interaction between the environment and Parkinsonian syndromes.
Conclusions: It appears that Parkinsonian syndromes are identified in Lower Guinea where the exploitation of bauxite is open-cast, which can evoke a major role in relation to the regions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1267 / #1483

Poster Topic: *Theme E : Vascular Diseases / E04. Genetics, Epidemiology*

ALZHEIMER'S DISEASE AND CAROTID ARTERY PLAQUE: A MENDELIAN RANDOMIZATION STUDY

POSTERS: E04. GENETICS, EPIDEMIOLOGY

Devendra Meena[1], Jian Huang[1], Marie-Joe Dib[2], Paul Elliot[1], Abbas Dehghan[1], Ioanna Tzoulaki[1]
[1]Imperial College London, Epidemiology And Biostatistics, London, United Kingdom, [2]Hospital of the University of Pennsylvania,, Division Of Cardiovascular Medicine, Philadelphia PA, United States of America

Aims: To explore the potential causal relationship between Alzheimer's disease and carotid artery plaque using a two-sample Mendelian randomization approach
Methods: We performed a Mendelian randomization (MR) study to investigate the potential causal effect of Alzheimer's disease (AD) on carotid artery plaque (CAP). Single nucleotide polymorphisms (SNPs; P<5e-8) for AD and CAP were obtained from the International Genomics of Alzheimer's Project (IGAP; n=63926 discovery sample, 18,845 replication and 11,666 post-replication) and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium and the UCL-LSHTM-Edinburgh-Bristol (UCLEB) (n=48,434) consortium, respectively. Inverse-variance weighted (IVW) was employed as the primary analysis and weighted median, MR-Egger, MR-PRESSO, and MR-Lasso as sensitivity analyses. In addition, we used Steiger filtering to identify SNPs that explain more variance in the exposure (AD) than the outcome (CAP).
Results: We found that genetically predicted AD was causally associated with CAP (β_{IVW}=0.10, 95%CI 0.03 to 0.1, P<0.0001). Sensitivity methods including weighted median, MR-Egger, and MR-Lasso showed consistent direction of effect with IVW. A multivariable MR of AD, high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) on CAP showed that AD was not associated with CAP after adjusting for HDL and LDL, with strong evidence of LDL leading to higher CAP (β_{IVW}=0.35, 95%CI 0.25 to 0.44, P<0.0001).
Conclusions: Our study suggests AD as a potential causal risk factor for CAP.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1268 / #2409

Poster Topic: *Theme E : Vascular Diseases / E05. Cell, Molecular and Systems Biology*

EARLY PLASMA YKL40 LEVEL IS ASSOCIATED WITH 3-MONTH FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE PATIENTS TREATED WITH ENDOVASCULAR THERAPY

POSTERS: E05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Ada Boutelier[1], Jean Philippe Desilles[2], Claire Paquet[3], Mikael Mazighi[2], Benoit Ho Tin Noe[4]
[1]Hopital Fernand Widal, Cognitive Neurology, Paris, France, [2]Rothschild Foundation hospital, Interventionnal Radiology, paris, France, [3]Universite Paris Cite, EA 4468, APHP, Hopital Broca, Memory Resource And Research Centre Of De Paris-broca, Paris, France, [4]inserm, Optimisation Thérapeutique En Neuropsychopharmacologie, paris, France

Aims: After acute ischemic stroke (AIS), more than 40% of patients with large vessel occlusion remain disabled at 3 months despite successful reperfusion therapies like intravenous thrombolysis and endovascular therapy (EVT). Glycoprotein YKL40 is a biomarker of astrocytic and microglial activation. It is elevated in plasma in numerous neurodegenerative disorders but also in AIS. We investigated dynamics of microglial activation at hyperacute phase of an AIS and tested the hypothesis that elevation of YKL40 was predictive of functional outcome at 3 months.
Methods: Monocentric prospective study included patients treated with EVT, for whom 3 blood samples (before, within 1-h, 24-h post-EVT) were drawn to measure plasma YKL40 concentration as a marker of microglial activation. Excellent outcome was defined as a modified Rankin scale (mRS) between 0-1 at 3 months.
Results: We included 120 patients between 2016-2020. Median NIHSS was 17 and median ASPECT score was 7. Reperfusion was achieved at a mean delay of 5h44. After three months, median mRS was 3 and 25% of patients with pre-stroke mRS< 2 had excellent outcome. We found that in patients presenting with large vessel occlusion treated by EVT, excellent clinical outcome was significantly associated with lower plasma YKL40 levels at time of stroke (before EVT and within 1h post-EVT) but not with YKL40 plasma levels at 24h post-AIS after adjustment on age, NIHSS and delay since onset.
Conclusions: Our results suggest that critical activation of microglia occurs very early in AIS course. Plasma YKL40 could a candidate predictor of the functional outcome at 3 months in AIS treated by EVT. This novel biomarker could help optimizing post-stroke care and give new insight on pathophysiology of pathological brain changes after AIS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1269 / #2009

Poster Topic: *Theme E : Vascular Diseases / E05. Cell, Molecular and Systems Biology*

DECIPHERING MOLECULAR MECHANISMS UNDERLYING BBB DYSFUNCTION IN ALZHEIMER'S DISEASE: A MULTI-OMICS SYSTEMS BIOLOGY APPROACH

POSTERS: E05. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Karunya Kandimalla[1], Zengtao Wang[1], Xiaojia Tang[2], Kevin Thompson[2], Krishna Kalari[2]
[1]University of Minnesota, Pharmaceutics And Brain Barriers Research Center, Minneapolis, United States of America, [2]Mayo Clinic, Quantitative Health Sciences, Rochester, United States of America

Aims: Time-series transcriptomics analyses have shown that insulin-signaling regulates critical blood-brain barrier (BBB) functions. Alternatively, insulin resistance triggers BBB dysfunction and exacerbates Alzheimer's progression. Our aim is to develop a mechanistic systems biology model to quantitatively describe the role of insulin signaling on BBB integrity and function and predict the impact of insulin resistance on cerebrovascular inflammation prevalent in Alzheimer's disease (AD).
Methods: A systems model incorporating multi-omics data was developed with two interrelated subsystems: insulin-signal transduction and turnover of VCAM1, a marker for cerebrovascular inflammation. Effects of time and insulin exposure on the expression of proteins/phosphoproteins were identified in BBB models *in-vitro* as well as in mouse cerebral microvasculature *in-vivo* using western blots and reverse-phase protein arrays (RPPA). Kinetic parameters were determined by fitting the model to both newly generated and previously published data, utilizing Matlab Simbiology®. The model was subsequently validated using independent datasets obtained from BBB endothelium overexpressing insulin receptors and AD transgenic mouse data. The high throughput RPPA data was incorporated into the validated model to predict insulin signal disruptions and the VCAM1 expression.
Results: As expected, insulin-signaling was triggered in a time- and dose-dependent manner in polarized BBB monolayers *in-vitro;* alternatively, VCAM1 expression was found to be reduced upon insulin exposure via PI3K/AKT/eNOS pathway. Moreover, Aβ exposure was shown to inhibit insulin signaling, but increased VCAM1 expression and the associated cerebrovascular inflammation. Moreover, the systems biology model has successfully predicted insulin-signaling disruptions and greater VCAM1 expression in the BBB endothelium upon Aβ exposure *in-vitro;* AD transgenic mice *in-vivo,* as well as in AD patients compared to normal individuals.
Conclusions: A multi-omics systems biology approach is effective in deciphering molecular mechanisms underlying BBB dysfunction in AD and metabolic syndrome.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1270 / #2951

Poster Topic: *Theme E : Vascular Diseases / E06. Animal Models*

THERAPEUTIC EFFECTS OF AR1001, A PHOSPHODIESTERASE 5 INHIBITOR, IN THE MIDDLE CEREBRAL ARTERY OCCLUSION MODEL OF STROKE IN RATS

POSTERS: E06. ANIMAL MODELS

Singh Padmanabh[1], Fred Kim[2], Ashish Kumar[1], Dong-Keun Song[1], Jai Jun Choung[2], Sae Kwang Ku[3]
[1]AriBio Co., Ltd., Brain Research Center, Seongnam-si, Korea, Republic of, [2]AriBio Co., Ltd., Management, Seongnam-si, Korea, Republic of, [3]DAEGU HAANY UNIVERSITY, Anatomy And Histology, Gyeongsan-si, Korea, Republic of

Aims: AR1001, mirodenafil, is a potent phosphodiesterase 5 (PDE5) inhibitor with blood-brain barrier permeability. AR1001 can effectively reduce Aβ and pTau levels and improve cognitive functions in Alzheimer's disease mouse models. In the present study, we investigated the effect of AR1001 in the transient and permanent middle cerebral artery occlusion (tMCAO and pMCAO) models of stroke in rats.
Methods: AR1001 was administered subcutaneously at the doses of 0.5, 1, and 2 mg/kg per day for 9 days starting 24 h after tMCAO induction or 1 mg/kg per day for 14 days starting 24, 72 or 168 h after pMCAO induction. Sensorimotor functions were evaluated using limb placing test and body swing test. For cognitive functions the time and distance to reach the escape platform were evaluated using the Morris water maze test. Brain morphological damage was evaluated by measuring the infarct volume, and the number of cleaved caspase-3 and PARP immunoreactive cells.
Results: Sensorimotor dysfunctions and cognitive impairment were observed in tMCAO and pMCAO rats as compared to the sham control. Further, brain atrophy and the number of cleaved caspase-3 and PARP-immunoreactive cells were increased compared to sham control rats. AR1001 significantly attenuated the tMAO-induced sensorimotor and cognitive dysfunctions and the increased number of cleaved caspase-3 and PARP-immunoreactive cells in a dose-dependent manner with the peak efficacy at 1 mg/kg. AR1001 also demonstrated protective effects in sensorimotor and cognitive dysfunctions after pMCAO induction. Furthermore, AR1001 significantly decreased cleaved caspase-3 and PARP - immunoreactive cells in pMCAO rats, but had minimal effects on the infarct volume for both tMCAO and pMCAO rats.
Conclusions: AR1001 demonstrated protective effects in MCAO-induced mild and severe stroke rate models.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1271 / #1580

Poster Topic: *Theme E : Vascular Diseases / E06. Animal Models*

THE ROLE OF CEREBROVASCULAR PERMEABILITY IN NEURODEGENERATION DURING TRAUMATIC BRAIN INJURY

POSTERS: E06. ANIMAL MODELS

David Lominadze, Nurul Sulimai, Jason Brown
University of South Florida, Department Of Surgery, Morsani College Of Medicine, Tampa, United States of America

Aims: Traumatic brain injury (TBI) triggers a cascade of effects that cause immediate and delayed pathologies contributing to neurodegeneration and cognitive impairment. Fibrinogen is not only a marker of inflammation, but also a cause of the inflammatory responses. We previously showed that when the blood content of fibrinogen increases during mild-to-moderate TBI (m-mTBI), it results in enhanced cerebrovascular permeability. Here we investigate the effects of the increased cerebrovascular permeability and the resultant extravascular deposition of fibrinogen during m-mTBI.
Methods: M-mTBI was generated in C57BL/6 mice. The resultant extravascular deposits of fibrinogen, astrocyte activation, neurodegeneration, and the expression of nuclear factor-κB (NF-kB) were assessed by immunohistochemistry 14 days after head injury. The specific effects of fibrinogen on neurons were tested using cultured mouse brain neurons and astrocytes. Astrocyte activation, neuronal death, neuronal NF-kB expression, and the generation of reactive oxygen species (ROS) were tested using immunohistochemistry, western blot, and ELISA. Short-term memory (STM) was assessed with novel object recognition and fear conditioning tests.
Results: Fibrinogen increased cerebrovascular permeability and resulted in an increase of fibrinogen deposits in the vasculo-astrocyte interface. These effects were associated with the increased activation of astrocytes, neurodegeneration, the enhanced expression of neuronal NF-kB, the generation of ROS, and a reduction in STM in mice.
Conclusions: Our results suggest that a TBI-induced increased blood level of fibrinogen contributes to increased cerebrovascular permeability, resulting in deposits of fibrinogen in the vasculo-astrocyte interface, leading to the activation of astrocytes and neurodegeneration. Neuronal activation can be a result of the overexpression of NF-kB and the overgeneration of ROS. These effects contribute to the reduction of STM, indicating that TBI-induced increased cerebrovascular permeability has a significant effect on cognition during neuroinflammatory diseases such as TBI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1272 / #498

Poster Topic: *Theme F: Prion Diseases / F01. Disease Mechanisms, Pathophysiology*

AN INCREASE IN PRION SUBSTRAIN DIVERSITY CORRESPONDS WITH PRION STRAIN EMERGENCE

POSTERS: F01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Jason Bartz, Tess Gunnels, Taylor York, Alyssa Block, Ronald Shikiya
Creighton University, Medical Microbiology And Immunology, Omaha, United States of America

Aims: Prions are composed of PrP^{Sc}, the disease specific conformation of the host encoded prion protein. Treatment of rodents with anti-prion drugs results in the emergence of drug-resistant prion strains, suggesting prions are comprised of a dominant strain and substrains. While considerable experimental evidence supports this hypothesis, direct observation of substrains has not been observed. The objective of this study was to directly investigate if prion strains contain substrain diversity.
Methods: We investigated the presence of substrain diversity in a biologically stable hamster-adapted prion strain, DY TME and a biologically unstable hamster-adapted prion strain 139H that, following serial passage at high titer, can breakdown into a strain with a shorter incubation period. Both strains were probed for substrains by selectively reducing the abundance of the dominant strain PrP^{Sc} using either extended digestion with proteinase K or with chaotropic treatment. The remaining PrP^{Sc} was subjected to protein misfolding cyclic amplification to probe for substrains.
Results: Selective reduction of DY or 139H PrP^{Sc} using a combination of biochemical methods resulted in the emergence of strains with properties that differed from DY or 139H and were consistent with the selection criteria. Substrains identified in 139H-infected brains were similar to the strains that emerged in animals following strain breakdown.
Conclusions: The substrain selection methods occurred outside of prion formation, providing direct evidence for the preexistence of substrains. Furthermore, we hypothesize that substrains are a common feature of prions as they were identified in a stable, biologically-cloned prion strain. The identification of preexisting substrains may contribute to the ability of prions to rapidly adapt to new replication environments such as transmission to a new species or replication in the presence of anti-prion drugs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1273 / #220

Poster Topic: *Theme F: Prion Diseases / F01. Disease Mechanisms, Pathophysiology*

INCREASE IN PLASMA PTAU181 LEVELS AND DECREASE OF EXECUTIVE FUNCTIONS IN HEALTHY CARRIERS OF E200K MUTATION

POSTERS: F01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Noa Bregman[1,2,3], Tamara Shiner[2], Yifat Alcalay[4], Aya Bar-David[3], Talya Nathan[3], Mali Gana-Weisz[5], Orly Goldstein[5], Tal Glinka[5], Roy Alcalay[5], Noa Trablus[3], Gitit Kave[6], Nurit Omer[3]
[1]Tel-Aviv University, Sackler School Of Medicine, Tel Aviv, Israel, [2]Tel Aviv Medical Center, Neurology, Tel Aviv, Israel, [3]Tel Aviv Medical Center, Cognitive Neurology, Tel Aviv, Israel, [4]2Sackler School of Medicine, Tel-aviv University, tel Aviv, Israel, [5]Laboratory of biomarkers and genomic of neurodegeneration,, Tel-aviv Medical Center, Tel Aviv, Israel, [6]The Open University, Department Of Education And Psychology, Ra'anana, Israel

Aims: This study investigated the relationship between pTau181 levels in plasma, expected symptom onset, and cognitive function in healthy individuals carrying E200K mutation
Methods: Data from 48 individuals were analyzed. The number of years to expected symptom onset (at the time of data and samples collection) was calculated based on a published model. Two groups were compared: the first included individuals more than 2 years before expected onset (n=39) and the second included individuals less than 2 years from expected onset (n=9)
Results: Mean age was 54.8 years (SD=5.6) vs. 67.8 years (SD=3) ($p<0.001$), mean years of education was 14.4 (SD=1.8) vs. 12.7 (SD=3.2) ($p=0.03$), 54% vs. 78% females ($p=0.27$) for the first and second groups, respectively. ANCOVA analysis was performed to compare pTau181 levels in plasma between the two groups, with age included as a covariate. The overall model was significant, indicating that the combination of the grouping variable and age explained a significant proportion of the variance in pTau181 levels (Adjusted R-squared = 0.310). The main effect of the grouping variable was also significant, with the second group having higher pTau181 levels than the first group (1.726 pg/ml vs. 1.026 pg/ml). ANCOVA was conducted to compare cognitive function between the groups, controlling for age and years of education. No significant differences were found in MoCA scores, TMT-A, and digit span. However, TMT-B and phonemic verbal fluency showed significant differences between the groups (TMT-B z-scores were -1.55 (SD=1.8) vs. -6.7 (SD=7.3), and phonemic verbal fluency z-scores were 0.09 (SD=1.24) vs. -1.37 (SD=0.89) in the first and second groups, respectively
Conclusions: healthy carriers of the E200K mutation may exhibit increased pTau181 levels in plasma and subtle changes in executive functions prior to symptoms onset.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1274 / #1230

Poster Topic: *Theme F: Prion Diseases / F01. Disease Mechanisms, Pathophysiology*

FAITHFUL SEEDED AMPLIFICATION OF PRION STRAIN-SPECIFIC CONFORMATION TO RECOMBINANT PROTEIN

POSTERS: F01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Fei Wang[1], Victor Banerjee[1], Carla Barria[1], Damian Gorski[1], Tyler Allison[1], Nicole De Gregorio Carbonell[1], Santiago Ramirez[1], Claudio Soto[1,2]
[1]University of Texas Health Science Center at Houston, Department Of Neurology, Houston, United States of America, [2]University of Texas Health Science Center at Houston, Neurology, Houston, United States of America

Aims: Neurodegenerative disease-associated protein aggregates, such as Amyloid beta plaques and Tau tangles in AD and Lewy bodies in PD, are believed to self-propagate and spread across brain regions following the "prion-like" mechanism. Prions replicate through the template-guided conversion of the normally folded prion protein (PrP^{C}) by its misfolded, infectious form (PrP^{Sc}). Prion strains composed of PrP^{Sc} sharing identical primary sequences are known to exhibit distinguishable biological and structural properties. Using the PMCA (Protein Misfolding Cyclic Amplification) technique, it has been reported that bona fide recombinant prions can be generated using bacterially expressed recombinant PrP (recPrP) with specific cofactors, either spontaneously or in seeded reactions. However, previous efforts to faithfully propagate native prion strain properties with recPrP as substrate have failed. Here, we studied whether recPrP can serve as the substrate for efficient and faithful *in vitro* propagations of a mouse prion under specific PMCA conditions.
Methods: In a seeded PMCA reaction supplemented with anionic cofactors, 10% brain homogenate (BH) from the RML mouse prion-infected terminally ill mouse was used as the template to amplify the protease-resistant PrP species (PrP-res) from the protease-sensitive recPrP. The newly generated recPrP-res was subjected to biological characterization using wild-type mice and structural studies using cryogenic electronic microscopy (Cryo-EM).
Results: Wild-type mice infected with RML-seeded recPrP-res developed classical prion clinical signs with a very synchronized incubation time, similar to that of the RML-infected mice. Further biochemical and histopathological analyses confirmed that these animals succumbed to the RML prion disease. Cryo-EM studies provided the structural evidence for the *in vitro* replication of RML-specific strain conformation.
Conclusions: As a proof of concept, our results support the notion that seeded amplification can faithfully replicate prion conformations to recombinant proteins under defined conditions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1275 / #760

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G01. Disease Mechanisms, Pathophysiology*

SPATIAL PROTEOMICS IN COMBINATION WITH PROXIMITY-DEPENDENT BIOTIN IDENTIFICATION TO UNRAVEL DISEASE PATHWAYS IMPORTANT FOR RNF216-ASSOCIATED NEURODEGENERATIVE PROTEINOPATHY

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Lauren Versluys[1,2], Nika Schuermans[1,2], Anne Sieben[3,4,5], Pedro Ervilha Pereira[1,2], Elisabeth Mondragon Rezola[6], Marie Christine Galas[7], Ward De Spiegelaere[8], Patrick Santens[9,10], Jo Van Dorpe[11], Bart Dermaut[1,2], Elke Bogaert[1,2]
[1]Ghent University Hospital, Center For Medical Genetics, Ghent, Belgium, [2]Ghent University, Department Of Biomolecular Medicine, Faculty Of Medicine And Health Sciences, Ghent, Belgium, [3]Antwerp University Hospital, Department Of Pathology, Edegem, Belgium, [4]University Antwerp, Insitut Born-bunge, Antwerp, Belgium, [5]Ghent University Hospital, Department Of Neruology, Ghent, Belgium, [6]University Hospital Donostia, Department Of Neurology, Donostia – San Sebastián Gipuzkoa, Spain, [7]Inserm,, Umrs1172, Jparc, Alsheimer & Tauopathies, Lille, France, [8]Ghent University, Faculty Of Veterinary Medicine, Merelbeke, Belgium, [9]Ghent University, Department Of Head And Skin, Ghent, Belgium, [10]Ghent University Hospital, Department Of Neurology, Ghent, Belgium, [11]Ghent University Hospital, Department Of Pathology, Ghent, Belgium

Aims: Mutations in RNF216, an E3-ubiquitin ligase, have been identified as the genetic cause of Gordon Holmes syndrome (GHS), a rare recessive neurodegenerative disease. Various loss-of-function (LOF) mutations inside and outside the catalytic domain of RNF216 have been described. However, how mutations outside the catalytic domain result in LOF and how mutations in RNF216 give rise to neurodegeneration, remains unclear. We hypothesize that the heterogenous group of mutations result in a common distorted pathway resulting in the formation of toxic aggregates and hence neurodegeneration. Identifying these pathways is our main objective.
Methods: Like most neurodegenerative diseases RNF216 mediated neurodegeneration is associated with the abnormal protein deposits in the brain of patients. We will use spatial proteomics to unravel its associated aggregome. In addition, the interactome of both WT and mutated RNF216 will be mapped using proximity-dependent biotin identification (BioID). A comparison of the interactome and an integration with the data obtained from the aggregome experiment will shed light on the disease pathways at play.
Results: Immunohistochemical analysis showed ubiquitin-positive and p62 immunoreactive intranuclear inclusions in the neurons of the neostriatum, CA1 and CA2 of the hippocampus and aria striata. These inclusions were negative for AT8,4G8 and TDP43. Aggregates are collected using laser capture microdissection and subsequently subjected to mass-spectrometry.
Conclusions: The physiological and pathological mechanisms explored in this project hold the potential to greatly improve our understanding of GHS, shed light on novel key players in neurodegeneration, and open new avenues for a novel therapeutic target for this rare neurodegenerative disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1276 / #581

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G01. Disease Mechanisms, Pathophysiology*

ANALYSIS OF VARIANTS IN THE SIRT1 GENE PROMOTER AND SIRT1 PROTEIN CONCENTRATION ASSOCIATED WITH CIRCADIAN RHYTHM DISTURBANCES IN PATIENTS WITH PARKINSON'S DISEASE

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Jolanta Dorszewska, Thomas Piekut, Jolanta Florczak-Wyspiańska, Wiktoria Szablikowska, Izabela Korczowska-Łącka, Wojciech Kozubski
Poznan University of Medical Sciences, Department Of Neurology, Labratory Of Neurobiology, Poznan, Poland

Aims: Objectives. Parkinson's disease (PD) is a common neurodegenerative disease. It is characterized by motor and non-motor disorders. Non-motor disorders include neuropsychiatric disorders, autonomic system disorders, pain, and sleep disorders. The most common sleep disorders are sleep fragmentation/premature rising and daytime sleepiness. Despite the update of the "Parkinson's Disease Sleep Scale" (PDSS), precisely determining whether these disorders constitute a disease state and whether they are related to PD remains a significant diagnostic problem. The *SIRT1* gene product is responsible for maintaining the endogenous circadian rhythm. The reduced levels of the SIRT1 protein in PD lead to reduced melatonin levels and more frequent night waking. The aim of this study is to analyze genetic variants in the *SIRT1* promoter and the concentration of its protein product in PD patients suffering from clinically diagnosed sleep disorders.
Methods: Methods. The studies were conducted on 85 individuals (PD and controls).
The *SIRT1* (rs12778366) genetic variants were determined by HRM and sequencing. The SIRT1 concentration was determined by the ELISA method.
Results: Results. We have demonstrated the presence in the *SIRT1* (rs12778366), one described genetic variant, *SIRT1* T>C, and two not yet described in the literature, ch10:67883352 G>A, and chr10:67883370 G>C. *SIRT1* genotypes occurred with variable frequency in PD and controls. The CG genotype of the *SIRT1* chr10:67883370 G>C gene was present only in PD ($p<0.05$). Moreover, a higher mean number of PDSS points was found in PD (23.3±10.3) compared to controls (12.0±8.4), ($p<0.001$), expressed by lower SIRT1 concentration in PD (10.6±15.0) as compared with controls (17.2±18.7), ($p<0.01$), indicating the occurrence of circadian rhythm disturbances.
Conclusions: Conclusions. Assessment of sleep disorders on the PDSS and analysis of the *SIRT1* gene may contribute to improving the diagnosis of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1277 / #812

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G01. Disease Mechanisms, Pathophysiology*

THE HUNTINGTIN-MEDIATED MEMBRANE INTERACTOME AND KINOME FROM NEURONS DIFFERENTIATED FROM HUNTINGTON'S DISEASE (HD) PATIENT-DERIVED IPSCS

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Shermali Gunawardena
SUNY at Buffalo, Department Of Biological Sciences, Hochstetter Hall Rm 540, Buffalo, United States of America

Aims: Huntingtin (HTT) can interact with a plethora of partners, but a clear cellular function has yet to emerge. A number of membrane-related functions for HTT have been isolated, but several questions still remain. Here we test the hypothesis that HTT acts as a scaffolding protein on membranes for distinct functions. Since the proposed HTT membrane binding regions are also post-translationally modified (PTM), we predict that PTMs play a key role in regulating HTT's scaffolding function.
Methods: To identify how the HTT interactome on membranes changes under normal and disease conditions we used neurons differentiated from HD patient-derived iPSCs coupled with quantitative LC–MS. To identify how PTM modifications in HTT affect function we isolated the HTT kinome network on membranes.
Results: LC-MS analysis of the HTT interactome on membranes showed 87 lost, 714 grained, 224 increased and 15 decreased proteins as a consequence of HD. PolyQ-HTT showed strong associations with cellular compartments related to neuronal translation, trafficking, axon guidance, and signal transduction postulating roles for HTT in these processes. Kinome analysis indicated a dramatic redistribution of HTT-kinase associations on HD membranes. 66 gained/increased and 3 lost/decreased associations were observed with polyQ-HTT. However, 31 kinases exhibited gained/increased associations with polyQ-HTT with a concomitant lost/decrease with membranes, suggesting that polyQ-HTT-mediated abnormal interactions may impede these kinases from being appropriately recruited to their respective target sites.
Conclusions: Our analysis provides evidence for how HTT likely functions as a scaffolding protein and how these functions are disrupted during disease. Further, the significant redistribution of kinase associations with HTT on membranes under disease conditions suggests that PTMs of HTT likely play key roles during disease. Future work will isolate the mechanistic aspects of how these kinases contribute to HD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1278 / #951

Poster Topic: *Theme F: Prion Diseases / F03. Imaging, Biomarkers, Diagnostics*

EFFECTS OF EMOTIONAL CHANGES IN BRAIN NEURAL ACTIVITY IN RELATION TO FOOD INTAKE.

POSTERS: F03. IMAGING, BIOMARKERS, DIAGNOSTICS

Yoko Hasegawa[1], Shogo Yoshimura[1], Tatsuya Suzuki[2], Masako Shiramizu[3], Ma. Therese Sta. Maria[1,4], Kensuke Yamamura[5], Yumie Ono[6], Takahiro Ono[7]
[1]Niigata University Graduate School of Medical and Dental Sciences, Division Of Comprehensive Prosthodontics, Niigata, Japan, [2]Graduate School of Science and Technology, Meiji University, Electrical Engineering Program, Kawasaki, Japan, [3]Otemae Junior College, Department Of Dental Hygiene, Nishinomiya, Japan, [4]Faculty of Dentistry, Manila Central University, Department Of Prosthodontics, Caloocan, Philippines, [5]Niigata University Graduate School of Medical and Dental Sciences, Division Of Oral Physiology, Niigata, Japan, [6]Meiji University, Department Of Electronics And Bioinformatics, School Of Science And Technology, Kawasaki, Japan, [7]Osaka Dental College School of Dentistry, Department Of Geriatric Dentistry, Osaka, Japan

Aims: This study aimed to explore the relationship between emotional changes and biological responses during eating by measuring brain neural activity through functional near-infrared spectroscopy (fNIRS). Unlike prior research that used uniform test foods, this study tailored the test foods to individual preferences to assess changes in cerebral hemodynamics when consuming palatable and unpalatable foods, shedding light on how emotional shifts affect neural activity during food intake.
Methods: Twenty-one right-handed, healthy individuals aged 20-35 (10 males, 11 females) participated. Food selection was based on answers obtained via Google Forms, considering allergies. A combination of closed and open questions was used to determine participants' food preferences. The experimental setup involved measuring cerebral blood flow with fNIRS during food intake of three foods: control (Aito® rice), palatable, and unpalatable, each ingested at 4g per spoonful. Participants rated food desirability on a visual analog scale (VAS). fNIRS data were analyzed with a general linear model.
Results: Increased activity was observed in the left dorsolateral prefrontal cortex (BA 9, BA 46) when emotional valence was high during food intake. Additionally, there was altered activity in parts of BA 6 in the right hemisphere. The dorsolateral prefrontal cortex plays a crucial role in appetite control, food craving, and executive functions, impacting memory, attention, learning, and behavior. These findings suggest that emotional changes related to eating may influence cognitive functions. Specifically, the "taste" of a meal could affect higher-order functions like memory and learning.
Conclusions: This study demonstrated that emotional responses to food can significantly impact neural activity in brain regions associated with cognitive functions, emphasizing the intricate connection between food preference, emotions, and cognitive processes during eating.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1279 / #1397

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G01. Disease Mechanisms, Pathophysiology*

CELL-TYPE SPECIFIC AND AGE-DEPENDENT EFFECTS OF THE ALS/FTD CAUSATIVE TBK1 P.E696K MUTATION

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Rosanna Parlato[1], Ibrahim Raya[1,2], Yasmin Douahem[1], David Brenner[1,3], Rüstem Yilmaz[1], Babak Loghmani[1], Volker Ast[4], Angelika Duda[4], Qi Gao[5], Riccardo Cristofani[2], Angelo Poletti[2], Jochen Weishaupt[1]
[1]Medical Faculty Mannheim, University Clinic Mannheim, Division Of Neurodegeneration, Mannheim, Germany, [2]University of Milan, Department Of Pharmacological And Biomolecular Sciences, Milano, Italy, [3]Ulm University Medical Faculty, Neurology, Ulm, Germany, [4]University Medicine Mannheim, Clinical Chemistry, Mannheim, Germany, [5]Medical Faculty Mannheim Heidelberg University, Core Facility Platform Mannheim, Mannheim, Germany

Aims: Deleterious mutations in the *TANK1-binding kinase 1* (*TBK1*) cause amyotrophic lateral sclerosis (ALS). Our group generated *Tbk1*^{E696K} knock-in mice carrying the *TBK1* missense mutation p.E696K leading to an impairment of autophagy. The mutant mice show age-dependent ALS-like motor and neuropathological phenotypes, such as distal muscle paresis and increased accumulation of cytosolic p62 positive inclusions. Previous evidence showed that TBK1 phosphorylates mutant Huntingtin (mHTT) and attenuates its aggregation in vitro and in less sophisticated organismal models. In this study, we apply the *Tbk1*^{E696K} knock-in mouse model to understand: 1) the cellular and molecular dysfunction linked to the onset and progression of mutant TBK1 (mTBK1) pathology, and 2) the functional interaction of TBK1 with mHTT during disease progression.
Methods: To investigate the cell type- and stage-specific molecular deficits triggered by mTBK1 in the vulnerable spinal cord tissue, we used single nuclei RNA-Sequencing (snRNA-Seq) by the 10x Genomics platform in the *Tbk1*^{E696K} knock-in at pre- and early-symptomatic stages. In parallel, we crossed the *Tbk1*^{E696K} knock-in with a model of Huntington's disease (HD) carrying a *mHTT* allele. In these double knock-in mice, we analyzed the impact of *Tbk1*^{E696K} on the accumulation of mHTT protein inclusions in different brain regions over time.
Results: In the *Tbk1*^{E696K} knock-in mice we detected transcriptional dysregulation in microglia and macrophages already at pre-symptomatic stages. Moreover, the number of mHTT and p62 positive inclusions increases in the double mutant mice, supporting that the p.E696K mutation can impair clearance of aggregation-prone proteins.
Conclusions: We identified cell-type and age-dependent dynamics of gene dysregulation in *Tbk1*^{E696K} knock-in mice. Moreover, we demonstrated during disease progression a role of TBK1 for the accumulation of mHTT inclusions in a mammalian model of HD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1280 / #160

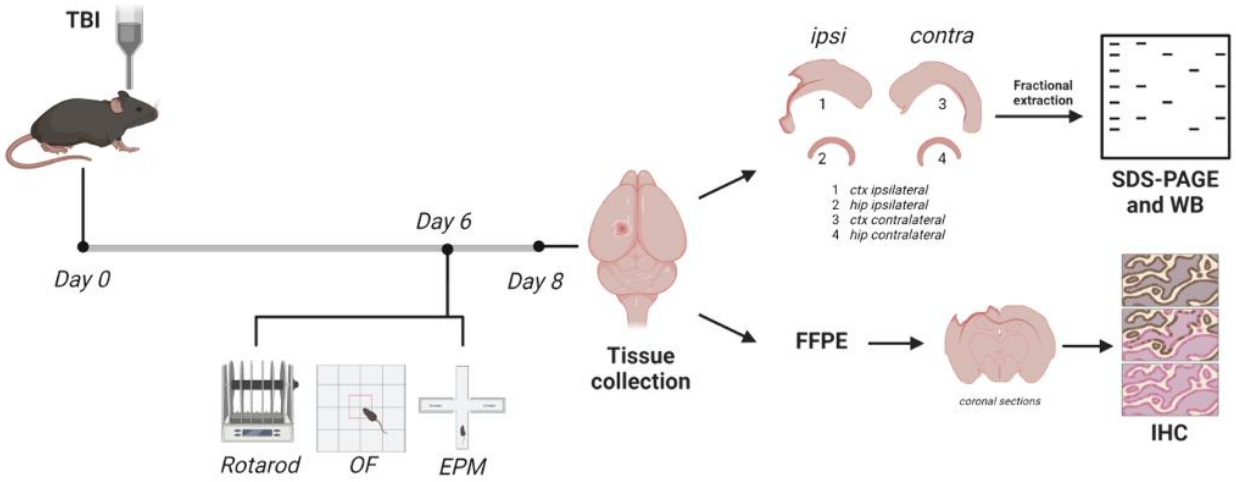
Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G01. Disease Mechanisms, Pathophysiology*

TRAUMATIC BRAIN INJURY EXACERBATES DISEASE PATHOLOGY IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Miheer Sabale[1], Lars Ittner[2], Yazi Ke[2]
[1]Macquarie University, Dementia Research Center, Macquarie Medical School, Macquarie Park, Australia, [2]Macquarie University, Dementia Research Center, Macquarie Medical School, Macquarie University, Australia

Aims: We established an in-vivo model to study traumatic brain injury (TBI) in the context of Alzheimer's disease (AD) pathogenesis (Aim 1) followed by investigating the role of pathologically mutated tau in disease progression (Aim 2)
Methods: This study uses two well characterized AD mouse models; Tau58/2 (tau P301L) and Alz17 (unmutated tau). At 3 months, mice underwent surgery to induce a single TBI using a controlled cortical impact (CCI) device. On day 6 after surgery mice underwent behaviour testing: rotarod (motor deficits), elevated plus maze (anxiety) and open field (exploratory and locomotor activity). Mice were perfused on day 8 and tissue was collected for analysis by western blot (contralateral and ipsilateral) and by immunohistochemistry (coronal)



Results: Our behavioural and biochemical data reveal that a single severe TBI induced by a CCI device leads to an earlier onset and increased severity of cognitive deficits in Tau58/2 mice when compared to Alz17 mice. This was observed alongside an increase in reactive astrocytosis and microgliosis
Conclusions: This study established two well characterized AD models as a tool to study the pathogenesis of TBI. Our findings indicate that injury in mice with tau mutated at P301L leads to an accelerated onset of AD-like symptoms, including increased astrocytosis and gliosis. Inflammation is a key mediator of both AD and TBI and clinical trials of immune modulation therapies after TBI are still in their infancy. The disease models described in this study will allow for the study of key mechanisms driving inflammation in both disorders and help identify novel therapeutic targets

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1281 / #2902

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G01. Disease Mechanisms, Pathophysiology*

PARAMETERS OF VARIATIONS IN AERODYNAMIC AND ACOUSTIC MEASUREMENTS IN WOMEN WITH PARKINSON'S DISEASE

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Clara Ponchard[1], Didier Demolin[1], Lise Crevier-Buchman[1,2], Alain Ghio[3], François Viallet[3,4]
[1]Laboratoire de Phonétique et Phonologie, (cnrs & U. Sorbonne Nouvelle), Paris, France, [2]Ho_pital Foch, Université Paris-saclay, Surennes, France, [3]Aix-Marseille Université, Cnrs Lpl, Umr 7309, Aix-en-Provence, France, [4]Service de Neurologie, Centre Hospitalier Du Pays D'aix, Aix-en-Provence, France

Aims: The main objective of this study is to contribute to the modeling of phonation in women with Parkinson's disease.
Methods: Our study stands out by (1) providing a conceptual and methodological framework for the segmentation of aerodynamic and acoustic data; (2) performing a multiparametric study; (3) identifying the sources of variation in aerodynamic and acoustic parameters; and (4) identifying parameters that characterize Parkinsonian speech. Data from 74 French native-speaking women (37 with Parkinson's, 37 controls) divided into age groups (under 60, 60-70, over 70 years) from the AHN corpus [1] were analyzed. For Parkinsonian women, data were assessed in two pharmacological states: with L-DOPA (ON-DOPA) and without (OFF-DOPA). Parameters included estimated subglottic pressure (ESGP) and fundamental frequency (F0) during sentence repetition, examining variations in age, /p/ position, F0 during its temporal course and at different positions in sentences, and the impact of L-DOPA treatment.
Results: Parkinsonian speech is characterized by significantly lower ESGP levels and a significant decline throughout sentences across three age groups. Parkinsonian F0 of women under 60 is significantly higher than healthy women. Between 60 and 70, there's no significant difference, but after 70, Parkinsonian women show significantly lower F0. A pronounced F0 decline was observed in all age groups. Our results also revealed that L-DOPA's impact on ESGP and F0 varies by age: in women under 70, L-DOPA administration led to a significant increase in ESGP. Similarly, a significant F0 increase is noted, but only in women under 60 years. L-DOPA effectively reduces F0 and ESGP decline across all age groups.
Conclusions: Our results are innovative in being the first to demonstrate a differentiated effect of Parkinson's disease alterations and L-DOPA administration based on the age of women.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1282 / #2314

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

TO INVESTIGATE THE EFFECT AND MECHANISM OF VERBASCOSIDE ON NEURAL TUBE DEFECTS BASED ON SONIC HEDGEHOG SIGNALING PATHWAY

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Lianggi Xie, Chai Zhi, Xin-Liang Wang, Yi Ru, Min Hu, Si Xiang Niu, Bao Guo Xiao, Hui-Jie Fan
shanxi university of chinese medicine, College Of Basic Medicine, shanxi, China

Aims: Neural tube defects (NTDs) are birth defects caused by incomplete closure of neural tubes during embryonic development, the common phenotypes are cerebral malformation, encephalocele, spina bifida, myelomeningoceled and so on. It is a common congenital malformation of newborns, second only to congenital heart disease in incidence. According to traditional Chinese medicine, kidney deficiency is the basic pathogenesis of NTDs. Verbascoside is one of the main active ingredients of Wuzi Yanzong Pill（ WYP）. The closure of neural tube is mainly affected by apoptosis and cytoskeleton regulation. We will explore the mechanism of VB prevention and control of NTDs through the Shh signaling pathway.
Methods: In this study, all-trans-retinoic acid (atRA) was used to establish NTDs model, the optimal dose group of VB was selected by statistical analysis of the NTDs rate of fetal mice, and the normal group, atRA group, VB group and FA group were set. Shh, Smo, P-smo ptch1 and Gil1 were detected by Western blot. HE staining was used to observe neural tube closure, We then add cyclopamine, an inhibitor of the SHH signaling pathway and detect the expression of downstream proteins. Tunel staining was used to detect apoptosis.
Results: Compared with the NTDs rate, it was found that the middle-dose group of VB had obvious therapeutic effect on NTDs, and HE staining showed that the neural tube of the malformed mice was not closed. Comparing the expression of Shh, Smo, P-smo ptch1 and Gil1 in different groups, it was found that VB could improve the expression of Shh, Smo, P-smo ptch1 and Gil1. Tunel staining also showed that VB could reduce neural tube cell apoptosis and inhibitor group increased apoptosis in fetal rats.
Conclusions: It is likely that VB prevents NTDs by regulating Shh signaling pathway to inhibit apoptosis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1283 / #888

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

PROTECTIVE EFFECTS OF X AND Y EXTRACTS IMPROVING BLOOD-BRAIN BARRIER, BLOCKING THE FORMATION OF AB PLAQUES AND INTESTINAL INFLAMMATION IN D-GALACTOSE INDUCED AGING IN MICE

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Ngoc Buu Tran, Haesung Lee, Ngo Hoang Long, Sook Jeong Lee
Jeonbuk national university, Bioactivematerials, Baekje-daero, Deokjin-gu, Jeonju-si, Jeollabuk-do,, Korea, Republic of

Aims: Aging is a complex biological process characterized by a gradual decline in individual adaptability, physiological, cognitive, and memory impairment. The problem of food reserves is considered urgent in the context of current shortages caused by epidemics, natural disasters and global climate change. Insects are evaluated as a potential source for used as a new food substitute rich in protein and nutritional value. This study evaluated the effects of *X* and *Y* extracts in a D-Galactose (D-Gal)-induced mouse model of aging.
Methods: We examined the expression level of tight junction protein through western blot method, and histology staining for the formation of amyloid β plaques, neuron damage and intestinal inflammation as well as biochemistry assay for oxidative stress.
Results: *X* and *Y* extracts increased levels of glutathione, superoxide dismutase, and catalase; protected neurons in the brain; prevent blood-brain barrier (BBB) disruption and cerebral edema; prevent the deposition of amyloid β (Aβ) plaques in various regions of the brain. Furthermore, both extracts prevent gut-blood barrier (GBB) disruption as well as improve intestinal inflammation.
Conclusions: Collectively, these new findings suggest a possible therapeutic role of insect extracts in D-Gal-induced damage and dysfunction through gut-brain axis control as a potential functional food.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1284 / #397

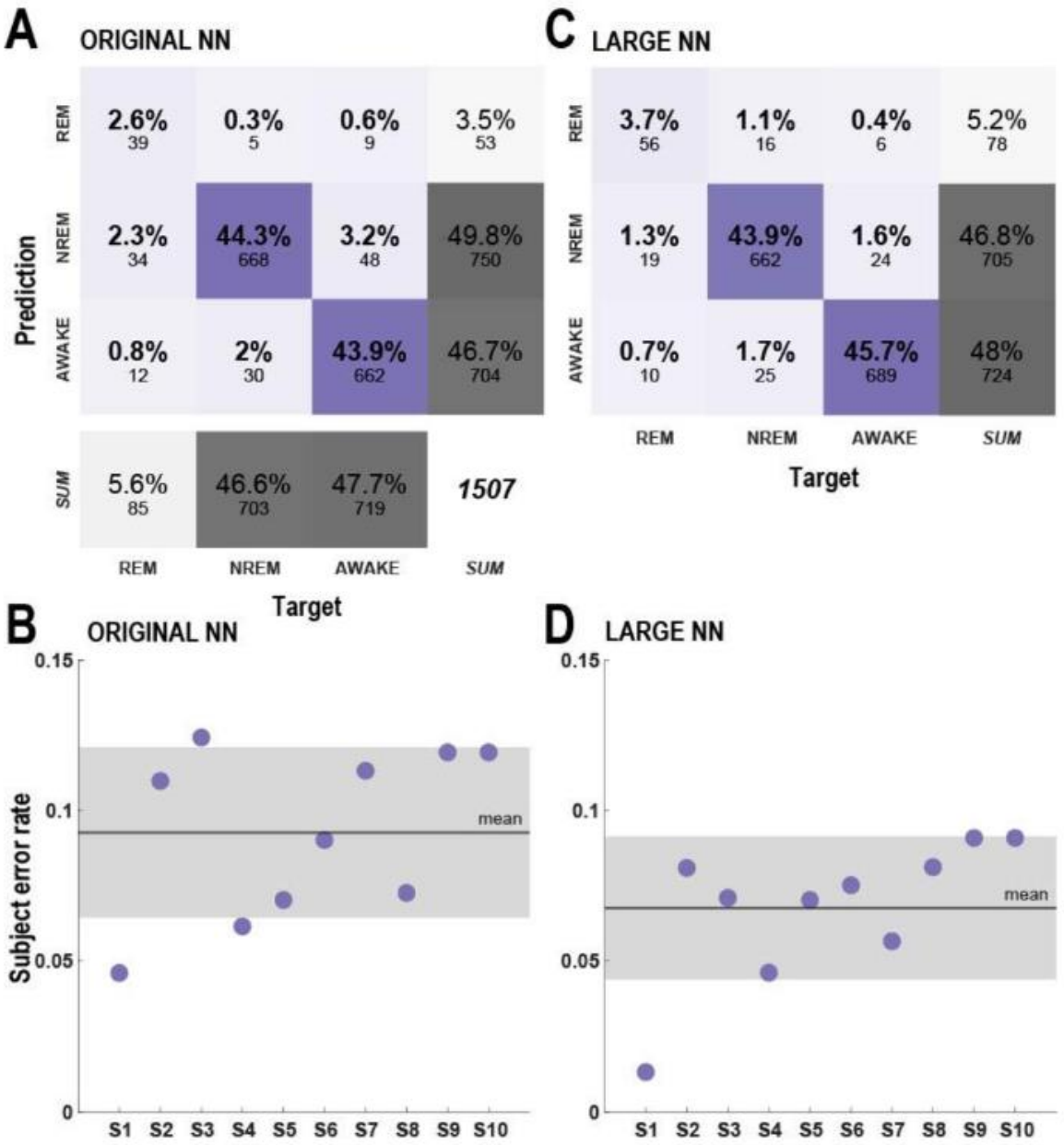
Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

TOWARDS ADAPTIVE DEEP BRAIN STIMULATION TARGETING PARKINSON'S DISEASE SLEEP DYSFUNCTION USING NEURAL NETWORKS

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Katrina Carver[1], Karin Saltoun[2], Elijah Christensen[3], Aviva Abosch[4], Joel Zylberberg[5], John Thompson[6]
[1]University of Toronto, Medical Biophysics, Toronto, Canada, [2]McGill University, Biomedical Engineering, Montreal, Canada, [3]University of Colorado, Anesthesiology, Aurora, United States of America, [4]University of Nebraska, Neurosurgery, Omaha, United States of America, [5]York University, Physics And Astronomy, Toronto, Canada, [6]University of Colorado, Neurosurgery, Aurora, United States of America

Aims: We address the demand for sleep dysfunction therapies in Parkinson's Disease (PD) by considering the concept of a deep brain stimulation (DBS) device which can determine the sleep state of the user and modify its stimulation for maximal benefit. Here, we create neural networks (NNs) that can classify sleep state using subthalamic nucleus (STN) local field potential (LFP) data collected by the DBS. We analyze the contribution of each recorded STN LFP frequency band (alpha, theta, etc.) to model prediction to analyze the viability of our NN in commercially available devices with lower sampling frequencies.
Methods: A feedforward artificial NN (ANN) was trained with STN LFP data transformed to 8 frequency power bands, from 10 idiopathic PD patients with unilateral DBS. Ground truth labels arose from simultaneous polysomnography recordings. A lower-resolution ANN was created to match the frequency range of commercial DBS by downsampling the LFP recordings. Finally, SHAP analysis was used to determine the contribution of each LFP band to the model's prediction using the full-resolution data.
Results: We compared the "Original" NN by Christensen et. al (2019) to our "Larger" NN with two hidden layers and 1000 rectified linear units. We found improved performance on the three-state (Awake, REM, NREM) labeling problem, and were able to differentiate multiple non-REM states (splitting NREM into NREM1 and a combined NREM2/3 label). SHAP analysis revealed that the highest frequency bands were less important to the model prediction than middling frequency bands.



Conclusions: In sum, this research explores a new treatment avenue for a more tailored approach to sleep dysfunction in PD, with the prospect of implementation on a wider range of commercially available DBS devices.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1285 / #470

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

NEW FORMULATION TO REDUCE THE PROGRESSION OF MOTOR DYSFUNCTION IN PARKINSON'S DISEASE.

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Mariana Fiadeiro[1,2], Ana A. Silva[1,2], Ana C. Sousa[3], Samuel Silvestre[1], Marco Almeida[1], Marcia Neves[4], Yoon-Seong Kim[5], João Coutinho[4], Mara Freire[4], Ana Clara Cristovão[1,2]
[1]University of Beira Interior, Cics-ubi Health Sciences Research Centre, Covilhã, Portugal, [2]Fastprinciple-lda, Neurosov, Covilhã, Portugal, [3]University of Évora, Comprehensive Health Research Centre (chrc) , Department Of Biology, Évora, Portugal, [4]University of Aveiro, Ciceco Aveiro Institute Of Materials, Aveiro, Portugal, [5]Robert Wood Johnson Medical School at Rutgers, Neurology, Piscataway, United States of America

Aims: Parkinson's Disease (PD) is a chronic neurodegenerative disorder affecting up to 10 million people worldwide, which current therapeutic approaches can only target the symptoms. As symptomatic therapies lose effectiveness over time, patients end up with no therapeutic options. Therefore, delaying the disease progression became a promising solution to deal with this disorder. PD pathogenesis is highly influenced by oxidative stress, and we have previously shown that ROS generated by NADPH oxidase 1 (Nox1) has detrimental impacts on dopaminergic neurons, being a valuable target for therapeutic developments. Inline, we aimed to test a chemical inhibitor ionic liquid for Nox1 inhibitor (N1inh-IL) capable of preventing neurodegeneration in experimental PD models.
Methods: N27 dopaminergic cell line were exposed to the neurotoxins 6-hydroxydopamine (6OHDA) and 1-methyl-4-phenylpyridinium (MPP+) and two animal models for PD, one induced by intrastriatal injection of 6OHDA and the other by chronic exposure to paraquat (PQ) were used. Dopaminergic cell viability and motor dysfunction were evaluated.
Results: *In vitro* studies showed that N1inh-IL has no cytotoxic effect on N27 neurons, while it significantly prevents the neurotoxic effect of two specific neurotoxins 6-hydroxydopamine (6OHDA) and 1-methyl-4-phenylpyridinium (MPP+). *In vivo*, the dopaminergic neuroprotective capacity of N1inh-IL was evaluated. The infusion of the N1inh-IL into the right ventricle did not cause neuronal toxicity, while it could prevent 6OHDA-induced neurodegeneration in the *substantia nigra* (SN) of mice. Moreover, four weeks after been exposed to PQ, the brain intraventricle diffusion or the intranasal delivery of N1inh-IL in rats was capable to prevent the motor dysfunction induced by the toxin and the accumulation of alpha-synuclein in the SN.
Conclusions: These results highlight that N1inh-IL can be an innovative therapy to reduce the speed of the progression of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1286 / #1773

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

MODIFIED IMAGING PROTOCOL FOR DBS IN IPD

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Sunil Gupta[1], Navneet Singla[1], Ashish Aggarwal[1], Sahil Mehta[2]
[1]PGIMER, Neurosurgery, Chandigarh, India, [2]PGIMER, Neurology, Chandigarh, India

Aims: Background: The success of DBS in IPD is dependent upon the precision with which the STN is localized. In the past, the STN was localized using standard atlas but with present day MRI, STN can be directly visualized. The steps required on the day of surgery include performing an MRI, fixing the frame and then repeating the MRI. This can be time consuming. We describe a different protocol to save time and for more patient convenience.
Methods: In our institution, CEMRI of the brain is done a few days before surgery. On the day of surgery Leksell frame is applied. Patient undergoes CECT head with frame. Both the MRI and CT images are then fused using a software (FRAMELINK). STN is localized using AC-PC method. Our rationale of using CT and not MRI after frame application is that it saves time on the day of surgery.
Results: Because of excessive patient load & since MRI is time consuming, we devised this protocol of performing CT on the day of surgery. After surgery and taking out frame, MRI is done to confirm lead placement in relation to STN. We found that in post-op MRI the lead placement is precise using this method. The clinical response in the patients also signifies that lead placement in STN is accurate using CECT after frame application.
Conclusions: This modified protocol saved time and was more comfortable for the patient with no loss of precision in electrode placement in patients with Idiopathic Parkinson's Disease

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1287 / #696

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

SMALL MOLECULE PKC A&B1 KINASE INHIBITOR PROTECTS HUNTINGTON'S DISEASE PATIENT-DERIVED HUMAN STRIATAL NEURONS

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Mali Jiang[1], Ritika Miryala[1], Tianze Shi[1], Ronald Wang[1], Matthew Rodriguez[1], Karim Belkas[1], Rashi Sultania[1], Lauren Guttman[1], Kimberly Mae Bockley Bockley[1], Anning Cui[1], Yuxuan Xue[1], Yuna Um[1], Ammy Yuan[1], Chloe Holland[1], Jing Jin[1], Juan Troncoso[2], Wenzhen Duan[3], Tamara Ratovitski[1], Wanli Smith[4], Christopher Ross[5]
[1]School of Medicine, Johns Hopkins University, Psychiatry, Baltimore, United States of America, [2]Johns Hopkins University, Neuropathology, Baltimore, United States of America, [3]School of Medicine, Johns Hopkins University, Psychiatry, Neuroscience,, Baltimore, United States of America, [4]School of Medicine, Johns Hopkins University, Psychiatry, Pharmacology, Baltimore, United States of America, [5]School of Medicine, Johns Hopkins University, Psychiatry, Pharmacology, Neuroscience, Neurology, Pathology, Baltimore, United States of America

Aims: To use human cell-based assays to identify small molecules as potential disease-modifying treatments for HD.
Methods: Previously we established a human neuronal model by immortalizing and differentiating HD patient iPSCs into highly homogeneous striatal precursor neurons (SPN), which resembled HD-like phenotypes of the parental iPSCs including expression of MAP2/DARPP32 (Akimov et al, Hum Mol Genet. 2021 Nov 30;30(24): 2469-2487). Further, we developed a 96-well plate screening platform using CellTiter-Glo luminescent cell viability assay in the SPNs and screened a kinase inhibitor library (ApexBio) containing 765 compounds in HD SPNs expressing 180 CAG repeats (180Q-SPNs).
Results: We identified approximately 20 compounds that exhibited protection to HD SPNs upon stress-induced neuronal toxicity. Among the hits, there was a small molecule PKC-a and ß1 inhibitor, GO6976, that we validated and prioritized. We found that GO6976 rescued HD SPNs from stress-induced toxicity through a dose-dependent manner. Furthermore, we examined PKCa / ß1 activity and protein expression levels in HD conditions. The activity of PKCa and PKCß1 was significantly increased in HD ISPNs, mouse brains, and human brains. Moreover, PKCa and PKCß1 interacted with both wild-type and mutant HTT and their overexpression was toxic to HD SPNs.
Conclusions: These findings suggest that PKCa/ß1 may play roles in neuronal cell toxicity in this model. Inhibition of PKCa/ß1 activity may attenuate mutant HTT toxicity and provide novel therapeutic targets for developing neuroprotective HD treatments.

P1288 / #2183

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

TABEBUIA IMPETIGINOSA BARK ANTIPARKINSONIAN ACTIVITY AND BIOCHEMICAL INVESTIGATION OF DOPAMINE IN RAT BRAIN HOMOGENATES

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Dr Sunil Kumar Kadiri
College of Pharmaceutical Sciences, Dayananda sagar university, Bengaluru, Pharmacology, Bengaluru, India

Aims: Improving economy and wellbeing in creating nations like India has expanded life expectancy and changed the accentuation from transferable to non transmittable sicknesses such as Parkinson's disease. *Tabebuia impetiginosa* has been utilized by cultivators as a general tonic, immunostimulant, adaptogen and also in motor disorders. The present investigation was to explore the antiparkinsonian activity of *Tabebuia impetiginosa* bark by experimental methods.
Methods: Control group-I was served with distilled water. Group-II was considered as pathological control [1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) 2 mg/nostrils i.n, Reserpine 40 mg/kg s.c, Haloperidol 0.5 mg/kg, i.p]. Group-III served with standard drug (Apomorphine 40 mg/kg, s.c). Group IV and V received aqueous extract of *Tabebuia impetiginosa* bark aqueous extract in doses of 300 and 500 mg/kg/ day respectively. Tremor, hypokinesia, muscular rigidity, catatonia, postural immobility, postural instability, and catalepsy were assessed for antiparkinsonian activity.
Results: The bark extract served group exhibited increased levels of dopamine (5700 ±1.84 ng/g) when compared to control groups (4300 ± 3.17 ng/g). The extract at both doses displayed a significant reduction in postural flexion, a moderate decrease in tremor, muscular rigidity, and postural immobility scores but did not exhibit significant lowering of hypokinesia score in reserpine induced Parkinsonian model. The reduction in catatonia and catalepsy scores is more remarkable in the case of a high dose of extract (500 mg/kg) compared to the standard drug in Neuroleptic induced Parkinsonism.
Conclusions: The findings demonstrate that *Tabebuia impetiginosa* bark extract has significant anti-cataleptic potentials and the antioxidant effect of the bark may also be a significant contributor to its antiparkinsonian activity. Traditionally reported napthoquinone compounds present in the bark such as Lapachol and β-Lapachone are responsible for neuroprotective effect in Parkinsonism.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1289 / #2188

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

APPLICATION OF DIRECT REPROGRAMMING TECHNIQUES TO STUDY THE PATHOGENESIS OF HUNTINGTON'S DISEASE

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Nina Kraskovskaia, Polina Parfionova, Arina Maligina, Mikhail Khotin, Natalia Mikhailova
Institute of cytology RAS, Cellular Technologies Center, Saint-Petersburg, Russian Federation

Aims: Aim of the study is to evaluate Huntington's disease (HD) phenotype in induced striatal neurons obtained with transdifferentiation from dermal fibroblasts of healthy individuals and HD patients
Methods: Using an optimized direct reprogramming protocol based on the use of microRNA9-124 and the transcription factors MYT1L, DLX2 and CTIP2 we obtained population of induced striatal neurons (ISN) from 3 patients with HD and from 3 healthy donors matched for gender and age.
Results: In induced stratum neurons (ISN) derived from fibroblasts from patients with HD were detected aggregates of mutant huntingtin , which is the main histopathological feature of this neuropathology. However, the number of cells containing such intracellular aggregates were less than 5%. ISNs derived from fibroblasts from patients with HD are also characterized by altered morphology, reflected in a decrease in the number of primary processes, the total number of processes, the length of dendrites and the branching of the dendritic tree. In addition, compared with the control, in ISNs from fibroblasts of patients with HD, a decrease in the mitochondrial membrane potential is observed, which indicates a decrease in metabolic activity in mitochondria. Finally, ISNs derived from fibroblasts from patients with HD are more susceptible to cell death upon application of a proteasome inhibitor MG132 as well as upon removal of brain-derived neurotrophic factor from the culture medium.
Conclusions: Thus, the proposed cellular model of HD reflects the main pathological changes that occur in neurons during the development of the disease and can be used as a platform for assessing the effectiveness of potential drugs at the preclinical stages of research.
The work was carried out with financial support from the Russian Science Foundation grant No. 22-75-00106.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1290 / #891

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

PROTECTIVE EFFECTS OF NATURAL EXTRACTS AS AN EFFECTIVE THERAPY FOR IMPROVING A BEHAVIORAL DISORDER AND TYROSINE HYDROXYLASE EXPRESSION IN MPTP INDUCED PARKINSON'S DISEASE MICE

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Haesung Lee, Ngoc Buu Tran, Ngo Hoang Long, Sook Jeong Lee
Jeonbuk national university, Bioactivematerials, Baekje-daero, Deokjin-gu, Jeonju-si, Jeollabuk-do,, Korea, Republic of

Aims: Parkinson's disease (PD) is a brain disorder that causes unintended or uncontrollable movements. Symptoms usually begin gradually and worsen over time. The most stand out signs and symptoms of PD occur when neuron cells in the substantia nigra pars compacta (SNpc), an region of the brain that controls movement, become impaired or die. Dopanminergic neurons, produce an important brain chemical known as dopamine, and the neurons die or become impaired from less dopamine production, finally leading to the movement problems associated with the disease. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), one of the most chemical for investigations into the mechanisms involved in the death of dopaminergic neurons in PD. We found extracted active ingredients using natural products A and B that are believed to be effective in various diseases and evaluated the therapeutic effect on PD.
Methods: A PD model was established by injecting or oral administration of MPTP and natural extracts in C57 mice for 4 weeks. In addition, the behavioral ability of PD mice was evaluated through Paraller bar and horizontal bar behavior experiments. After the behavioral experiment, mice was sacrifice and isolation the brains. SNpc was isolated to confirm protein expression with Western blot.
Results: MPTP caused behavior impairment and loss of dopaminergic neurons. Extracts increased levels of tyrosine hydroxylase expression and improved a behavioral disorder like tremor, impaired posture and balance, and slowed movements.
Conclusions: As a results, these new theraputic findings suggest a possible role of natural extracts in behavioral disorders and cranial nerve damage caused by PD and the potential function of improving its symptoms.

P1291 / #576

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G01. Disease Mechanisms, Pathophysiology*

ALTERED GUT MICROBIOTA AND PHYSIOLOGY IN A DROSOPHILA MODEL OF HUNTINGTON'S DISEASE

POSTERS: G01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Jasmine Speranza, Julian Ketley, Flaviano Giorgini
University of Leicester, Department Of Genetics & Genome Biology, Leicester, United Kingdom

Aims: Huntington's disease (HD) is a fatal neurodegenerative condition caused by the expansion of a CAG trinucleotide repeat in the *HTT* gene, which encodes a mutant form of the HTT protein with an extended polyglutamine tract. Recent research suggests that the gut microbiota (GM) – a complex ecosystem composed of bacteria, viruses, and fungi – modulates host metabolism, inflammation, and immune responses, possibly influencing the pathogenesis of brain disorders/diseases, including HD. Therefore, we have used a *Drosophila* model of HD to investigate the effects of pan-neuronal mutant HTT (mHTT) expression on the GM and gut physiology.
Methods: GM were analysed *via* the colony forming unit assay and metagenomics analysis. The faecal transplantation assay was performed as an approach to modulate the observed gut dysbiosis. Gut physiology was studied through the Smurf assay and RNAseq analysis.
Results: mHTT flies exhibited a higher abundance of culturable bacteria compared to wild-type HTT *Drosophila,* specifically *Lactobacillus ssp.* and *Acetobacter ssp.* This gut dysbiosis was treated by faecal transplantation, which increased the lifespan and median survival of mHTT flies. mHTT flies exhibited an increased permeability to blue dye, suggesting dysfunction or loss of the intestinal barrier, a phenomenon commonly associated with ageing and altered metabolism/immunity in *Drosophila*. Differentially expressed genes in the gut of mHTT flies highlight alterations in cell proliferation/differentiation processes (*chinmo*, *D*, *Notum*), as well as lipid (*FASN3*, *Fad2*), carbohydrate (*LMan*, *Mal-B1*) and chitin metabolism (*Cht5*, *Cht9*).
Conclusions: Our study supports the influence of HD on GM content and epithelial physiology, suggesting a possible causative relationship between mHTT and altered gut bacteria homeostasis, dysregulation of cell gut proliferation/differentiation processes and disruption of gut metabolism.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1292 / #1980

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

EXPLORING ATAXIN-3 PATHOGENIC AGGREGATION PATHWAYS VIA SUPRAMOLECULAR INHIBITION: IMPLICATIONS FOR THERAPEUTIC DEVELOPMENT

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Alexandra Silva[1], Sara Duarte-Silva[2], Pedro Martins[1], Beatriz Rodrigues[3], Débora Serrenho[3], Daniela Vilasboas-Campos[2], Andreia Teixeira-Castro[2], Julio Vieyto-Nuñez[4], Joel Mieres-Pérez[4], Francisco Figueiredo[1], Carter Lanz[5], Niki Sepanj[6], Joseph Loo[5], Frank-Gerrit Klärner[7], Thomas Schrader[7], Annalisa Pastore[8], Elsa Sanchez-Garcia[4], Gal Bitan[6], Ana Luísa Carvalho[3], Patricia Maciel[2], Sandra Macedo-Ribeiro[1]
[1]Institute for Research and Innovation in Health, Biomolecular Structure And Function Group, Porto, Portugal, [2]School of Medicine, University of Minho, Life And Health Sciences Research Institute (icvs), Braga, Portugal, [3]CNC-UC, Universidade de Coimbra, Neuroscience And Disease, Coimbra, Portugal, [4]TU Dortmund University, Department Of Biochemical And Chemical Engineering, Dortmund, Germany, [5]University of California, Los Angeles, Department Of Chemistry And Biochemistry, Los Angeles, United States of America, [6]University of California Los Angeles, Department Of Neurology, Brain Research Institute And Molecular Biology Institute, Los Angeles, United States of America, [7]University of Duisburg-Essen, Institute Of Organic Chemistry, Essen, Germany, [8]King's College London, Uk Dementia Research Institute, London, United Kingdom

Aims: Spinocerebellar ataxia type-3 (SCA3) is a rare form of inherited ataxia without cure. It is caused by an expansion of a trinucleotide CAG repeat in the ATXN3 gene, translated to an expanded polyglutamine (PolyQ) tract in the ataxin-3 protein (Atx3). When the PolyQ tract in Atx3 expands, it causes the protein to aggregate and accumulate Atx3 in degenerating brain regions. Atx3 follows a complex self-assembly pathway initiated by an aggregation-prone region in its globular Josephin (JD) domain. As many of the critical structural elements driving JD self-assembly contain several positively charged residues, we hypothesized that CLR01, a molecular tweezer that binds to exposed lysines and arginines, could interfere with Atx3 aggregation both in vitro and in vivo.
Methods: We employed a comprehensive and interdisciplinary approach to assess how CLR01 affects Atx3 self-assembly. Our investigation began with molecular-scale analyses to examine the interaction mechanisms, followed by assessing its impact on in vitro aggregation and amyloid fibril formation. Finally, we validated our discoveries using SCA3 cell and animal models.
Results: Our results show that CLR01 binds to Atx3 JD, limiting its flexibility and altering Atx3 aggregation pathways. In line with the biophysical data, CLR01 decreases aggregation and reverses synaptic defects in primary neurons expressing polyQ-expanded Atx3, and reduces motor defects in a SCA3 worm model. Furthermore, treatment of the CMVMJD135 SCA3 mouse model with CLR01 delayed symptom onset and improved motor function in correlation with rescued motor neuron pathology.
Conclusions: CLR01 has the potential to mitigate the harmful effects of Atx3 aggregation in SCA3 and can contribute to the development of molecules that specifically target neurotoxic pathways.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1293 / #408

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

THE MITOCHONDRIA-TARGETED ANTIOXIDANT ANTIOXCIN4 COUNTERACTS OXIDATIVE/NITROSATIVE STRESS IN THE BRAIN AND SKELETAL MUSCLE OF THE AMYOTROPHIC LATERAL SCLEROSIS SOD1G93A MOUSE

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Débora Mena[1,2,3], Fernando Cagide[4], Sofia Benfeito[4], Luís Grilo[1,2,3], Daniela F. Silva[1], Paulo Pinheiro[1], Katarzyna Michalik[1], Elisabete Ferreiro[1,2], José Teixeira[1,2], Filomena Silva[1], Fernanda Borges[4], Paulo J. Oliveira[1,2,3], Ana I. Duarte[1,2,3,5]
[1]CNC - Center for Neuroscience and Cell Biology, University Of Coimbra, Coimbra, Portugal, [2]CIBB - Center for Innovative Biomedicine and Biotechnology, University Of Coimbra, Coimbra, Portugal, [3]IIIUC - Institute for Interdisciplinary Research, University Of Coimbra, Coimbra, Portugal, [4]CIQUP-IMS/Department of Chemistry and Biochemistry, Faculty of Sciences, University Of Porto, Porto, Portugal, [5]Institute of Pharmacology and Experimental Therapeutics, Faculty of Medicine, University Of Coimbra, Coimbra, Portugal

Aims: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease, defined by motor neuron loss, muscle paralysis, and death. Mitochondrial dysfunction and oxidative stress are implicated in ALS pathology. Thus, ameliorating mitochondrial function and/or antioxidant defenses with novel mitochondria-targeted antioxidants (*e.g.,* AntiOxCIN4), may constitute promising therapies to delay ALS progression. We hypothesized that AntiOxCIN4 can mitigate brain and skeletal muscle oxidative/nitrosative stress in the *SOD1^{G93A}* ALS mice.
Methods: Early adult *SOD1^{G93A}* ALS mice were subcutaneously injected with AntiOxCIN4 (0.1 mg/Kg/day), for 2 months. We prepared brain cortical and skeletal muscle homogenates and used colorimetry-/fluorimetry-based methods to assess the effect of AntiOxCIN4 in animal's longevity, oxidative/nitrosative stress markers, and activities of the antioxidant enzymes superoxide dismutase (total SOD, SOD-2) and glutathione reductase (GRed).
Results: AntiOxCIN4 extended the survival rate of female ALS mice (P=0.05). This was accompanied by a slight increase of 51 and 92% in brain total SOD and SOD-2 activities, while their skeletal muscle activities were reduced by 42 and 32% (P=0.07, P=0.08). Moreover, AntiOxCIN4 enhanced skeletal muscle GRed activity (P=0.01), while reducing the levels of hydroperoxides in skeletal muscle (P=0.009) and nitrites in brain and skeletal muscle (P=0.002, P<0.001) of ALS mice.
Conclusions: In sum, AntiOxCIN4-associated increase in longevity of ALS mice may result from a protection from brain and skeletal muscle oxidative/nitrosative stress. However, more studies are required to uncover why this protection delays ALS progression. Funded by ERDF: Centro2020 Operational Programme (POCI-01-0145-FEDER-029391 (Mito4ALS)), COMPETE 2020; FCT: POCI-01-0145-FEDER-029391, PTDC/MED-FAR/29391/2017, UIDB/04539/2020, UIDP/04539/2020, LA/P/0058/2020, UIDB/00081/2020; European Social Fund: 2021.04707.BD, Mito4ALS-PTDC/MED-FAR/29391/2017 (D.M.); FCT/P2020/COMPETE, PTDC/MED-QUI/29164/2017 (S.B.); EU Horizon2020 R&I Program/Marie Sklodowska-Curie grant 895144 (P.S.); FCT Contract 2020.01560.CEECIND (J.T.); SFRH/BD/5539/2020 (L.F.G.); DL57/2016 (FC); DL57/2016-SFRH/BPD/84473/2012 & EU HORIZON Excellence Hubs/CHAngeing/II0347.01 (AID.).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1294 / #605

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

PATH TO PREVENTION (P2P) THERAPEUTICS PLATFORM TRIAL IN BIOMARKER DEFINED PRODROMAL PARKINSON'S DISEASE: STUDY DESIGN

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Tanya Simuni[1], Christopher Coffey[2], Andrew Siderowf[3], Caroline Tanner[4], Michael Brumm[2], Sohini Chowdhury[5], Todd Sherer[5], Catherine Kopil[5], Karl Kieburtz[6], Ben Saville[7], Cora Allen-Savietta[7], Amy Crawford[7], Kimberly Fabrizio[8], Ken Marek[8]
[1]Northwestern University, Neurology, Chicago, United States of America, [2]The University of Iowa, Neurology, iowa City, United States of America, [3]University of Pennsylvania, Neurology, Philadelphia, United States of America, [4]University of California San Francisco, Neurology, San Fransisco, United States of America, [5]Michael J. Fox Foundation, N/a, Hagerstown, United States of America, [6]University of Rochester, Neurology, Rochester, United States of America, [7]Berry Consultants, LLC, N/a, Austin, United States of America, [8]Institute for Neurodegenerative Disorders, N/a, New Haven, United States of America

Aims: To describe the study design and proposed timeline of the first interventional study in participants with early Neuronal α-Synuclein Disease (NSD). Background: we have recently proposed new biological definition and Integrated Staging System of Neuronal Alpha-Synuclein Disease (NSD-ISS). The major objective of NSD-ISS is to inform our understanding of early disease and accelerate development of disease-targeted therapies. We plan to apply NSD-ISS staging as inclusion criteria for P2P study.
Methods: P2P is planned as a platform, Phase 2 randomized double blind multi-center, multi-regimen clinical trial evaluating the safety and early efficacy of investigational products for the treatment of early, stage 2B, NSD. The study is "nested" within PPMI and sponsored by the MJFF. Qualified participants will be recruited from PPMI, based on the presence of aSN neuronal pathology (SAA in spinal fluid), dopaminergic dysfunction (DaTscan imaging) and subtle clinical features (stage 2B NSD) but no functional impairment. The study's Multiple Primary Endpoints include 1) DAT imaging as measured by the rate of progression in the mean striatum Specific Binding Ratio (SBR) and 2) rate of progression in the MDS-UPDRS part III score. Secondary endpoints include safety, tolerability and feasibility. The study will have an array of exploratory clinical (including digital) and biomarker measures. Intervention duration will be at least 24 months.
Results: Interventions are being selected by a Therapeutic Evaluation Committee from > 15 industry submitted applications. The study targets to start enrolment in the first 2 regimens in 2025.
Conclusions: We report the design of the first platform interventional study targeting the stage 2B NSD population. Platform design allows efficiency of operational infrastructure, ability to share placebo arm and perpetual testing of the promising interventional candidates.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1295 / #2731

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

AN EXOSOME-RICH CONDITIONED MEDIUM FROM AMNIOTIC MEMBRANE STEM CELLS IMPROVES NEUROBEHAVIORAL FUNCTIONS OF CEREBRAL PALSY MODEL ANIMALS

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Zolzaya Bavuu[1], Dae Hwan Kim[2], Sangryong Park[2], Hyunju Jeong[2], Chanho Noh[1,2], Hye-Rim Seong[2], Uk Lee[2], Ah-Young Lee[2], Tae Myoung Kim[1,2], Ehn-Kyoung Choi[2], Yun-Bae Kim[1,2], Dongsun Park[3]
[1]Chungbuk National University, College Of Veterinary Medicine, Cheongju-si, Korea, Republic of, [2]Designed Cells Co., Ltd., Central Research Institute, Cheongju-si, Korea, Republic of, [3]Korea National University of Education, Department Of Biology Education, Cheongju-si, Korea, Republic of

Aims: Cerebral palsy (CP) is one of the most-devastating neurological disorders in children. Since neuroprotective molecules are released from stem cells, the CP-therapeutic effects of an exosome rich-conditioned medium (ERCM) derived from human amniotic membrane stem cells (AMSCs) were investigated.
Methods: ERCM containing a large amount of growth factors (GFs) and neurotrophic factors (NFs) was obtained via hypoxic (2% O_2) culture of AMSCs. In vitro cytoprotective activity was assessed against lipopolysaccharide (LPS) and KCN cytotoxicity in human neural stem cells (F3) and oligodendrocyte progenitor cells (F3.olig2). Male neonatal rats (at postnatal day 5) were subjected to hypoxia-ischemia-LPS (HIL) surgery, and treated IV once or 4 times with ERCM. Neurobehavioral functions were assessed via locomotor activity, rota-rod running, passive avoidance, and Morris water-maze performances. Neuroprotective effects were evaluated by analyzing neuronal apoptosis and inflammatory response, GFs and NFs, demyelination in the corpus callosum, and oligodendrocyte makers.
Results: ERCM protected against LPS and KCN cytotoxicity in F3 and F3.olig2 cells by regulating apoptotic and inflammatory genes. ERCM markedly recovered the motor and cognitive functions in HIL animals. As shown in vitro, ERCM suppressed neuronal apoptosis and inflammatory responses, which was supported by the recovery of brain GFs and NFs including BDNF, NGF, CNTF, GDNF, NT-3, and PDGF. It was confirmed that ERCM attenuated demyelination in the corpus callosum, a white matter region vulnerable to CP, wherein oligodendrocyte makers such as NKX2.2, Olig2, CNPase, and MBP were restored.
Conclusions: The results indicate that ERCM exerts CP-therapeutic effects in vitro and in vivo by preserving neural stem cells and oligodendrocyte progenitor cells through regulation of apoptotic signaling, inflammatory response, and differentiation and maturation of stem and progenitor cells to oligodendrocytes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1296 / #548

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

ACCELERATING THE DEVELOPMENT OF THERAPIES USING AN ENGINEERED HUMAN NEUROMUSCULAR JUNCTION- ON-A-CHIP PLATFORM

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Carolin Madwar, Margaret Magdesian, Victoria Kwok
Ananda Devices Inc., Biochemistry, Laval, Canada

Aims: Currently available in-vitro models fail to reproduce the pathological complexities of most neuromuscular diseases, including Myasthenia gravis (gMG), a rare autoimmune disease driven by autoantibodies targeting components of the neuromuscular junction (NMJ). For the successful development of new therapies, robust alternative approaches methods (NAMs) that specifically mimic the human NMJ function are required to elucidate the toxicity mechanism of autoantibodies in gMG.
Methods: In this study, the Ananda Devices microfluidic platform NeuroMuscle™ was used to create an in vitro 3D co-culture of motor neurospheres derived from human induced pluripotent cells and primary human skeletal muscle fibers that reproduces a functional NMJ.
Results: The platform was validated for robust detection of muscle contraction after stimulation with acetylcholine; reproducible detection of NMJ function by quantifying muscle contraction after neuronal stimulation with glutamate and rapid detection of NMJ function inhibition by alpha-bungarotoxin and D-tubocurarine. Functional connectivity was assessed with glutamate stimulation of neurospheres and subsequent calcium transients in GCaMP6-transduced muscle fibres. AChR antagonists also confirmed functional connections of NMJ co-cultures developed in the NeuroMuscle™ platform. Next, the NMJ cultures in the NeuroMuscle™ platform were incubated with sera from healthy and gMG patients which induced complement activation and impaired neurotransmission.
Conclusions: The data highlight how Ananda Devices' human based, in vitro, NeuroMuscle™ platform could support drug discovery in NMJ-related diseases and could be used to test compounds to understand efficacy and mechanistic rationale. In addition, Ananda Devices' NeuroMuscle™ platform is scalable, compatible with standard laboratory equipment and uses human derived reagents and cells.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1297 / #1792

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

NEUROPROTECTIVE EVALUATION OF OCCIDENTALIN-1202 PEPTIDE IN A MURINE MODEL OF PARKINSON'S DISEASE

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Henrique Amaral[1], Miguel Tavares[2], Márcia Renata Mortari[3]
[1]University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil, [2]NeuropharmaLab, Department Of Physiology, Brasília, Brazil, [3]Institute of Biological Science, Department Of Physiology, Brasília, Brazil

Aims: The purpose of this study was to investigate the antiparkinsonian effect of the OcTx-1202 peptide in a mouse model of parkinsonism, using three different doses (1, 2.5, and 4 mg/kg).
Methods: The animals were divided into three experimental groups: 6-OHDA group consisting of animals with parkinsonism treated with vehicle solution (n=6), OcTx-1202 group consisting of animals with parkinsonism treated with the peptide at three different doses: 1 mg/kg (n=6), 2.5 mg/kg (n=8), and 4.5 mg/kg (n=6), and healthy group consisting of healthy animals treated with vehicle solution (n=8). The behavioral tests consisted on the Rotarod test for evaluation of motor activity, conducted over a period of 6 hours on the Rotarod apparatus, and the apomorphine-induced rotation test. Subsequently, an immunohistochemical analysis was conducted to quantify the proportion of viable neurons in the SN.For groups with more than two samples, one-way analysis of variance (ANOVA) followed by Tukey's test was employed for normally distributed data with similar variances. A significance level of $p<0.05$ was considered, with Bartlett's test being performed afterwards. Results that exhibited normal distribution and two variables were subjected to two-way repeated measures analysis of variance (two-way ANOVA), with Bonferroni's post-test being used.
Results: Regarding the immunohistochemical, the peptide was not able to reduce neuronal death. In the motor coordination test on the Rotarod, animals that received the dose of 4 mg/kg showed improvement in motor condition ($p<0.0001$). Additionally, in the apomorphine test, both doses of 2.5 and 4 mg/kg decreased the number of rotations ($p<0.001$).
Conclusions: These results suggest that the OcTx-1202 peptide may have a positive effect on improving motor symptoms associated with Parkinson's disease. However, the assays conducted did not show a significant neuroprotective effect of the peptide.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1298 / #2844

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G02. Therapeutic Targets, Mechanisms for Treatment*

PR006A GENE THERAPY INCREASES PROGRANULIN LEVELS AND IMPROVES FTD-GRN RELATED PHENOTYPES IN AN IN VITRO AND AN IN VIVO MODEL

POSTERS: G02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Ambika Tewari[1], Patty Biezonski[1], Laura Heckman[1], Suzanne Burstein[1], Li Chin Wong[2], Asa Abeliovich[1], Sid Kamalakaran[1], Jorge Haller[1], Stuart Nelson[1], Priyam Raut[1], Raghu Gowda[1], Zoe Zhaostein[1], Zhaohui Yang[1], Hsuan-Ni Lin[1], Franz Hefti[1]
[1]Prevail Therapeutics, a wholly owned subsidiary of Eli Lilly and Company, Neuroscience, New York, United States of America, [2]Prevail Therapeutics, Clinical Development, New York, United States of America

Aims: Objective: *GRN* haploinsufficiency in humans leads to a very high risk of developing FTD-GRN. FTD-GRN is a neurogenerative disease characterized by impairment of executive function, changes in behavior, and language difficulties. To address an unmet clinical need, we developed PR006A, an investigational gene therapy comprising an AAV9 capsid and *GRN* transgene, with the aim of increasing human progranulin levels in the CNS, thereby slowing disease progression.
Methods: PR006A was tested in two models of FTD-GRN: (1) an *in vitro* induced pluripotent stem cell (iPSC)-derived neuronal model using cells from patients carrying heterozygous GRN mutations and (2) an *in vivo Grn* knockout (KO) genetic mouse model that have a complete loss of progranulin, display age-dependent phenotypes, including lysosomal alterations, lipofuscin accumulation, microgliosis, and neuroinflammation, thus reflecting key pathological features of human FTD-GRN.
Results: PR006A effectively transduced human FTD-GRN iPSC-neurons *in vitro*, resulting in a dose-dependent production of progranulin which reversed functional deficits of the lysosomal enzyme cathepsin D and ameliorated TDP-43 pathology. PR006A administered to *Grn* KO mice via intracerebroventricular (ICV) injections reduced key FTD-GRN-related phenotypes in the brain, including accumulation of lipofuscin and ubiquitin, markers indicative of lysosomal abnormalities, and proinflammatory cytokine expression and microgliosis, markers indicative of CNS inflammation. Safety endpoints captured as part of the GRN KO mouse experiments revealed no adverse PR006A-related histopathological findings. A 6-month GLP toxicity study in non-human primates revealed no adverse in-life observations or histopathological findings.
Conclusions: PR006A treatment was well tolerated and without adverse findings in mouse and non-human primate studies and demonstrated efficacy in human *in vitro* and mouse *in vivo* models of FTD-GRN. PR006A is currently being studied in the Phase 1/2 PROCLAIM clinical trial.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1299 / #2446

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

DATA FUSION IN HUNTINGTON'S DISEASE RESEARCH: A HOLISTIC APPROACH TO NEUROIMAGING BIOMARKERS

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

H. Bockholt[1], Bradley Baker[1], Cara Joyce[2], William Adams[2], Jordan Clemsen[1], Nicholas Pasley[1], Vince Calhoun[1], Jane Paulsen[3]
[1]Tri-Institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, and Emory University, Neuroinformatics, Atlanta, United States of America, [2]Loyola University Chicago, Biostatistics, Chicago, United States of America, [3]University of Wisconsin-Madison, Neurology, Madison, WI, United States of America

Aims: As the complexity of understanding Huntington's Disease (HD) advances, it becomes imperative to harness the vast array of neuroimaging data types in a synergistic manner. This study champions a data fusion approach, combining functional network connectivity (FNC), diffusion tensor imaging (DTI), structural connectivity, and volumetric measures to provide a comprehensive understanding of HD's neural underpinnings. The emphasis is placed on the basal ganglia, given its vital role in HD pathology.
Methods: The study encompasses 101 gene-positive individuals and 28 gene-negative family controls. Each participant undergoes a series of neuroimaging protocols to capture the multifaceted nature of HD-induced brain changes. Beyond individual analyses, the study employs a cutting-edge data fusion technique known as the Joint Estimation of Linked Functional Network Variability and Structural Covariation. This approach leverages the interplay between different neuroimaging measures to derive more holistic and nuanced insights into HD progression.
Results: Preliminary findings reveal that while individual neuroimaging metrics shed light on specific aspects of HD pathology, the combined data fusion approach offers a more integrative understanding of disease dynamics. For instance, the interrelationship between structural connectivity changes and FNC variability becomes clearer, providing a multi-dimensional perspective of neural alterations.
Conclusions: This innovative approach underscores the potential of combining multiple neuroimaging datasets, moving towards a more unified framework in HD research. Such a holistic perspective not only enhances diagnostic accuracy and disease tracking but also paves the way for tailored therapeutic interventions, drawing from a broader understanding of HD's neural landscape.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1300 / #2469

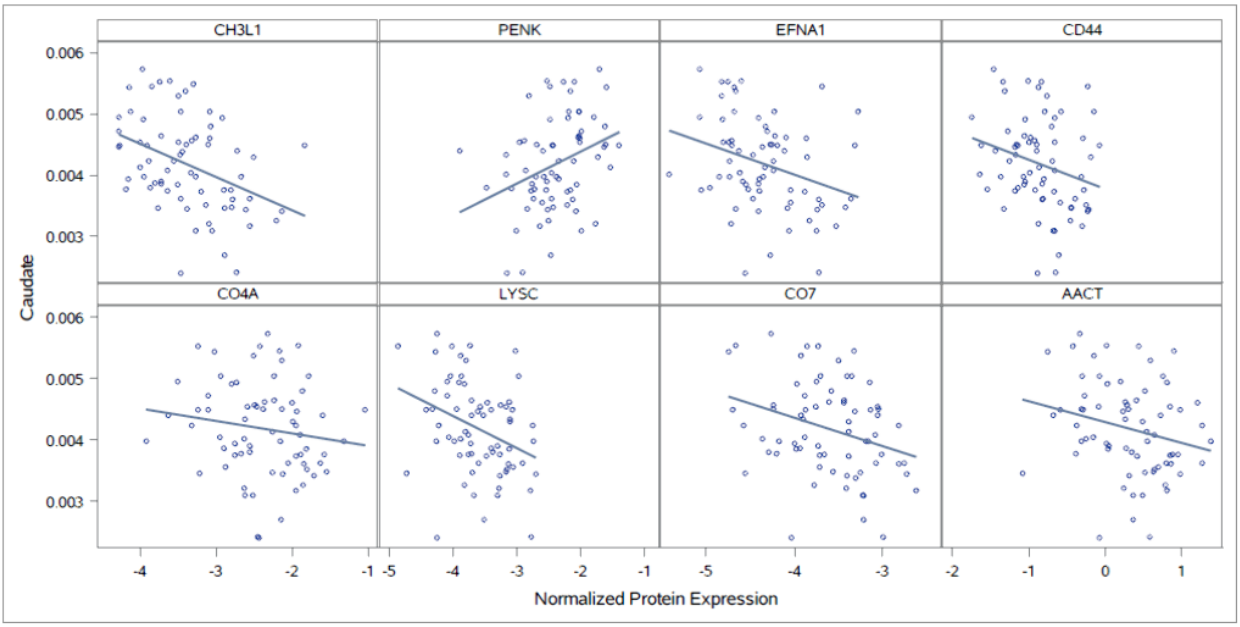
Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

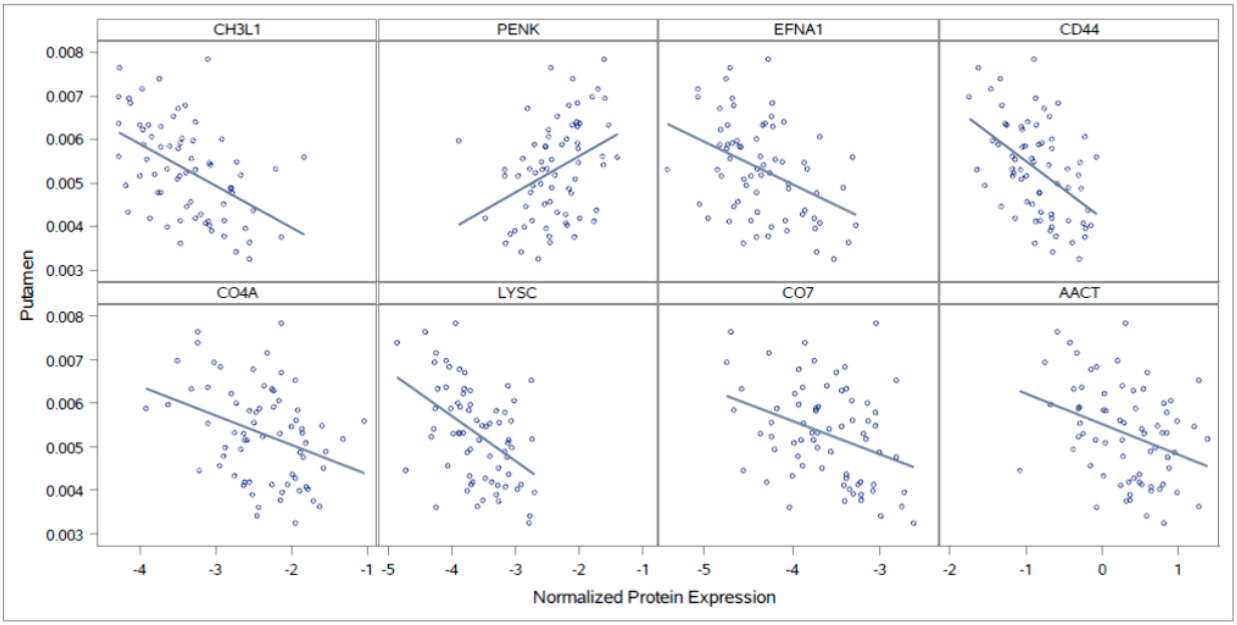
BIOFLUID AND NEUROIMAGING MARKERS IN PRODROMAL HUNTINGTON'S DISEASE MAY REVEAL A MULTI-MODAL BIOMARKER FOR TIMING OF DISEASE PREVENTION

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

H. Bockholt[1], Jordan Clemsen[1], Daniel Chelsky[2], Cara Joyce[3], William Adams[3], Michael Newton[4], Vince Calhoun[1], Jane Paulsen[5]
[1]Tri-Institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, and Emory University, Neuroinformatics, Atlanta, United States of America, [2]Caprion Proteomics, Proteomics, Montreal, Canada, [3]Loyola University Chicago, Biostatistics, Chicago, United States of America, [4]University of Wisconsin-Madison, Biostatistics And Medical Informatics, Madison, United States of America, [5]University of Wisconsin-Madison, Neurology, Madison, WI, United States of America

Aims: To examine the associations among CSF-based proteomics markers and MRI basal ganglia markers in prodromal Huntington's Disease (HD) and discern consistency among biomarkers for indications of early abnormality.
Methods: A sample of participants with the gene-mutation for HD (n=69) was selected from the PREDICT-HD study based on those with both proteomic and brain imaging volumetric outcomes acquired at a study visit. Proteins associated with disease burden (product of CAG repeat length and age) were selected for evaluation with putamen and caudate volumes. Spearman's rank correlation coefficients were calculated to examine relationships between proteins and imaging measures.
Results:





A sample of 69 patients was included with mean age 41±14 and 64% (n=44) female. Multiple proteins, including Chitinase 3 Like 1 (CH3L1) and proenkephalin (PENK), had moderate and statistically significant associations with volumetrics. Higher expression was associated with lower putamen and caudate volumes for all proteins except for PENK where the inverse was observed.

Conclusions: The proteins demonstrated a strong relationship to the MRI biomarkers. However, the direction of the relationship was not ubiquitous across proteins. Nearly all proteins associated with inflammation and apoptosis were upregulated as caudate and putamen volumes decreased. In contrast to the protein elevations expressed in most of these findings, PENK was downregulated and was associated with volumetric loss. Strong associations validate HD pathology models indicating the prominence of the medium spiny neuron in the indirect corticostriatal circuits of the basal ganglia. Future research with larger sample sizes would examine multi-modal biomarkers to determine the best prognostic model for time for intervention in clinical trials for prevention of HD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1301 / #707

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

USING PAIRED-PULSE TMS-EEG TO INVESTIGATE CEREBELLAR-CORTICAL CONNECTIVITY

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Po-Yu Fong[1,2], Danny Spampinato[3], Lorenzo Rocchi[4], Anna Latorre[1], John Rothwell[1]
[1]UCL Queen Square Institute of Neurology, Department Of Clinical And Movement Neurosciences, London, United Kingdom, [2]Chang Gung Memorial Hospital at Linkou, Division Of Movement Disorders, Department Of Neurology And Neuroscience Research Center, Taoyuan City, Taiwan, [3]IRCCS Santa Lucia Foundation, Non-invasive Brain Stimulation Unit, Rome, Italy, [4]University of Cagliari, Department Of Medical Sciences And Public Health, Cagliari CA, Italy

Aims: The combined technique of TMS (transcranial magnetic stimulation) and EEG co-registration has been extensively applied to explore cortico-cortical connectivity. Here, we explore its use in probing cerebello-cortical connections.
Methods: Twenty-five healthy subjects received the cerebellar-brain Inhibition (CBI) protocol, consisting of a subthreshold cerebellar conditioning stimulus preceding a suprathreshold test stimulation over the contralateral motor cortex by 5ms. Motor-evoked potentials (MEPs) and EEG were recorded simultaneously. CBI over both hemispheres was tested, together with an active control condition on twenty subjects using low-intensity cerebellar conditioning stimuli. During EEG recording, white noise was played via earphones to minimise auditory input from TMS coil activation, and the residual auditory evoked potential (AEP) was removed in pre-processing. Results were analysed in both time and frequency domains.
Results: As expected, conditioned MEPs were significantly reduced; on average left CBI (LCBI) was more effective than right CBI (RCBI). The EEG data showed that during LCBI, TMS-evoked potentials over left M1 (M1 TEP) were suppressed from very early to late latencies. Results from RCBI were similar to LCBI, except that the N100 was unchanged. The active control condition showed that a low-intensity cerebellar conditioning stimulus had no effect on the M1 TEP. A frequency domain analysis revealed desynchronisation in multiple frequency bands, consistent with dis-facilitation on the dentate nucleus by active Purkinje cells.
Conclusions: CBI explored with TMS-EEG produces clear effects on cerebellar-evoked TEPs in healthy subjects, and could be a potential clinical tool for investigating cerebello-motor cortex connectivity in patients with cerebellar dysfunction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1302 / #1479

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

PARKINSONISM AS A MANIFESTATION OF SPS

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Mohammad Golzarian, Mehri Salari
shahid beheshti university, Medicine School Of Shahid Beheshti University, tehran, Iran

Aims: We investigate the relationship between anti-amphiphysin antibody with parkinsonism and cortical ribbon sign by reporting 2 cases. Our case series expand the phenotypic spectrum of antiamphyphisin related disorders. We report 2 antiamphiphysin positive cases with parkinsonism. One of them manifested with cortical ribbon's sign beside parkinsonism which has not been reported yet.
Methods: We conducted a systematic review of papers in English indexed in PubMed with no time restriction reporting cases of positive antiamphyphisin. We used the following search terms, either as plain text or as MeSH terms: ("amphyphisin) AND ("parkinsonism" OR "parkinsonian disorder*) , "Autoimmune Diseases of the Nervous System" AND "amphiphysin" , ("stiff-man syndrome" OR "stiff-person syndrome") AND ("anti amphiphisin antibody") , "ribbon sign" AND "antiamphyphisin" , "cortical ribboning" AND "antiamphiphysin" , "cortical diffusion restriction" AND "amphiphysin" , "movement disorder*" AND "antiamphiphysin" , "movement disorder*" AND "neuronal antibod*" , ("parkinsonian disorder" OR "parkinsonism") AND ("neuronal antibod") and "antiamphyphisin". All results of the literature search were reviewed and relevant information was extracted and summarized. References of the included articles were also screened for eligible studies. Finally with duplication a total of 74 records were identified and assessed for eligibility, with 32 articles included in the review, some of these studies reviewed several cases retrospectively 1 additional article was identified via screening of references of articles, with 33 studies finally included in the review.
Results: We ruled out all of differential diagnosis of parkinsonism and cortical ribbon sign and realized that there might be a novel relationship between anti-amphyphisin antibody with parkinsonism and cortical ribbon sign.
Conclusions: Prkinsonism and cortical ribbon sign should be considered as new manifestations in the phenotypic spectrum of antiamphyphisin antibody-related disorders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1303 / #985

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

DIGITAL MEASUREMENT OF OCULAR MICROTREMOR IN PARKINSON'S DISEASE: PRELIMINARY RELIABILITY AND CLINICAL VALIDATION EVIDENCE

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Lisa Graham[1,2], Rodrigo Vitorio[2], Patrick Tait[2], Claire Mcdonald[1], Richard Walker[3], Alan Godfrey[4], Rosie Morris[2,3], Samuel Stuart[2,3,5]
[1]Gateshead Health NHS Foundation Trust, Qe Hospital Gateshead, Gateshead, United Kingdom, [2]Northumbria University, Sports, Exercise And Rehabilitation, Newcastle upon Tyne, United Kingdom, [3]Northumbria NHS Foundation Trust, North Tyneside General Hospital, North Shields, United Kingdom, [4]Northumbria University, Computer And Information Sciences, Newcastle upon Tyne, United Kingdom, [5]Oregon Health & Science University, Neurology, Portland, United States of America

Aims: Ocular microtremor (OMT) is a fixational eye movement linked to brainstem activity. OMT frequency is typically 70-80Hz in healthy adults and research suggests that this is reduced neurological diseases like Parkinson's Disease (PD) making it a potential biomarker. This study aimed to; 1) examine the reliability of the novel iTremor ONE device (Head Diagnostics Ltd., Dublin, Ireland) in measuring OMT frequency (Hz) in people with PD (PwPD); and 2) investigate the clinical validity of OMT as a relevant disease measure through relationship with traditional clinical rating scales.
Methods: 16 PwPD participated in a home-based assessment involving cognitive (Montreal Cognitive Assessment, MoCA), motor (motor section of the Unified Parkinson's Disease Rating Scale, UPDRS-III) and OMT measures (three readings taken from each eye to get an average). PwPD completed a test-retest reliability assessment at the same time, exactly one week apart. Interclass correlation coefficients (ICC) and paired samples t-tests were used to assess reliability. Pearson's correlations were used to compare OMT frequency to relevant clinical rating scales (MoCA, UPDRS-III).
Results: OMT frequency was 64.75Hz (SD 4.1) in the right, 64.05Hz (SD 4.6) in the left, and 64.38Hz (SD 4.3) for both eyes together. The iTremor ONE device reliably measured OMT in in PwPD. OMT frequency showed good agreement in the right (ICC 0.81), left (ICC 0.88), and both eyes averaged (ICC 0.89). Average OMT frequency was positively correlated with MoCA (r = 0.583, *p*= .018), and negatively correlated with UPDRS-III score (r= -0.564, *p*= .036). Highlighting that reduced OMT frequency relates to worse cognitive ability and increased disease severity.
Conclusions: These preliminary findings show the iTremor ONE device reliably measures OMT frequency in PwPD, and OMT frequency is associated with cognition and disease severity in PwPD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1304 / #1919

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

TRANSCRANIAL MAGNETIC STIMULATION (TMS) EVOKED POTENTIALS (TEP) FOR PREDICTION OF RESPONSE TO VENTRICULO-PERITONEAL SHUNT (VPS) IN NORMAL PRESSURE HYDROCEPHALUS (NPH)

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Sharon Hassin-Baer, Tal Davidy, Saar Anis, Alexandra Suminski, Yakov Zauberman, Orit Lesman-Segev, Tsvia Fay-Karmon
Sheba Medical Centre and Tel Aviv University, Neurology, Ramat Gan, Israel

Aims: To assess the utility of a TEP-based evaluation, for prediction of response to VPS in NPH, as an alternative for the CSF tap test (CTT).
Methods: 37 "possible iNPH" patients and 16 age-matched healthy controls underwent a neurological exam, cognitive evaluation and brain MRI scans. All subjects performed Delphi, a TMS-EEG based evaluation, measuring TEPs using proprietary algorithm. All probable iNPH patients underwent a CTT (removal of 30-50 ml of CSF while measuring change in the "Timed Up and Go ", TUG test) and 17 patients underwent VPS and were evaluated for their symptoms after 3-4 months. Response was rated using the CGIC scale and a repeated TUG, by a multidisciplinary team of movement disorders neurologists and a neurosurgeon.
Results: Gait improved in 14 operated patients; these responders had a significantly earlier 'early phase latency' (P60, p=0.0044) compared to HC. Furthermore, their TEP's early and late phase slopes were highly associated with the degree of response to VPS. Additionally, both the late phase slope ($N100\text{-}P180_{Mo}$, r=0.79, p=0.0033) and the early phase slope ($P60\_N100_{Fr}$, r=-0.88, p=0.0003) were correlated to the change in TUG after VPS. CTT was not significantly correlated with VPS response (r=0.35, p=0.198).
Conclusions: The results suggest that TEPS, measured by Delphi, may be an alternative for CTT, in prediction of response to VPS in patients suspected as iNPH, exhibiting higher efficacy with reduced patient discomfort and risks.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1305 / #2345

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

DOPAMINERGIC ALTERATIONS IN PATIENTS WITH ALZHEIMER'S DISEASE

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Rao Nargis Jahan[1], Mohammad Azharuddin[2]
[1]School of Pharmaceutical Education and Research, Jamia Hamdard, Pharmaceutics, New Delhi, India, [2]School of Pharmaceutical Education and Research, Jamia Hamdard, Pharmacology, New Delhi, India

Aims: Low levels of Dopamine may contribute to Alzheimer's disease. However, the relationship between Alzheimer's disease and dopaminergic measures remains unclear.
This study aimed to perform a meta-analysis to calculate the pooled mean difference (MD) of dopaminergic measures between Alzheimer's disease and control groups.
Methods: A systematic search on, MEDLINE/PubMed and Cochrane Central Register of Controlled Trials was performed from inception to June 2023. Eligible studies measuring the dopaminergic levels in patients with Alzheimer's disease. Subgroup analysis was performed by the stratification of the dopamine receptors. Heterogeneity was assessed by using the Cochrane Q test statistic and inconsistency index (I^2). A random effects model was used to calculate the MD with a 95% confidence interval (CI) to assess differences in the levels of dopaminergic neurometabolites.
Results: A total of 10 studies were included in this meta-analysis. Results from the meta-analysis showed significantly lower levels of dopamine 1 receptor, dopamine 2, and dopamine 3 receptor in patients with Alzheimer's disease compared with controls (MD = -22.78, 95% CI: -35.03, -10.54; $p < 0.003$), (MD = -15.81, 95% CI: -29.03, -2.58; $p < 0.002$), and (MD = -10.50, 95% CI: --20.09, -0.92; $p < 0.03$) respectively. However, there was no significant differences were observed in dopamine 4 and dopamine 5 receptor in patients with Alzheimer's disease compared with controls (MD = -30.32, 95% CI: -109.70, 49.06; $p= 0.45$), and (MD = 17.62, 95% CI: -15.70, 50.94; $p= 0.30$).
Conclusions: The current finding suggests that low dopaminergic levels were associated with the risk of Alzheimer's disease. Moreover, further study is needed to robust the present finding.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1306 / #1185

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

LC-MS/MS-BASED ANALYSIS OF N-GLYCAN CHANGES IN POST-MORTEM BRAIN TISSUE OF PARKINSON'S DISEASE

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Yehia Mechref, Oluwatosin Daramola, Andrew Bennett, Judith Nwaiwu, Mojibola Fowowe, Sherifdeen Onigbinde, Hanh Minh Nguyen
Texas Tech University, Dept. Of Chemistry And Biochemistry, Lubbock, United States of America

Aims: This research aims to find unique Parkinson's Disease (PD) glycome and glycosite specific biosignatures indicative of PD progression.
Methods: In this study, LC-MS/MS analysis of *N*-glycomics of 10 post-mortem human brain tissues from PD patients and 19 healthy controls was done. The tissue samples were lysed and then digested using PNGase F enzyme before they were analyzed with LC-MS/MS. We identified 90 *N*-glycans in the 29 brain tissue samples using Multiglycan software, X-Calibur, and quantified using Skyline MS.
Results: All the identified *N*-glycans were grouped into sialylated, fucosylated, sialofucosylated, oligomannose, NeuGc, and others (*N*-glycans without the sialic acid, fucose, and are not oligomannose). We observed that there was a significant decrease in the abundance of the fucosylated, and sialofucosylated *N*-glycans in the PD samples compared to the control while the high mannose *N*-glycans increased significantly in the PD samples compared to the control ($p<0.05$). Typically, a decrease in sialylated and fucosylated *N*-glycan, as well as an increase in the concentrations of high mannose in the PD can be autonomously associated with neuroinflammation and brain disorder critically affecting function and recovery. Furthermore, we observed 23 statistically significant *N*-glycans ($p<0.05$) of which 12 were observed to be downregulated in PD, while 11 were upregulated.
Conclusions: Notably, the dysregulated *N*-glycans observed in PD include fucosylated, sialylated, and bisecting *N*-glycans which have been linked to unique brain functions and implicated in various brain-related diseases, including Traumatic Brain Injury, Mild Cognitive Impairment, and Alzheimer's disease. Furthermore, the isomeric changes in the *N*-glycans will be further investigated and the glycosite related to the observed changes will be investigated as well.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1307 / #2449

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

FRONTOTEMPORAL DEMENTIA IN ASSOCIATION WITH INCLUSION BODY MYOPATHY AND PAGET'S DISEASE: A CASE REPORT WITH THE VCP GENE MUTATION (C.383G>C)

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Vuk Milošević[1], Radomir Damjanović[1], Eva Antić[1], Marina Malobabić[1], Jelena Bašić[2], Stojan Perić[3]
[1]University Clinical Center Niš, Clinic Of Neurology, Niš, Serbia, [2]Faculty of Medicine, University of Niš, Department Of Biochemistry, Niš, Serbia, [3]University Clinical Center of Serbia, Clinic Of Neurology, Belgrade, Serbia

Aims: This paper aimed to present a case of Inclusion Body Myopathy associated with Paget's disease of bone and Frontotemporal Dementia (IBMPFD), a rare autosomal dominant multisystem disorder caused by mutations in the valosin-containing protein (VCP) gene.
Methods: We presented a comprehensive clinical evaluation of a 62-year-old male with a missense mutation in the VCP gene, highlighting the diverse clinical manifestations of this complex disorder.
Results: The patient initially presented with progressive behavioral changes characterized by socially inappropriate behavior, repetitive movements, apathy, and altered food preferences, which began two years ago. The patient had been treated for unspecified myopathy seven years prior to the first reported behavioral changes. Neurological examination revealed proximal muscle weakness, generalized rigidity, and marked muscle atrophy. Laboratory tests were unremarkable except for elevated alkaline phosphatase levels. Brain MRI demonstrated global cortical atrophy, while arterial spin labeling (ASL) revealed decreased perfusion in the left frontal, temporal, and parietooccipital regions. Electromyography showed fibrillation, positive sharp waves at rest, and myopathic motor unit potentials during contraction. Subsequent skull imaging identified cranial bone thickening and sclerosis, consistent with Paget's disease. The behavioral and cognitive assessment led to a diagnosis of probable behavioral variant frontotemporal dementia (bvFTD). Genetic testing identified a likely pathogenic VCP gene mutation (c.383G>C), confirming IBMPFD. Treatment included escitalopram and atypical antipsychotics, resulting in a modest reduction in behavioral symptoms.
Conclusions: This case highlights the importance of considering IBMPFD in patients presenting with a constellation of symptoms, including behavioral changes, muscle weakness, and Paget's disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1308 / #1060

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

POLYGENIC RISK FOR ESSENTIAL TREMOR IS ASSOCIATED WITH MICROSTRUCTURAL DIFFERENCES IN GREY AND WHITE MATTER

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Alexandre Pastor-Bernier[1], Miranda Medeiros[2], Houman Azizi[1], Zoe Schmilovich[2], Patrick Dion[2], Alain Dagher[1], Guy Rouleau[2]
[1]Montreal Neurological Institute and Hospital, McGill University, Neurology And Neurosurgery, Montreal, Canada, [2]McGill University, Department Of Human Genetics, Montreal, Canada

Aims: Elucidation of essential tremor neuroanatomical vulnerabilities by investigating the associations between polygenic risk and brain magnetic resonance images (MRI).
Methods: We paired genetic and imagining data from the UK Biobank (UKBB) to model the associations of essential tremor (ET) polygenic risk scores (PRS) and brain structure. Individual-level genotyping and neuroimaging measures on 31,386 adults were used to correlate ET-PRS to brain morphometry. PRS-CS was used to infer SNP posterior effects and a PRS for each subject was obtained with PLINK. Principal component analysis (PCA) was performed to correct for population stratification. White matter tractography (WM DTI), mean diffusivity (MD), Free Water (FW) and NODDI models derived from diffusion weighted MRI (dMRI) were used to map WM integrity. Grey matter dMRI, along with cortical and subcortical anatomical data were also used.
Results: Our results indicate significant associations between ET-PRS in WM DTI cerebellar microstructure. We found positive associations of ET-PRS with MD in the corticospinal tract, external capsule, corpus callosum, middle cerebellar peduncle, intracerebellar-input and purkinje tract, superficial-frontal and uncinate fasciculus tracts. We also found extensive positive associations between ET-PRS and MD in several GM structures including the cerebellum, hypothalamus, caudate, putamen, thalamus and pedunculopontine nucleus. Also, the MD in thalamic deep brain stimulation hotzones VPL, VPM and VIM were positively associated with ET-PRS.We found ET-PRS negative associations with cortical volume in superior parietal and superior frontal areas. The subcortical volumes in the caudate, putamen, ventral diencephalon, midbrain, pons and medulla oblongata were all found to be negatively associated with ET-PRS.
Conclusions: Brain structural vulnerabilities in healthy subjects at risk of developing ET correspond to WM and GM areas that are also known to be involved in the rythmogenesis and pathology of ET.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1309 / #1600

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

SERUM BIOMARKERS IN PRIMARY BRAIN CALCIFICATION

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Janine Schwahn[1], Olivia Kosche[1], Sophie Hebestreit[1], Vesile Sandikci[2], Mate E Maros[3], Petra Steinacker[4], Franziska Bachhuber[5], Ivan Valkadinov[1], Jasper Hesebeck-Brinckmann[1], Rüstem Yilmaz[1], Marvin Spreyer[1], Lukas Eckrich[1], Hayrettin Tumani[5], David Brenner[5], Holger Wenz[3], Markus Otto[4], Anne Ebert[2], Julian Conrad[1], Jochen Weishaupt[1]
[1]Division of Neurodegenerative Disorders, Mannheim Center for Translational Neurosciences, Medical Faculty Mannheim, Heidelberg University, Neurology, Mannheim, Germany, [2]Medical Faculty Mannheim, Heidelberg University, Neurology, Mannheim, Germany, [3]Medical Faculty Mannheim, Heidelberg University, Neuroradiology, Mannheim, Germany, [4]Martin-Luther-University Halle-Wittenberg, Department Of Neurology, Halle (Saale), Germany, [5]University Hospital Ulm, Neurology, Ulm, Germany

Aims: Primary brain calcification (PBC; formerly Fahr's syndrome; primary familial brain calcification (PFBC) in inherited cases) is an often-genetic disease that is characterized by calcifications most often in the basal ganglia but also cerebellum, thalamus or cerebral cortex. It causes a broad clinical syndrome involving neurological and psychiatric deficits. Mutations in several genes, including PDGFB, PDGFRB, SLC20A2, MYORG and XPR1, can cause autosomal-recessively or -dominantly inherited PBC/PFBC. However, sporadic brain calcifications are frequently observed also in healthy, often elderly individuals. PBC/Fahr's syndrome has therefore been questioned as a disease entity, and the role of less extended calcification at higher ages remained elusive. The aim of this study is to better understand the differences between symptomatic and asymptomatic PBC.
Methods: We subjected individuals with various degrees of PBC from the German *Fahr-NET* patient register to an extensive study protocol including neurological, neuropsychological, imaging, genetic and laboratory biomarker assessment. Furthermore we tested several established serum markers linked to neurodegeneration and glial activation.
Results: The data show that almost all individuals with calcifications going beyond the putamen were symptomatic. In addition, we found that Serum GFAP was significantly increased in individuals with PBC, in line with the predominant expression of PBC genes in cells forming the blood-brain-barrier, including astrocytes.
Conclusions: Our results define a clinically relevant imaging cut-off indicating the presence of PBC-related symptoms. Moreover, an increase in serum GFAP indicates pathology in the sense of glial reactivity in PBC.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1310 / #2869

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G05. Genetics, Epidemiology*

ANALYSIS OF THE GGC REPEAT LENGTH OF THE NOTCH2NLC GENE RESPONSIBLE FOR NEURONAL INTRANUCLEAR INCLUSION DISEASE IN A JAPANESE PSYCHIATRIC DEMENTIA COHORT

POSTERS: G05. GENETICS, EPIDEMIOLOGY

Tesshin Miyamoto[1], Kohji Mori[1], Shoshin Akamine[1], Ryota Uozumi[1], Shiho Gotoh[2], Shizuko Kondo[2], Sumiyo Umeda[2], Yuto Satake[2], Takashi Suehiro[2], Hideki Kanemoto[2], Kenji Yoshiyama[2], Takashi Morihara[2], Manabu Ikeda[2]
[1]Osaka University, Department Of Psychiatry, Osaka, Japan, [2]Osaska University, Department Of Psychiatry, Osaka, Japan

Aims: A GGC repeat expansion in the 5' untranslated region of the *NOTCH2NLC* is a genetic cause of Neuronal Intranuclear Inclusion Disease (NIID). Although proving the presence of intranuclear inclusion body by skin biopsy facilitated clinical identification of *NOTCH2NLC*-NIID patients, it is only performed in a few cases because of its invasive nature. Since patients with *NOTCH2NLC*-NIID heterogeneously exhibit cognitive, motor and autonomic dysfunction, it is difficult to diagnose it based on symptoms alone. Therefore, there may be a significant number of undiagnosed *NOTCH2NLC*-NIID cases.
Methods: We performed a comprehensive genetic screening of *NOTCH2NLC* GGC repeat expansion by Repeat-Primed PCR and Amplicon-Length PCR in a total of 745 cases of our psychiatric dementia cohort including non-demented cases with suspected cognitive dysfunction. All cases were clinically classified according to the International Classification of Diseases (ICD)-10 system and cases of organic, including symptomatic, mental disorders (F0) were further subclassified into dementia subtypes. This study was approved by the Ethics Committee of Osaka University. Genomic DNA has been collected from patients of Psychiatric clinic of Osaka University Medical Hospital under written informed consent.
Results: Two of the 745 cases were confirmed to have aberrant GGC repeat expansion in *NOTCH2NLC*. Subsequent skin biopsy revealed that both cases were positive for ubiquitin- and p62-positive intranuclear inclusion. One case of *NOTCH2NLC*-NIID showed anxiety and food intake disturbances with mild cognitive dysfunction, without MRI findings characteristic of NIID.
Conclusions: *NOTCH2NLC*-NIID is one potential cause of cognitive dysfunction in our Japanese psychiatric dementia cohort.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1311 / #468

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G04. Imaging, Biomarkers, Diagnostics*

ASSOCIATION OF NEUROMELANIN AND IRON CONTENT WITH MRI MEASUREMENTS IN POST-MORTEM MIDBRAIN TISSUES OF PARKINSON AND ALZHEIMER SUBJECTS

POSTERS: G04. IMAGING, BIOMARKERS, DIAGNOSTICS

Luigi Zecca[1,2], Clifford M. Cassidy[3], Michela Sturini[4], Lauri Tuominen[3], Fulvio Adorni[2], Victoria Cheung[3], Luigi Casella[4], David Sulzer[5,6], Gianni Pezzoli[1,7], Ioannis U. Isaias[7,8], Guillermo Horga[9,10], Fabio A. Zucca[2]
[1]Fondazione Grigioni per il Morbo di Parkinson, -, Milan, Italy, [2]National Research Council of Italy, Institute Of Biomedical Technologies, Segrate, Italy, [3]University of Ottawa, Institute Of Mental Health Research Affiliated With The Royal, Ottawa, Canada, [4]University of Pavia, Department Of Chemistry, Pavia, Italy, [5]Columbia University Medical Center, Departments Of Psychiatry, Neurology, And Pharmacology, New York, United States of America, [6]New York State Psychiatric Institute, Division Of Molecular Therapeutics, New York, United States of America, [7]Parkinson Institute Milan, Asst G. Pini-cto, Milan, Italy, [8]University Hospital and Julius Maximilian University, Department Of Neurology, Würzburg, Germany, [9]Columbia University, Department Of Psychiatry, New York, United States of America, [10]New York State Psychiatric Institute, Division Of Translational Imaging, New York, United States of America

Aims: In Parkinson's disease (PD) the dopamine neurons containing neuromelanin (NM) are lost in the substantia nigra (SN), resulting in decreased NM and increased Fe concentrations. In Alzheimer's disease (AD) neurons are lost in cortical regions where an increase of Fe occurs. We aimed to measure NM and Fe concentrations in human midbrain subregions of PD and AD subjects and to investigate the effect of NM and Fe on NM-sensitive magnetic resonance imaging (NM-MRI) signal, in order to evaluate the reliability of MRI in detecting the loss of dopamine neurons in PD.
Methods: We imaged NM and Fe in slices of PD (n = 4) and AD (n = 7) subjects using NM and T_2-weighted MRI sequences. Results were then compared with a precise measurement of NM and Fe concentrations in the same midbrain slices, then imaging maps were calculated for each subject.
Results: Compared to AD, the PD subjects showed increased NM-MRI values in superior colliculus and periaqueductal gray matter, and higher Fe concentration in substantia nigra. Both NM and Fe concentrations had unique significant contributions to the NM-MRI signal (mixed-effects model controlling for diagnosis, 163 grid sections, 11 specimens).
Conclusions: Our results support the use of NM-MRI to study NM in the SN and midbrain regions like superior colliculus and periaqueductal gray matter for better monitoring of neuropathological damage in patients with PD and possibly in patients at risk of developing this disease.

P1312 / #2096

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G05. Genetics, Epidemiology*

ASSOCIATION OF C12ORF65 GENE MUTATION IN PATIENT WITH NOONAN SYNDROME

POSTERS: G05. GENETICS, EPIDEMIOLOGY

Gomathi Mohan, Kalaivanan Gokul
Karpagam Academy of Higher Education, Biotechnology, Coimbatore, India

Aims: Pathogenic mutations in C12orf65 gene leads to cause optic atrophy and progressive encephalomyopathy. This mutation was implicated in spastic paraplegia 55. In this study, we delineate and expand the clinical manifestation of C12orf65 mutation from an Indian case.
Methods: Whole exome sequencing, deletion or duplication analysis and mitochondrial genome sequencing were done.
Results: A 6 year old girl with global developmental delay, microcephaly, hypertelorism, epicanthic fold, webbed neck, camptodactyly of bilateral little finger, laterally placed nipples, and tongue tie. The clinical characteristics of the child made us to suspect mutation in Noonan syndrome related genes. But, WGS resulted in pathogenic mutation in C12orf65 gene at NM_152269.5; c.346del, deletion of one nucleotide at position c.346 leads to loss of normal protein function either through protein truncation or non-sense mediated mRNA decay. This homozygous mutation was found to be autosomal recessive in nature.
Conclusions: This study confirms the clinical and genetic spectrum of Noonan syndrome patient from India.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1313 / #2240

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G05. Genetics, Epidemiology*

WHOLE EXOME SEQUENCING BASED IDENTIFICATION OF GLASS SYNDROME ASSOCIATED WITH CHILTON-OKUR-CHUNG NEURODEVELOPMENTAL SYNDROME

POSTERS: G05. GENETICS, EPIDEMIOLOGY

Dr. Kaviya Mohandass[1], Dr. Pradeep Kumar Murugasamy[2], Gomathi Mohan[3]
[1]GeneOmm Medical Centre, Medical Genetics, Coimbatore, India, [2]KMCH Institute of Health Sciences and Research, Medical Genetics, Coimbatore, India, [3]Karpagam Academy of Higher Education, Centre For Neuroscience, Department Of Biotechnology, Coimbatore, India

Aims: The Glass Syndrome is a rare neurogenic multisystem disorder that occurs due to the mutation in *SATB2* (OMIM-608148 and PMIM:612313). The clinical features of this syndrome include, delay in development and speech, hypotonia, abnormal dental features and cleft palate, difficulty in behavior, seizures and bone abnormalities. The present study aims in the identification of genetic background behind the patient present with features of cleft palate and developmental delay.
Methods: The Whole exome sequencing and targeted sequencing analysis was performed to the Index patient and to her daughter exhibiting the same clinical conditions respectively
Results: On the genetic analysis through whole exome sequencing, it was found that index had a mutation in the SATB2 gene with a rare variant c.1741-2A>C; p.R239X variant at intron 11. This is a substitution of base A at the place of C, two nucleotides before the initiation of the exon. This variant is reported to be pathogenic and causative of the Glass syndrome. There were also other uncertain significant mutations found in the CDCD42BP and SMARCC2 with variants c.3658C>T and c.2527G>A subjective of Chilton-Okur-Chung neurodevelopmental syndrome and Coffin-siris syndrome 8 respectively.
Conclusions: The whole exome exome sequening identifies the rare pathogenic variant of Glass syndrome and its association with neurodevelopmental disorders

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1314 / #1822

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G05. Genetics, Epidemiology*

THE PROSTAGLANDIN D2 SYNTHASE GENE IS DIFFERENTIALLY METHYLATED IN HD.

POSTERS: G05. GENETICS, EPIDEMIOLOGY

Greg Wheildon[1], Adam Smith[2], Claire Troakes[3], Katie Lunnon[2]
[1]University of Exeter, Clinical And Biomedical Sciences, Exeter, United Kingdom, [2]University of Exeter, Department Of Biomedical And Clinical Sciences, Exeter, United Kingdom, [3]King's College London, Institute Of Psychiatry, Psychology And Neuroscience, London, United Kingdom

Aims: Huntington's disease (HD) is an autosomal dominant condition causing severe neurodegeneration in the striatum and the entorhinal cortex (EC). An epigenome wide association study of DNA methylation in HD by our group, identified potential hypomethylation at the *PTGDS* gene in the striatum. We aimed to validate this result through pyrosequencing, examining the locus in fine detail, and to assess the signal specificity by profiling multiple neurodegenerative diseases.
Methods: 379 EC and striatal DNA samples from 85 control, 73 Alzheimer's disease (AD), 90 dementia with Lewy bodies (DLB), 20 HD, 34 Parkinson's disease (PD) and 24 vascular dementia (VaD) subjects were matched for sex and age. DNA was bisulfite converted, before *PTGDS* target region amplification and subsequent pyrosequencing. Samples were analysed using linear models comparing the control group to each disease, controlling for sex, age, and batch effects. Average methylation levels across the amplicon were also compared. Additional analysis stratifying DLB and VaD cases by co-existing AD pathology was also performed.
Results: We confirmed our previous findings of DNA hypomethylation at *PTGDS* in the striatum in HD. Furthermore, we found significant hypomethylation in the targeted region, both at the level of individual CpG sites, and across the amplicon in the EC. We also observed nominally significant changes in PD and DLB with co-existing AD pathology across the amplicon, but these did not pass multiple correction.
Conclusions: This study validates our previous findings of *PTGDS* hypomethylation in HD in the striatum and presents novel associations at the EC. Together, these findings suggest further investigation of *PTGDS*, given others report differential expression in HD oligodendrocytes. Future studies should address the cell-specific profile of *PTGDS* methylation and its transcriptional regulation in HD through fluorescent activated cell sorting.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1315 / #1346

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G06. Cell, Molecular and Systems Biology*

DEFICIENT DIETARY FOLIC ACID AND SYSTEMIC DSP-4 INDUCED LOCUS COERULEUS LOSS ASSESSED AS NEURODEGENERATIVE COGNITIVE MODEL IN ADULT CB57/J6 MICE

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Susan Helm[1], Gabriel Kong[1], Aristotle Zeng[2], Theodore Helm[3], Simon Khorani[1], Rohan Rampal[2], Smayana Kurapati[2], Riva Rainier[2]
[1]Pepperdine University, Nutritional Science, Malibu, United States of America, [2]Pepperdine University, Biology, Malibu, United States of America, [3]Pepperdine University, Computer Science/math, Malibu, United States of America

Aims: Assessment of a potential neurodegenerative cognitive mouse model subjected to a dietary deficiency of folic acid (FA) by using DSP-4 to knockout the locus coeruleus (LC), notably, a major norepinephrine source in the DG and frontal cortex (FC).
Methods: For 16 weeks, adult CB57/J6 mice (N=66) were provided 4 dietary/DSP-4 treatments: NFCS (n=16, normal FA control, saline injected [0.2 mg FA/kg BW]); NFCD (n=18, normal FA, DSP-4 injected (50 mg DSP-4/kg BW); FADS (n=16, FA deficient, saline injected); and, FADD (n=16, FA deficient, DSP-4 injected). NE in FC was measured in addition to significant loss of LC neurons; astrocytes, calcium signaling, and embryonic neurons using, respectively, immunohistochemical methods for tyrosine hydroxylase (TH), GABA fibrillary acidic protein (GFAP), parvalbumin (PV), doublecortin (DCX) were analyzed.
Results: Confirmation of phenotypic cognitive behavior with Nesting Behavior; decreased distance traveled with Novel Object Recognition (NOR); and, decreased rearing and latency to explore to the center of the field in Open Field Testing (OFT) were enumerated between NFCS and FADD ($p<0.05$). Elevated plasma homocysteine (Hcy) and decreased methyltransferase activity ($p<0.05$) established folic acid deficiency between NFCS and FADS/FADD.
Conclusions: Results support that grievous injury to the LC noradrenergic system via systemic NE specific neurotoxin DSP-4 disrupts motor activity, contextual learning and memory, and perhaps significantly, the supportive cellular environment for the LC and efficient dispersion of NE. Understanding the molecular mechanisms underlying LC degeneration during disease progression or aging is yet to be fully understood.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1316 / #1896

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G05. Genetics, Epidemiology*

IDENTIFICATION OF DISEASE CAUSING VARIANTS IN A COHORT OF 60 INDIVIDUALS WITH PRIMARY FAMILIAL BRAIN CALCIFICATION

POSTERS: G05. GENETICS, EPIDEMIOLOGY

Rüstem Yilmaz[1], Janine Schwahn[1], Sophie Hebestreit[1], Olivia Kosche[1], Vesile Sandikci[2], Mate E Maros[3], Ivan Valkadinov[1], Jasper Hesebeck-Brinckmann[1], Marvin Spreyer[1], Lukas Eckrich[1], David Brenner[4], Holger Wenz[3], Anne Ebert[2], Julian Conrad[1], Jochen Weishaupt[1]
[1]Division of Neurodegenerative Disorders, Mannheim Center for Translational Neurosciences, Medical Faculty Mannheim, Heidelberg University, Neurology, Mannheim, Germany, [2]Medical Faculty Mannheim, Heidelberg University, Neurology, Mannheim, Germany, [3]Medical Faculty Mannheim, Heidelberg University, Neuroradiology, Mannheim, Germany, [4]University Hospital Ulm, Neurology, Ulm, Germany

Aims: Primary familial brain calcification (PFBC), also known as familial idiopathic basal ganglia calcification or Fahr's disease, is a rare neurodegenerative disorder characterized by calcium deposits mainly in the basal ganglia, cerebellum, thalamus, and subcortical white matter. The disorder manifests with a wide range of neuropsychiatric symptoms and movement abnormalities. There are several genes linked to PFBC: autosomal dominant mutations in *PDGFB*, *PDGFRB*, *SLC20A2*, and *XPR1*, and biallelic mutations in *MYORG* and *JAM2* are causative. In this study, we set out to investigate the genetic causes of our PFBC study cohort from the German Fahr-NET register, evaluate pathogenicity of the variants, and analyze phenotype-genotype correlation.
Methods: We performed whole-exome sequencing in 60 patients affected with PFBC as confirmed by brain imaging and neurological as well as neuropsychological examination. We filtered for rare variants affecting a splice site, or causing missense, nonsense, stop-loss, and/or frameshift alteration. The patients were examined thoroughly in our clinics.
Results: In 18 patients from 16 unrelated families, we identified rare variants in the known PFBC genes: six in *SLC20A2*, six in *MYORG*, three in *PDGFB*, and one in *PDGFRB* and *XPR1* each. While a minority of these variants have been previously reported as pathogenic, most of those detected in our cohort are novel. Moreover, we identified two rare variants in *XPR1* and one in *PDGFRB* in our control cohort, which are not pathogenic according to brain imaging. We identified a rare variant in *JAM2* in heterozygous state.
Conclusions: In 30% of our patients, we identified a potentially causative variant in a known PFBC gene. As expected, variants in *SLC20A2* were more frequent than in other genes; whereas variants in MYORG (33%) were more frequent than expected.

P1317 / #1323

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G06. Cell, Molecular and Systems Biology*

DEFINING THE MECHANISMS BY WHICH MUTATIONS IN DNAJC7 INCREASE SUSCEPTIBILITY TO ALS/FTD

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Andrew Fleming
Northwestern University, Neurology, Chicago, United States of America

Aims: Aim 1: Identify endogenous interacting partners of DNAJC7 in human neurons and develop genetic tools to study DNAJC7-ALS/FTD. Aim 2: Define the mechanistic role of DNAJC7 in the neuronal stress response. Aim 3: Determine the contribution of pathogenic DNAJC7 on RNA metabolism.
Methods: We used mutant DNAJC7 cellular models, patient induced pluripotent stem cell (iPSC)-derived spinal motor neurons (MNs) and CRISPR/Cas9 gene-editing, in combination with mass spectrometry (MS)-based quantitative proteomics and RNA-Sequencing to elucidate how ALS/FTD-associated mutations in *DNAJC7* contribute towards neuronal dysfunction and degeneration.
Results: DNAJC7 interactome is highly enriched for genes involved in both the stress response and RNA metabolism. Introduction of ALS/FTD-causative mutation in neurons negatively impacted multiple levels of RNA processing at basal conditions. Furthermore, mutant neurons displayed a marked reduction in response to molecular insults, ultimately resulting in neurotoxicity.
Conclusions: Taken together, our work suggests DNAJC7 plays a critical role in function of its interacting partners, highlighting critical neuronal homeostasis pathways that may be perturbed in ALS/FTD. This study contributes towards the understanding of heat shock protein-dependent proteostasis mechanisms in human neurons as well as to how rare ALS/FTD genetic mutations lead to neuron dysfunction and loss.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1318 / #880

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G06. Cell, Molecular and Systems Biology*

MITOCHONDRIAL FRAGMENTATION IN HUNTINGTON'S DISEASE IS INDEPENDENT OF HUNTINGTIN FUNCTION AND IS DISTINCT FROM TRAUMATIC BRAIN INJURY (TBI)-MEDIATED FRAGMENTATION.

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Shermali Gunawardena
SUNY at Buffalo, Department Of Biological Sciences, Hochstetter Hall Rm 540, Buffalo, United States of America

Aims: Mitochondrial dysfunction has been reported in several Huntington's disease (HD) models with altered levels of the fission protein DRP1 and fusion protein MFN2. Impaired calcium homeostasis with increased cytoplasmic calcium and depletion of mitochondrial calcium stores have also been reported in HD. However, the mechanistic details of how mitochondrial dysfunction occurs in HD are unknown. Here we test the hypothesis that disruption of HTT function in the context of pathogenic HTT contributes to mitochondrial dysfunction.
Methods: To test this hypothesis we use humanized *Drosophila* models of HD, polyQ disease, or mechanically induced traumatic brain injury (TBI), together with pharmacological inhibitors and in vivo mitochondrial health reporters to examine mitochondrial defects.
Results: Expression of pathogenic HTT caused fragmented mitochondria compared to normal HTT, but HTT did not co-localize with mitochondria under normal or pathogenic conditions. Expression of pathogenic polyQ (127Q) alone or in the context of Machado Joseph Disease (MJD) also caused fragmented mitochondria. While mitochondrial fragmentation was not dependent on the cellular location of polyQ accumulations, expression of a chaperone protein, excess of mitofusin (MFN), or depletion of dynamin-related protein 1 (DRP1) rescued fragmentation. Intriguingly, a higher concentration of nitric oxide (NO) was observed in polyQ-expressing larval brains, and inhibiting NO production rescued polyQ-mediated fragmented mitochondria, postulating that DRP1 nitrosylation could contribute to excess fission. Further, while excess PI3K which suppresses polyQ-induced cell death did not rescue polyQ-mediated fragmentation, it did rescue fragmentation caused by mechanical stress/TBI.
Conclusions: Our observations suggest that pathogenic polyQ alone is sufficient to cause DRP1-dependent mitochondrial fragmentation upstream of cell death. Conversely, mechanical stress/TBI-mediated mitochondrial fragmentation is likely caused by cell death. Our work uncovers distinct physiological mechanisms for mitochondrial dysfunction in polyQ disease and under mechanical stress.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1319 / #2780

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G06. Cell, Molecular and Systems Biology*

VGAMMA1 AND VGAMMA4 GAMMA-DELTA T CELLS PLAY OPPOSING ROLES IN THE IMMUNOPATHOLOGY OF TRAUMATIC BRAIN INJURY IN MALES

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Hadi Abou-El-Hassan[1], Rafael Machado Rezende[1], Saef Izzy[1], Taha Yahya[1], Zhuoran Yin[1], Marilia Garcia De Oliveira[1], Laura Michelle Cox[1], Oleg Butovsky[1], Howard Weiner[2]
[1]Brigham and Women's Hospital, Harvard Medical School, Neurology, Boston, United States of America, [2]Brigham and Women's Hospital, Neurology, Boston, United States of America

Aims: To investigate the role of γδ T cells in a model of traumatic brain injury (TBI) in mice, a model that shares features with AD.
Methods: TBI was induced to 8-12 weeks old TCRγδ knockout and wild-type mice. Rotarod, Morris water maze and probe tests were performed. Flow cytometry was performed to quantify total γδ T cells and Vγ4 subset. APP and pTau expression were shown by bright field staining. Cytokines and other factors were measured by qPCR. Microglia were sorted and sequenced. Vγ1 and Vγ4 subsets were depleted by the administration of monoclonal antibodies.
Results: After TBI, γδ-/- mice showed improvement in motor (Fig. 1A), and memory function (Fig. 1B-F). γδ T cell were increased in WT brain (Fig. 1G), mainly Vγ4 subset (Fig. 1H). WT mice had increased APP and pTau immunoreactivity compared to γδ-/- mice (Fig. 2A). γδ-/- mice showed reduction of brain inflammatory cytokines whereas Foxp3 was increased (Fig. 2B). 2,437 genes were differentially expressed (DEGs) in microglia from young WT-TBI vs. WT-Sham mice (Fig. 2C-E). 1,062 microglial DEGs from young WT-TBI compared to γδ-/-TBI mice (Fig. 2E). Homeostatic genes were increased in microglia from γδ-/- mice whereas inflammatory genes were reduced (Fig. 2C-E). In the chronic phase of TBI, 1,376 and 59 microglial DEGs from aged WT-TBI vs. WT-Sham and vs. γδ-/-TBI mice (Fig. 2F-H). Vγ4 and total γδ T cell-blocked mice displayed a greater reduction of CNS inflammatory cytokines whereas Vγ1-blocked mice had less regulatory cytokine (Fig. 3B). Microglia isolated from Vγ4 or total γδ T cell depleted mice had downregulation of inflammatory genes compared to Vγ1-depleted mice (Fig. 3C, D).
Conclusions: Taken together, these findings indicate that γδ T cells play a critical role in TBI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1320 / #267

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G06. Cell, Molecular and Systems Biology*

NEUROTOXIC EFFECT OF SALSOLINOL ON NE-4C NEURAL STEM CELL MEDIATED THROUGH MTOR PATHWAY

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Rhun Yian Koh[1], Salini Mohan Kumar[1], Yiing Jye Yap[2], Soi Moi Chye[1], Kenny Gah Leong Voon[3], Khuen Yen Ng[4], Anna Pick Kiong Ling[1]
[1]International Medical University, Division Of Applied Biomedical Science And Biotechnology, Bukit Jalil, Malaysia, [2]Monash University Malaysia, School Of Medicine, Subang Jaya, Malaysia, [3]University of Nottingham Malaysia, Division Of Biomedical Science, Semenyih, Malaysia, [4]Monash University Malaysia, School Of Pharmacy, Subang Jaya, Malaysia

Aims: Parkinson's disease is a common neurological disease characterised by motor and non-motor symptoms. Cell therapy is a promising alternative therapeutic strategy in Parkinson's disease. It restores the damaged neurons in the nigrostriatal pathway. Transplanted neuronal stem cells are multipotent and are capable of differentiating to several types of cells in the central nervous system, including neurons and other brain cells. However, salsolinol, a neurotoxin exerts substantial toxicity on the transplanted neuronal stem cells. Salsolinol has diverse neuropharmacological effects including inducing oxidative stress besides being able to inhibit the mitochondrial energy supply. Salsolinol also inhibits some key enzymes involved in the production of dopamine such monoamine oxidase, tyrosine hydroxylase and catechol-O-methyltransferase. Additionally, salsolinol also prevents the uptake of catecholamines. This study aims to evaluate neurotoxicity and apoptogenic effect of salsolinol on NE-4C neuronal stem cells through mammalian target of rapamycin signalling pathway.
Methods: Salsolinol was added to NE-4C cells. Cell viability and apoptosis were evaluated by using trypan blue exclusion method and mitochondrial membrane potential staining assay, respectively. Additionally, some key regulatory proteins that could mediate cell apoptosis through mTOR signalling pathway was analysed. The relative expressions of mTOR, phospho-mTOR, raptor and GßL proteins were determined using enzyme- linked immunosorbent assay.
Results: revealed that when NE-4C cells were treated with salsolinol (0-100µM) for 24, 48 and 72 hours, salsolinol induced death in NE-4C cells mainly by alteration of mitochondrial membrane potential. Additionally, the change of the level of phospho-mTOR indicates the contribution of this protein in the death of the NE-4C cells.
Conclusions: In conclusion, salsolinol induced neuronal cell death via mitochondrial membrane potential alteration and down-regulation of phospho-mTOR protein.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1321 / #297

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G06. Cell, Molecular and Systems Biology*

COMPREHENSIVE CROSS-PATHOLOGIES STUDY AND NEURONAL SUBTYPE ANALYSIS REVEALS MOLECULAR SIGNATURES OF NEURODEGENERATIVE DISORDERS

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Zhaohui Man
Duke University, Neurology, Durham, United States of America

Aims: Late-onset Alzheimer's Disease (LOAD), Parkinson's Disease (PD), and Dementia with Lewy Bodies (DLB) represent three neurodegenerative disorders with overlapping clinical characteristics. Disentangling their molecular subtypes and identifying distinct biomarkers remains challenging. In this study, we conducted a comprehensive cross-pathologies investigation utilizing single-cell RNA sequencing (scRNA-seq) data derived from post-mortem brain tissues of individuals affected by these three debilitating conditions. Our study encompassed three pivotal comparisons: LOAD vs. PD, PD vs. DLB, and DLB vs. LOAD, aimed at identifying differentially expressed genes (DEGs) crucial to understanding the unique molecular signatures of each disorder.
Methods: Pathway analysis of the DEGs from these comparisons unveiled intricate molecular networks, emphasizing the convergence of neuroinflammatory, synaptic, and protein homeostasis pathways as common denominators across these disorders. This collective insight into shared pathways deepens our comprehension of their overlapping pathogenic mechanisms.Furthermore, our research aspired to uncover biomarkers capable of distinguishing subtypes within the spectrum of neurodegenerative diseases. Leveraging the scRNA-seq data, we deployed the MASC (Marker Gene Analysis with Single-Cell RNA-Seq) method to pinpoint depleted or vulnerable neuronal subtypes and signature/marker genes. Our analysis focused on PD vs. Normal, LOAD vs. Normal, and DLB vs. Normal comparisons, providing novel insights into the distinct neuronal vulnerabilities associated with each disorder.
Results: This multi-faceted investigation harnesses the potential of single-cell transcriptomics and MASC analysis to not only delineate the intricate molecular landscapes of AD, PD, and DLB but also to uncover unique neuronal vulnerabilities and potential biomarkers. Our findings advance our understanding of these neurodegenerative diseases, opening avenues for more precise diagnoses and targeted therapies tailored to distinct subtypes within this challenging clinical landscape.
Conclusions: Subtypes of NDD have their shared pathways and unique molecular signatures.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1322 / #2295

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G06. Cell, Molecular and Systems Biology*

NOVEL PLATFORMS TO INVESTIGATE CENTRAL NERVOUS SYSTEM DISEASES FOR DISCOVERY PURPOSES

POSTERS: G06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Matteo Zanella[1], Malika Bsibsi[1], Blanca Torroba[1], Marta Da Silva[1], Laila Ritsma[1], Dario Magnani[2], Mariangela Iovino[2], Roxana Redis[1], Maria Herva Moyano[2], Ludovico Buti[1], Marijn Vlaming[1]
[1]Charles River Laboratory, Early Discovery, Leiden, Netherlands, [2]Charles River Laboratory, Early Discovery, Saffron Walden, United Kingdom

Aims: There is an urgent need for reproducible and up scalable platforms for discovery of modifiers of Central Nervous System (CNS) diseases in high throughput formats. Recent advances in the areas of 2D and 3D stem cell research and gene/RNA editing have translated into opportunities to better understand brain diseases. Application within a drug discovery setting enables discovery of potential treatments using the most relevant cell models.
Methods: Both induced pluripotent stem cells (iPSCs) and organoids represent promising resources for modeling CNS diseases. iPSCs can be used to generate patient-specific neurons or glial cells either as single cell types or in co-cultures. Organoids offer a three-dimensional representation of the brain, enabling the investigation of CNS architecture, connectivity and function; thus allowing *in-vivo* conditions to be simulated.
Results: Our recent results confirm that iPSC-derived neurons and microglia are robust platforms for the study of neurodegenerative disorders, such as Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's Disease (AD). We demonstrate that these models possess phenotypical and functional properties similar to those observed in the human body, both in mono- and co-culture experiments, including electrical activity (neurons) and cytokine release (microglia). Differences can be observed between healthy and diseased cell lines which mimic pathological conditions, such as reduced firing activity in neurons with mutations in ALS causative genes. Additionally, we demonstrate downregulation of target genes in these cell types using either a siRNA- or ASO-based approach.
Conclusions: Together, these platforms can help identify novel therapeutic targets and improve our understanding of disease mechanisms, with the goal of establishing effective treatments for CNS diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1323 / #2142

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G07. Animal Models*

BAICALIN PREVENTS CEREBRAL ISCHEMIA-INDUCED NEUROBEHAVIORAL DISORDERS AND BRAIN DAMAGE

POSTERS: G07. ANIMAL MODELS

Phil-Ok Koh, Hyun-Kyoung Son
Gyeongsang National University, College Of Veterinary Medicine, Jinju, Korea, Republic of

Aims: Cerebral ischemia is known that causes neurological disorder, neuronal cell death, and permanent disability. Baicalin has antioxidant and anti-apoptotic properties. The aim of this study was to investigate the neuroprotective effect of baicalin in animal models of stroke.
Methods: Middle cerebral artery occlusion (MCAO) was performed to induce focal cerebral ischemia and baicalin (30 mg/kg) or vehicle was injected intraperitoneally just before MCAO surgery. Neurological behavior tests including neurobehavioral scores, corner test, adhesive removal test, and vibrissae-evoked forelimb placing test were performed 24 h after MCAO. Brain edema and infarct volume were measured. To investigate the antioxidant effect of baicalin, reactive oxygen species (ROS) and lipid peroxidation (LPO) levels were measured. Hematoxylin and eosin staining and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) histochemical staining were performed.
Results: There were significant neurobehavioral defects in MCAO-treated animals. However, in the presence of baicalin, neurobehavioral defects due to MCAO surgery were significantly attenuated. MCAO damage causes severe cerebral edema and increases infarct volume, and baicalin treatment alleviates these changes caused by MCAO. The cerebral cortex of MCAO animals showed histopathological changes with condensed nuclei and expanded cytoplasm and increased TUNEL positive responses. However, administration of baicalin attenuated histological lesions caused by MCAO. In addition, baicalin treatment alleviated MCAO-induced increases in ROS and LPO levels.
Conclusions: We showed that MCAO damage caused severe neurobehavioral impairment and brain tissue damage, and baicalin exerted neuroprotective effects by regulating apoptosis and oxidative stress. Therefore, these results suggest that baicalin acts as a neuroprotective agent in stroke animal models.
This research was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) [RS-2023-00248145].

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1324 / #248

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G07. Animal Models*

FERULIC ACID'S AMELIORATE MYCOTOXIN-INDUCED NEUROTOXICITY IN RATS

POSTERS: G07. ANIMAL MODELS

Puneet Kumar[1], Surbhi Singh[2]
[1]Central University of Punjab, Pharmacology, bathinda, India, [2]Central University of Punjab, Pharmacology, Bathinda, India

Aims: Huntington's disease (HD) is a neurological ailment marked by chorea, aberrant movement patterns, cognitive and mental challenges. Few therapies are available for the management of HD, and the majority of these drugs have side effects affecting patient compliance and treatment outcomes. Plant and their phytoconstituents have long been a hub for identifying novel and alternative drug compounds. It has been hypothesized that ferulic acid (FA), a polyphenolic molecule with antioxidant properties, can reduce oxidative stress, contributing to CNS disorders' pathophysiology, including Huntington's disease.
Methods: In this study, 3-NP a mycotoxin that inhibits mitochondrial complex 2 was used to induce Neurotoxicity in rats to assess the neuroprotective potential of ferulic acid (FA). Wistar rats were given FA (25,50 and 100 mg/kg) p.o. one hour before 3-NP treatment (10 mg/kg) i.p., for 21 days. Body weight and physical qualities (activity, muscular coordination, and gait abnormalities) were assessed every 7 days. Animals were euthanized on the 22nd day, brain cells extracted, and striatal sections excised to determine oxidative stress indicators and inflammatory cytokines. The level of proapoptotic proteins was evaluated using Western blot.
Results: 3-NP administration affected experimental animals' body weight, motor coordination, and biochemical indicators. Compared to the 3-NP groups, FA (50 and 100 mg/kg) mitigated abnormalities in behavioral, oxidative, inflammatory, and apoptotic markers.
Conclusions: In conclusion, FA could exert its neuroprotective effect via its antioxidant, anti-inflammatory, and anti-apoptotic properties. **Acknowledgement:** The authors would like to thank Central University of Punjab for providing Research Seed Money and animal house facilities.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1325 / #1235

Poster Topic: *Theme H: Demyelinating Diseases / H01. Therapeutic Targets, Mechanisms for Treatment*

SELECTIVE RNAI-SILENCING OF SCHWANN CELL PIEZO1 ALLEVIATES MECHANICAL HYPERSENSITIZATION FOLLOWING PERIPHERAL NERVE INJURY

POSTERS: H01. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Hongwei Yu[1], Brandon Itson-Zoske[1], Uarda Gani[1], Chensheng Qiu[1], Fan Fan[2], Quinn Hogan[1], Seung Min Shin[1]
[1]Medical College of Wisconsin, Anesthesiology, MIlwaukee, United States of America, [2]Augusta University, Physiology, Augusta, United States of America

Aims: We previously reported functional mechanosensitive Piezo1 expression in Schwann cells of the peripheral nervous system, which plays a role in the regulation of myelination. The present study is designed to further investigate the role of Schwann cell Piezo1 in peripheral nociception.
Methods: We first developed an adeno-associated viral (AAV) vector that has primary Schwann cell tropism after delivery into the sciatic nerve. This was achieved by packing AAV-GFP transcribed by a hybrid CMV enhancer/chicken β-actin (CBA) promoter using a capsid AAVolig001 to generate AAVolig001-CBA-GFP. Five weeks after intrasciatic injection of AAVolig001-CBA-GFP in naïve rats, GFP expression was detected selectively in the Schwann cells of the sciatic nerve. A short hairpin RNA against rat Piezo1 (PZ1shRNA) was designed that showed efficient physical and functional knockdown of Piezo1 in NG108 neuronal cells. A dual promoter and bidirectional AAV encoding a U6-driven PZ1shRNA and CBA-transcribed GFP was packed with capsid olig001 (AAVolig001-PZ1shRNA), and AAV was injected into unilateral sciatic nerve immediately after induction of common peroneal nerve injury (CPNI).
Results: showed that the development of mechanical hypersensitivity in the CPNI rats injected with AAVolig001-PZ1shRNA was mitigated, compared to rats subjected with AAVolig001-scramble. Selective *in vivo* Schwann cell transduction and functional block of Piezo1 channel activity of primary cultured Schwann cells was confirmed.
Conclusions: Our data demonstrate that 1) AAVolig001 has unique and selective primary tropism to Schwann cells via intrasciatic delivery, which provides a useful tool in studying demyelinating disorders, and 2) Schwann cell Piezo1 contributes to mechanical hypersensitivity following nerve injury.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1326 / #981

Poster Topic: *Theme H: Demyelinating Diseases / H01. Therapeutic Targets, Mechanisms for Treatment*

DHCB ALLEVIATE MOUSE EAE MODEL IN GUT MICROBIOTA DEPENDENT MANNER

POSTERS: H01. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Haoran Wang, Zhou Jiawei
Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Laboratory Of Development And Degeneration Of Basal Ganglia, Shanghai, China

Aims: Multiple sclerosis is an inflammatory demyelinating disease of the CNS which specific nosogenesis remains unkonwn. We intented to study MS by using mouse EAE model and tried to alleviate this disease in the context of regulating gut microbiota.
Methods: The main methods we used is mouse EAE model. The mouse experimental autoimmune encephalomyelitis (EAE) model is widely used to study multiple sclerosis (MS), an autoimmune disease that affects the central nervous system. In this model, mice are immunized with myelin antigens, such as myelin basic protein (MBP) or proteolipid protein (PLP), to induce an immune response against their own myelin. This leads to the development of inflammation and demyelination in the central nervous system, similar to what is observed in MS patients.
Results: We gavage DHCB to mice following EAE model and found that DHCB could significantly reduce the severity of the EAE. By using16s rRNA sequencing technology, we found that gut micobiota were dramatically changes after gavage of DHCB which is critical for the neuroprotective role of DHCB.
Conclusions: In conclusion, we found that Chinese herb extracts, DHCB could prevent experimental autoimmune encephalomyelitis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1327 / #1567

Poster Topic: *Theme G: Huntington's and Other Neurodegenerative Diseases / G07. Animal Models*

UNTANGLING LONG-TERM EFFECTS OF BOTULINUM TOXIN AS THERAPY FOR MOTOR SYMPTOMS

POSTERS: G07. ANIMAL MODELS

Petra Šoštarić Mužić[1], Patrik Meglić[2], Ivica Matak[1]
[1]University Of Zagreb School Of Medicine, Department Of Pharmacology, Zagreb, Croatia, [2]School of Medicine University of Zagreb, Pharmacology, Zagreb, Croatia

Aims: Botulinum toxin A (BoNT-A) is often used as therapy for various motor disorders, including motor symptoms in Parkinsons disease and Parkinsonian syndromes. Its therapeutic effects are mostly associated with neuroparalysis of muscular motor terminals, but recent studies revealed that lasting effects on focal muscle hypertonia, are at least in part due to the toxin's central transcytosis. Here we examined action of botulinum toxin and its relative contribution of peripheral and central effects on normal and hyperactive muscles by implying neutralizing antitoxin and evoked focal spasticity by i.m. tetanus injection.
Methods: Male Wistar rats were unilaterally injected into gastrocnemius muscle with BoNT-A (Clostridium botulinum type A neurotoxin complex, 5 U/kg). After 24 hours, BoNT-A-neutralizing antitoxin (5 I.U.) was administered intrathecally to prevent the toxin's central transcytosis. Motor tests such as gait ability test, digit abduction score (DAS) and electrophysiological measurements were repeatedly performed to assess motor performance recovery. After the animals recovered, unilateral injection of TeNT (1,5 ng) was administered to gastrocnemius to induce spastic paralysis and assessed by ankle dorsiflexion resistance test, Basso–Beattie–Bresnahan locomotor rating scale (BBB) and monosynaptic H-reflex measurements.
Results: The BoNT-A induced lasting and reversible impairment of examined motor functions, which mostly recovered by day 70 post i.m toxin injection. The TeNT increased monosynaptic H-reflex was not decreased by BoNT-A. TeNT-evoked spastic paralysis was affected by BoNT-A central and peripheral effects showed during dorsiflexion test and BBB score.
Conclusions: This data suggest that combined peripheral and central effects of the peripherally administered BoNT-A are responsible for its lasting action in hyperactive muscle, while peripheral toxin effect are more important in motor performance impairment and lasting muscle atrophy. Funding: CSF-UIP-2019-04-8277

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1328 / #2848

Poster Topic: *Theme H: Demyelinating Diseases / H01. Therapeutic Targets, Mechanisms for Treatment*

CORPUS CALLOSUM MYELIN AND VOLUME PRESERVATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE: MRI OUTCOMES FROM THE OVERTURE STUDY

POSTERS: H01. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Xiao Da, Mihaly Hajos, Ralph Kern, Aylin Cimenser
Cognito Therapeutics, R&d, Cambridge, United States of America

Aims: In the OVERTURE study, 1-hour daily treatment of Alzheimer's Disease (AD) participants with Cognito Therapeutics' medical device preserved function, cognition, reduced brain atrophy, and preserved white matter volume and myelin content compared to sham treatment over 6 months (Da et al, 2023). We evaluated the effect of treatment on corpus callosum (CC) volume and myelin content.
Methods: OVERTURE (NCT03556280) participants across the AD spectrum were randomized 2:1 (Active:Sham) to receive daily, 1-hour, 40-Hz gamma sensory stimulation or sham treatment for six months. Structural MRI data from 50 participants were analyzed using DRAMMS (Ou et al, 2011) and MRTool (Ganzetti et al, 2014) to evaluate longitudinal changes in the CC (Mori et al, 2005). T1w and T1w/T2w ratio were used for volumetric and myelin content assessment, respectively. Bayesian linear mixed-effects modeling was used for statistical analysis.
Results: After 6 months, active treatment showed preserved corpus callosum myelin content (T1w/T2w ratio) and volume (T1w) compared to the sham treatment with a lower % change from baseline of myelin content in CC-total (4.14±1.50%, $p<.008$), CC-Body (4.21±1.60%, $p<.01$), CC-Genu (6.32±1.84%, $p<.001$) and CC-genu volume (2.94±0.93%, $p<.003$). We did not observe significant changes in the CC-splenium.
Conclusions: Six months of active treatment with Cognito Therapeutics' medical device preserved CC myelin content and volume compared to sham treatment in participants with AD. Myelin and white matter are important AD biomarkers that will be evaluated in the ongoing phase 3 HOPE study (NCT05637801).

P1329 / #1053

Poster Topic: *Theme H: Demyelinating Diseases / H01. Therapeutic Targets, Mechanisms for Treatment*

MENINGEAL LYMPHATIC DRAINAGE REGULATES OLIGODENDROCYTE SURVIVAL AND BRAIN MYELINATION

POSTERS: H01. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Sandro Da Mesquita
Mayo Clinic, Department Of Neuroscience, Jacksonville, United States of America

Aims: The meningeal lymphatic vessels are constantly draining cerebrospinal fluid content to the cervical lymph nodes, and functional defects in this previously unappreciated brain lymphatic cleansing pathway have been linked to accumulation of toxic protein aggregates, exacerbated neuroinflammation, and poor cognitive function. However, the impact of impaired meningeal lymphatic drainage on the function of specific brain cells and on the regulation of particular brain molecules, namely lipids, is still unknown. The main purpose of this study was to test whether and how decreased meningeal lymphatic drainage alters brain lipid composition and myelination.
Methods: To test the effect of meningeal lymphatic vessel ablation on brain myelination, we took advantage of two different mouse models, the VEGF-C/D trap and a genetic model that relies on the conditional deletion of *Prox1* from endothelial cells. Additionally, the cuprizone model was used to investigate the role of meningeal lymphatic drainage during the process of brain remyelination.
Results: Meningeal lymphatic vessel ablation resulted in altered oligodendrocyte gene expression, reduced myelin integrity, loss of specific lipid classes and decreased numbers of oligodendrocytes. Most of these results were recapitulated in a genetic model of meningeal lymphatic endothelial cell loss. Importantly, the loss of oligodendrocytes was not recapitulated in models with compromised adaptive or innate immune responses. Additionally, we observed that animals with impaired meningeal lymphatic function show a delay in the spontaneous remyelination process that occurs after cuprizone withdrawal.
Conclusions: Decreased meningeal lymphatic drainage is associated with a marked changes in mature oligodendrocytes, brain demyelination, and delayed remyelination.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1330 / #952

Poster Topic: *Theme H: Demyelinating Diseases / H01. Therapeutic Targets, Mechanisms for Treatment*

6-PYRUVOYL-TETRAHYDROPTERIN SYNTHASE MODULATES THE FUNCTION OF OPCS IN MULTIPLE SCLEROSIS

POSTERS: H01. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Hui Xiao[1], Zhou Jiawei[2]
[1]Center for Excellence in Brain Science and Intelligence Technology, Laboratory Of Development And Degeneration Of Basal Ganglia, Shanghai, China, [2]Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Laboratory Of Development And Degeneration Of Basal Ganglia, Shanghai, China

Aims: During multiple sclerosis (MS), remyelination is occurred at the early stage of the disease but is finally failed. The most likely reason is the dysfunction of oligodendrocyte precursor cells (OPCs). Therefore, maintaining the function of OPCs has been proposed as a potential therapeutic approach for MS. Patients with deficiency of 6-Pyruvoyl-tetrahydropterin synthase (PTS) exhibited abnormal myelination, which indicated the correlation of PTS and myelination. We investigated the role of PTS in OPCs during the process of experimental autoimmune encephalomyelitis (EAE), an animal model of MS.
Methods: Mice lacking PTS in OPCs (*Pts*^{pdgfra} cKO mice) were used to investigate the impact of *Pts* in OPCs on the process of EAE. The number of oligodendrocyte lineage cells were evaluated by immunohistochemistry, Western blot, and quantitative PCR. RNA sequencing analysis was carried out to identify differentially expressed genes in spinal cord of *Pts*^{pdgfra} cKO mice with EAE. Primary OPCs and oli-neu cells were used to examine the regulation of PTS to OPCs.
Results: We show the upregulation of PTS in MS brain. Mice lacking PTS in OPCs exhibit a delay in the onset of EAE and decreased demyelination. The proliferation of OPCs and the level of *Mbp* was increased in spinal cord of PTS deletion mice. Mechanistically, PTS regulates the expression of hydroxy-3-methylglutary-coenzyme-A synthase 1 (HMGCS1), which is the first enzyme catalyze cholesterol de novo synthesis. In OPCs, knockdown of PTS and overexpress HMGCS1 both increased the expression of *Cspg4*, which regulates the proliferation of OPCs.
Conclusions: Our findings suggest that PTS modulates the proliferation of OPCs and demyelination during EAE, and provide a new drug target to regulate the proliferation of OPCs to treat demyelinating diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1331 / #670

Poster Topic: *Theme H: Demyelinating Diseases / H01. Therapeutic Targets, Mechanisms for Treatment*

INHIBITION OF ASTROCYTIC DRD2 SUPPRESSES CNS INFLAMMATION VIA PTS IN AN ANIMAL MODEL OF MULTIPLE SCLEROSIS

POSTERS: H01. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Guo Yongshun, Lu Shenzhao, Wu Yue, Zhou Jiawei
Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Laboratory Of Development And Degeneration Of Basal Ganglia, Shanghai, China

Aims: Astrocytes, which are the most abundant type of glial cell in the central nervous system, play essential roles in the maintenance of central nervous system homeostasis and contribute to the pathogenesis of neurodegeneration diseases. Dopamine is one of the abundant neurotransmitters, regulating multiple important physical processes. Although dopamine receptors are expressed in astrocytes, the impact of dopamine on glial cells is largely unknown. In this study, we investigated the function of astrocytic dopamine D2 receptor (Drd2) and its downstream signaling pathway in the pathogenesis of multiple sclerosis (MS).
Methods: Astrocytic Drd2 conditional knockout mice were used to investigate the their role in experimental autoimmune encephalomyelitis (EAE), an animal model of MS. RNAseq was perform to explore the downstream pathway of Drd2 to regualte the inflammation. Drd2 antagonists were also screened to verify whether it could be used as a new target for the treatment of MS.
Results: We showed the upregulation of Drd2 in reactive astrocytes in MS brain. Mice deficient in astrocytic Drd2 exhibited a remarkable suppression of reactive astrocytes and inflammation which were correlated with the amelioration of EAE. Comparison of the transcriptional profiles between mice deficient in astrocytic Drd2 and control revealed that astrocytic Drd2 regulated the expression of 6-pyruvoyl-tetrahydropterin synthase (PTS) which modulated NF-κB activity through protein kinase C delta. Pharmacological blockade of astrocytic Drd2 with Drd2 antagonist dehydrocorybulbine remarkably inhibited the inflammatory response in vitro and in vivo.
Conclusions: Our findings reveal a crucial role of astrocytic Drd2, and its downstream signaling pathway in the modulation of inflammatory response in astrocytes during MS pathogenesis. This study also provides new insights into the role of astrocytes in neurodegenerative processes and development of potential therapeutics for treatment of neurodegeneration diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1332 / #2933

Poster Topic: *Theme H: Demyelinating Diseases / H01. Therapeutic Targets, Mechanisms for Treatment*

MULTIPHASIC ADEM IN A 14 YEAR OLD BOY

POSTERS: H01. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Pratyush Kumar
HIMALAYAN INSTITUTE OF MEDICAL SCIENCES, Department Of Neurology, DEHRADUN, India

Aims: To explore the clinical features and prognostic factors for relapse of acute disseminated encephalomyeltis (ADEM) in an adolescent .
Methods: A 14 year old boy was prospectively analyyzed on the basis of clinical manifestations , laboratory features , magnetic resonance imaging (MRI) , treatment and prognosis .
Results: A 14 year old boy presented to us with recurrent episodes of focal neurological deficit .The patient was apparently alright until June 2022 when he developed fever followed by quadriparesis. Mri was suggestive of focal hyperintensities in left frontal lobe and subcortical and periventricular white matter. Similar signals were seen were also seen in splenium of corpus callosum and on pons in the right side . T2 weighted images showed with hyperintense signal involving long segment of cervical cord from . Csf analysis revealed albuminocytological dissociation .Oligoclonal band cells were negative in Csf . Serum anti mog and anti aquaporin 4 antibody in were also negative. VEP was b/l abnormal. Patient was given pulse methylprednisolone for 5 days after which he recovered with residual weakness. This episode was followed by similar episodes of neurological deficit at 6 months and 12 months respectively with new lesions on MRI.
Conclusions: Multiphasic ADEM involves two or more episodes that are separated by at least 3 months.It is a rare entity. The treatment of multiphasic ADEM is aimed at reducing inflammation and preventing further damage to myelin .The main treatment is high dose corticosteroids which are usually given intravenously for a few days . Other immunosuppressive or immunomodulatory drugs may be used like IVIG ,Plasmapharesis, rituximab or cyclophosphamide.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1333 / #328

Poster Topic: *Theme H: Demyelinating Diseases / H02. Imaging, Biomarkers, Diagnostics*

LOWER MYELIN CONTENT IS ASSOCIATED WITH STEEPER LONGITUDINAL DECLINE IN MOTOR FUNCTION: NEW INSIGHTS USING ADVANCED MAGNETIC RESONANCE PHYSICS

POSTERS: H02. IMAGING, BIOMARKERS, DIAGNOSTICS

Mustapha Bouhrara, Siddique Akhonda, Mary Faulkner, John Laporte, Zhaoyuan Gong
National Institutes of Health, National Institute On Aging, Baltimore, United States of America

Aims: Mounting evidence indicates that myelin breakdown is a major hallmark of Alzheimer's and Parkinson's diseases. We previously have provided evidence of the role of myelination in cognitive changes (PMC10387505). We also showed that lower myelin content is associated with lower gait speed (GS) (PMC10395567). Here, we expanded our work to provide original results linking myelin content to changes in motor function.
Methods: Our study cohort included 123 cognitively unimpaired participants. For each participant, myelin content was probed using our advanced MRI method of myelin water fraction (MWF), a direct measure of myelin content. Rapid and Usual gait speeds (UGS, RGS), two integrative measures of motor function, were measured longitudinally over a long time period. Voxel-wise linear mixed-effects models were used to assess the associations between MWF and longitudinal changes in UGS and RGS. Statistical significance was defined as $p < .001$ with a cluster size > 400 voxels.
Results: Our results showed regional associations between MWF and UGS or RGS, with lower myelin content, that is, lower MWF, associated with steeper declines in gait speeds. These associations were significant in various cerebral white matter structures investigated.
Conclusions: For the first time, we showed a strong and significant relationship between myelin content and the rate of changes in motor function in cognitively normal individuals. These findings advance our understanding on the implication of myelination in gait impairment among cognitively unimpaired adults, providing further evidence of the interconnection between white matter integrity and motor function. Finally, MWF may serve as a potential sensitive and specific imaging biomarker for predicting motor changes in normative aging and cognitive impairments, including Alzheimer's and Parkinson's diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1334 / #283

Poster Topic: *Theme H: Demyelinating Diseases / H02. Imaging, Biomarkers, Diagnostics*

BIG-TAU AND BRAIN-DERIVED TAU DYNAMIC IN GUILLAIN-BARRÉ SYNDROME AND ALZHEIMER'S DISEASE

POSTERS: H02. IMAGING, BIOMARKERS, DIAGNOSTICS

Fernando Gonzalez-Ortiz[1], Kaj Blennow[2], Thomas Karikari[3], Hlin Kvartsberg[4], Henrik Zetterberg[2], Luis Querol Gutierrez[5], Lorena Martin Aguilar[5]
[1]Gothenburg University, Psychiatry And Neurochemistry, Göteborg, Sweden, [2]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Molndal, Sweden, [3]University of Gothenburg, Psychiatry And Neurochemistry, Göteborg, Sweden, [4]Sahlgrenska University Hospital, Psychiatry And Neurochemistry, Göteborg, Sweden, [5]hospital sant pau, Neuromuscular Unit, Barcelona, Spain

Aims: Biomarkers for monitoring disease activity and treatment outcomes in patients with neuropathies are lacking. A high-molecular-weight isoform of tau protein, called big-tau, is predominantly expressed in PNS. Our objective is to study the dynamic of big-tau and brain-derived tau (BD-tau) in blood in patients with Guillain-Barré syndrome (GBS), including the Miller-Fisher syndrome (MFS) variant, and Alzheimer's disease (AD).
Methods: We measured big-tau and BD-tau in serum samples from 101 GBS patients, 89 of them prospectively included in the IGOS study (at baseline and at different timepoints), 12 MFS patients, 41 healthy controls (HC) and 20 AD patients.
Results: GBS patients had significantly higher big-tau levels than AD (11.43 vs 2.77pg/ml, p<0.001). BD-tau levels were higher in AD compared to the GBS group (11.29 vs 3.29 pg/ml, p<0.001). Big-tau levels increased at week 1 and 2 to subsequently decrease up to 1 year. BD-tau levels maintained stable or with a slight increase at follow-up in most GBS patients. Patients with MFS had higher BD-tau levels than other forms of GBS (12.72 vs 3pg/ml, p=0.003) and lower big-tau levels (5.39 vs 11.43pg/ml, p=0.002). GBS patients with ganglioside antibodies had higher levels of both biomarkers (for BD-tau 3.76 vs 2.51pg/ml, p=0.01 and for big-tau 13.23 vs 8.26 pg/ml, p=0.001).
Conclusions: Big tau is a potential new marker in GBS. Patients with GBS had higher big-tau levels than AD and HC. Patients with MFS had higher levels of BD-tau and lower levels of big-tau compared to other forms of GBS, supporting the role of CNS involvement in those patients. The dynamic Big tau/BD-tau in blood may help to determine the magnitude of CNS or PNS affection in different pathologies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1335 / #2689

Poster Topic: *Theme H: Demyelinating Diseases / H03. Animal Models*

INVESTIGATION OF MOTOR COORDINATION AND MEMORY PROCESSES DURING THE DEMYELINATION AND REMYELINATION PERIODS IN A CUPRIZONE MODEL OF MULTIPLE SCLEROSIS

POSTERS: H03. ANIMAL MODELS

Ivalina Valchinkova[1], Ivanka Kostadinova[2], Aleksandar Iliev[3], Stancho Stanchev[4], Nikola Stamenov[3], Lyubomir Gaydarski[3], Boycho Landzhov[3]
[1]Faculty of pharmacy, Medical university-Sofia, Pharmacology, Pharmacotherapy And Toxicology, Sofia, Bulgaria, [2]Faculty of pharmacy, Medical university of Sofia, Pharmacology, Pharmacotherapy And Toxicology, Sofia, Bulgaria, [3]Faculty of Medicine, Medical university of Sofia, Anatomy, Hystology And Embryology, Sofia, Bulgaria, [4]Faculty of Medicine, Medical university ot Sofia, Anatomy, Hystology And Embryology, Sofia, Bulgaria

Aims: The aim of this study was to determine the changes in the body weight, motor coordination and memory processes in the context of a cuprizone model of multiple sclerosis in mice.
Methods: The neurotoxicant, cuprizone, was administered to 8-week-old C57BL/6 mice with the drinking water at a concentration of 0.2% for 5 weeks in order to induce demyelination. After 5 weeks, cuprizone intake was discontinued and the mice received only drinking water for the next 5 weeks to allow remyelination. The body weight of the mice was measured daily during the first week and then once a week for the entire period of the experiment. Motor coordination and passive avoidance experiments were conducted at the end of each week. After the period of demyelination and remyelination, an immunohistochemical study with antibodies for apelin receptor and progenitor oligodendrocytes was also performed.
Results: The body mass of the mice did not change significantly throughout the experiment. During the remyelination period, a gradual improvement in balance and memory processes in the mice was observed.
Conclusions: 5-week administration of the neurotoxicant cuprizone did not result in a significant change in the body mass of the mice. Compared to the demyelination period, the removal of cuprizone from the drinking water lead to an improvement in mice's gait, coordination, and memory. **Funding: The investigations were conducted with the financial support from Grant 2023, Contract №: D-178/03.08.2023 to the Council of Medical Science of the Medical University of Sofia, Bulgaria**

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1336 / #2192

Poster Topic: *Theme H: Demyelinating Diseases / H02. Imaging, Biomarkers, Diagnostics*

QUANTITATIVE ANALYSIS OF S1PR1 EXPRESSION IN THE BRAIN OF MS PATIENT USING [3H]CS1P1

POSTERS: H02. IMAGING, BIOMARKERS, DIAGNOSTICS

Zhude Tu[1], Jiang Hao[1], Charles Zhou[1], Lin Qiu[1], Stephen Moerlein[1], Robert Gropler[1], Matthew Brier[1,2], Gregory Wu[2], Anne Cross[2], Joel Perlmutter[1,2], Tammie Benzinger[1,2]
[1]Washington University School of Medicine in Saint Louis, Radiology, Saint Louis, United States of America, [2]Washington University School of Medicine in Saint Louis, Neurology, Saint Louis, United States of America

Aims: Multiple sclerosis (MS) is an immune-mediated disease characterized by demyelination and inflammation in the central nervous system (CNS). Previous studies demonstrated sphingosine-1-phosphate receptor (S1PR) modulators effectively reduce expression of S1PRs, especially S1PR1, from the surface of most lymphocytes, thereby reducing immune cell trafficking out of secondary lymphoid tissues and reducing entry of pathogenic cells into CNS. Studies have also implicated direct CNS effects of S1PR modulators in MS with several lines of evidence suggesting a non-immune, inflammatory role of S1PR1 within the CNS.
Methods: In this study, we explored the role of S1PR1 in the development and progression of demyelinating pathology of MS by quantitative assessment of S1PR1 expression using our S1PR1 specific radioligand, [^{3}H]CS1P1, in post-mortem CNS tissues including cortex, cerebellum, and spinal cord of MS and neurologically healthy cases. Immunohistochemistry and whole slide scanning of S1PR1 along with various myelin proteins were also performed.
Results: Autoradiography analysis using [^{3}H]CS1P1 showed the expression of S1PR1 was significantly elevated in lesions compared to non-lesion tissue in MS cases, as well as neurologically healthy controls. Gray and non-lesion white matter did not significantly differ between controls and MS CNS tissues. Saturation autoradiography analysis showed an increased binding affinity (K_d) of [^{3}H]CS1P1 to S1PR1 in both gray matter and white matter of MS brains compared to healthy brains. Our findings demonstrated the activation of S1PR1 and an increased uptake of [^{3}H]CS1P1 in the lesions of MS CNS. The elevated binding affinity [^{3}H]CS1P1 to S1PR1 in MS brains suggested physical or biochemical changes of S1PR1 in MS brains that can impact ligand-receptor binding.
Conclusions: Our quantitative autoradiography analysis using [^{3}H]CS1P1 on human postmortem tissues demonstrates the feasibility of novel diagnostic strategies for MS by targeting S1PR1.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1337 / #1913

Poster Topic: *Theme I: Lysosomal Storage Diseases / I01. Disease Mechanisms, Pathophysiology*

INVESTIGATING THE ROLE OF LYSOSOMAL HYDROLASES IN ALZHEIMERS DISEASE: FROM ZEBRAFISH TO HUMAN.

POSTERS: I01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

George Sigalas[1], Anders Wallin[1,2], Petronella Kettunen[1,2]
[1]University of Gothenburg, Neuroscience And Physiology, Gothenburg, Sweden, [2]Sahlgrenska University Hospital, Psychiatry, Cognition And Old-age Psychiatry, Mölndal, Sweden

Aims: Cathepsin B and D are lysosomal hydrolases that are implicated in Alzheimer's disease (AD). During the past years, research has produced contradictory results regarding their role in pathological processes, some of which show an increase in the expression levels of cathepsins in AD, while others show a decrease. Hence, the exact mechanism underlying their function and correlation with AD pathology remains unclear. In this study, we aimed at investigating their role in lysosomal function by using the zebrafish and compare our results to CSF biomarker analysis of control and AD patients from the Gothenburg Mild Cognitive Impairment study at the Memory Clinic in Gothenburg, for which brain imaging data, neuropsychological tests, as well as the core AD CSF biomarkers are available.
Methods: To manipulate cathepsin signaling we used Pepstatin A and CA-074, two drugs that inhibit cathepsin D and B respectively, in transgenic ApoE:GFP zebrafish marking microglia. Moreover, the cathepsin levels were analyzed in CSF of control, as well as AD patients.
Results: We explored cathepsin function in live zebrafish, focusing on microglia function. In short, microglia morphology, phagocytosis, as well as lysosomal function were investigated in vivo using confocal microscopy. Moreover, cathepsins were measured in human CSF and data were correlated to other patient variables, such as the core AD CSF biomarkers indicating disease progression.
Conclusions: Our study combining an innovative new model for microglia function in neurodegenerative diseases, with analysis in well-characterized human samples helps unravel the function of cathepsins in AD pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1338 / #2776

Poster Topic: *Theme I: Lysosomal Storage Diseases / I01. Disease Mechanisms, Pathophysiology*

DEMENTIA WITH LEWY BODIES IN A PATIENT WITH GAUCHER DISEASE

POSTERS: I01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Marta Villa Lopez[1], Oksana Suchowersky[2,3], Shailly Jain[3]
[1]University of Alberta, Medical Genetics, Edmonton, Canada, [2]University of Alberta, Department Of Neurology, Edmonton, Canada, [3]University of Alberta, Medical Genetics, EDMONTON, Canada

Aims: This clinical case report aims to deepen our understanding of the relationship between GBA1 mutations and synucleinopathies. Biallelic GBA1 mutations typically result in Gaucher disease (GD). Not only patients with GD, but patients with GBA1 heterozygous mutations have an increased risk of Parkinson's disease (3.5-6 times) and dementia with Lewy bodies (8.28 times).
Methods: We conducted a comprehensive evaluation of a 67-year-old male with a history of Gaucher disease type 1 who exhibited a two-year decline in cognition and parkinsonism. Our assessment involved cognitive testing, neurological examination, neuroimaging, analysis of genetic history related to GBA1 mutations, and documentation of the response to dopamine replacement therapy, along with a literature review.
Results: Cognitive assessments revealed notable decline, especially in attention and visuospatial domains. The physical examination indicated mild symmetric parkinsonism, and MRI showed mild generalized atrophy. The patient experienced improved motor symptoms with levodopa, but higher doses were intolerable due to cognitive issues.
Conclusions: With the increasing use of enzyme replacement therapy in Gaucher disease, more patients are reaching ages at which they may develop parkinsonism. While the association between Parkinson's disease and Gaucher disease has been extensively studied, there is limited literature on the connection between Lewy body dementia and Gaucher disease. Thus, it is crucial to consider this diagnosis in GBA1 mutation carriers experiencing cognitive decline, as it could have significant implications for their clinical management in the future.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1339 / #1271

Poster Topic: *Theme H: Demyelinating Diseases / H03. Animal Models*

THE EFFECTS OF MELATONIN ON CLINICAL SEVERITY IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS MODEL OF MULTIPLE SCLEROSIS; A SYSTEMATIC REVIEW AND META-ANALYSIS

POSTERS: H03. ANIMAL MODELS

Reza Mosaddeghi-Heris[1], Hadis Razmaray[2], Ehsan Nasiri[2], Pouya Vakilipour[2], Soroush Morsali[2], Afshin Moradi[2], Asal Ebrahimian[2], Sahel Rashidi[2], Amirreza Naseri[2], Saeed Sadigh-Eteghad[1]
[1]Tabriz university of medical sciences, Neurosciences Research Center (nsrc), Tabriz, Iran, [2]Tabriz university of medical sciences, Student Research Committee, Tabriz, Iran

Aims: Through the antioxidant and anti-inflammation pathways, melatonin is proposed as a safe and effective intervention in neurological diseases. This study aims to evaluate the effects of melatonin supplementation on the clinical outcomes in the experimental autoimmune encephalomyelitis (EAE) model, which is the most common animal model for MS.
Methods: This study was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Animal studies that reported the effects of melatonin in preclinical EAE models are included in this study. Letters to the editors, conference papers, studies with overlapping data, human studies, reviews, and articles published in languages other than English were excluded. A systematic search in PubMed, Web of Science, Embase, and Scopus up was conducted in April 2023. The collaborative Approach to Meta-Analysis and Review of Animal Experimental Studies (CAMARADES) critical appraisal tool was used for the quality assessment of the studies and the quantitative synthetizes were conducted using the comprehensive meta-analysis software.
Results: Out of 542 studies, finally 10 studies were included in this study. The route of administration was intraperitoneal in 7 studies, oral in 2 studies, and subcutaneous in 1 study. The quantitative synthesis of the EAE clinical severity scale was associated with significant differences (standardized mean difference [SDM]: -2.52; -3.61 to -1.42; p-value<0.01). In subgroup analyses, the difference was statistically significant in the mouse subgroup (p-value<0.01) but not in the rat subgroup (p-value=0.39). Partially, in two studies, melatonin treatment was not effective, but in 8 other studies, it was reported to be effective.
Conclusions: This study encountered that melatonin may be associated with improved clinical outcomes of the preclinical EAE model, which suggested future well-designed clinical studies on this topic.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1340 / #933

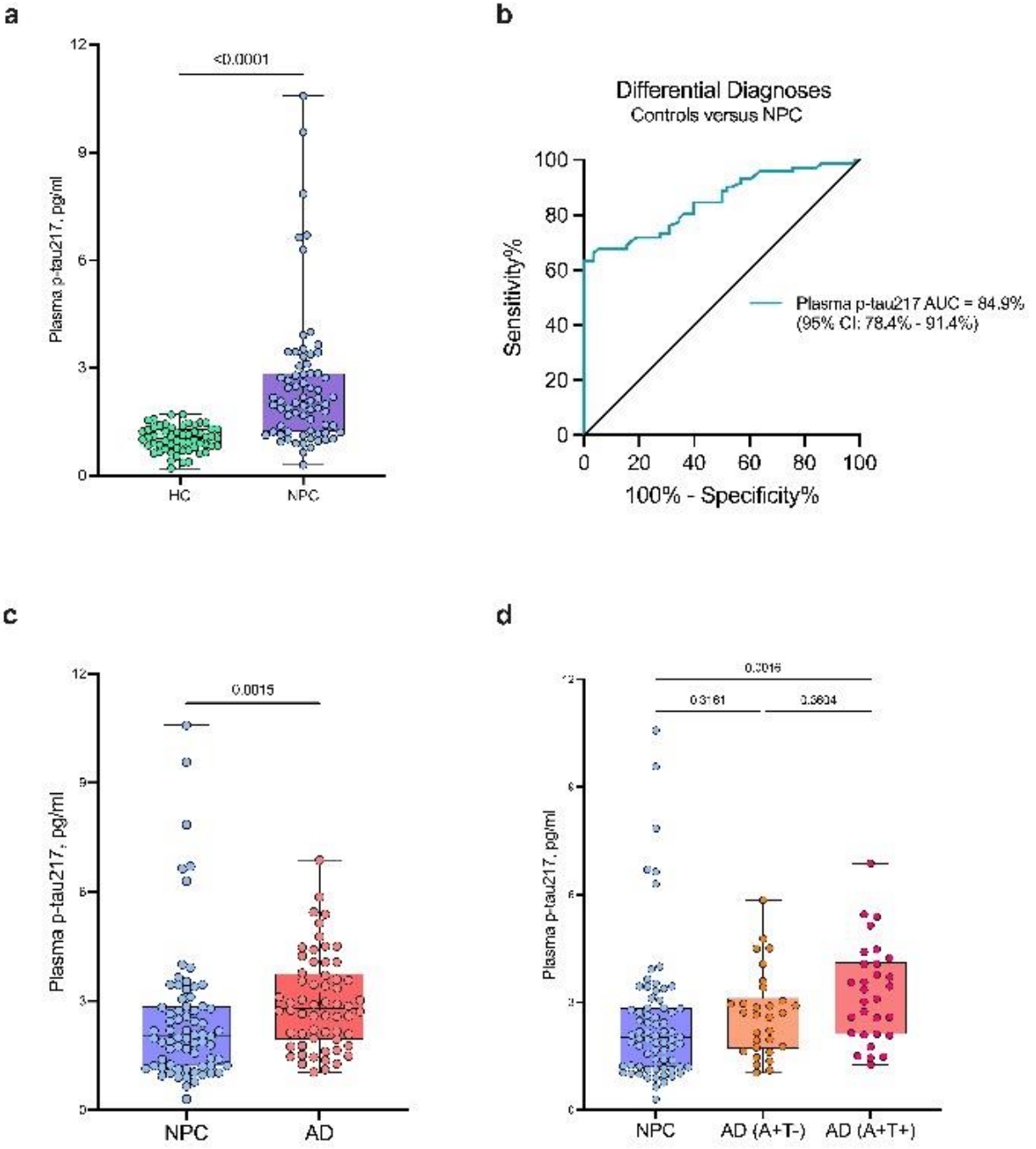
Poster Topic: *Theme I: Lysosomal Storage Diseases / I01. Disease Mechanisms, Pathophysiology*

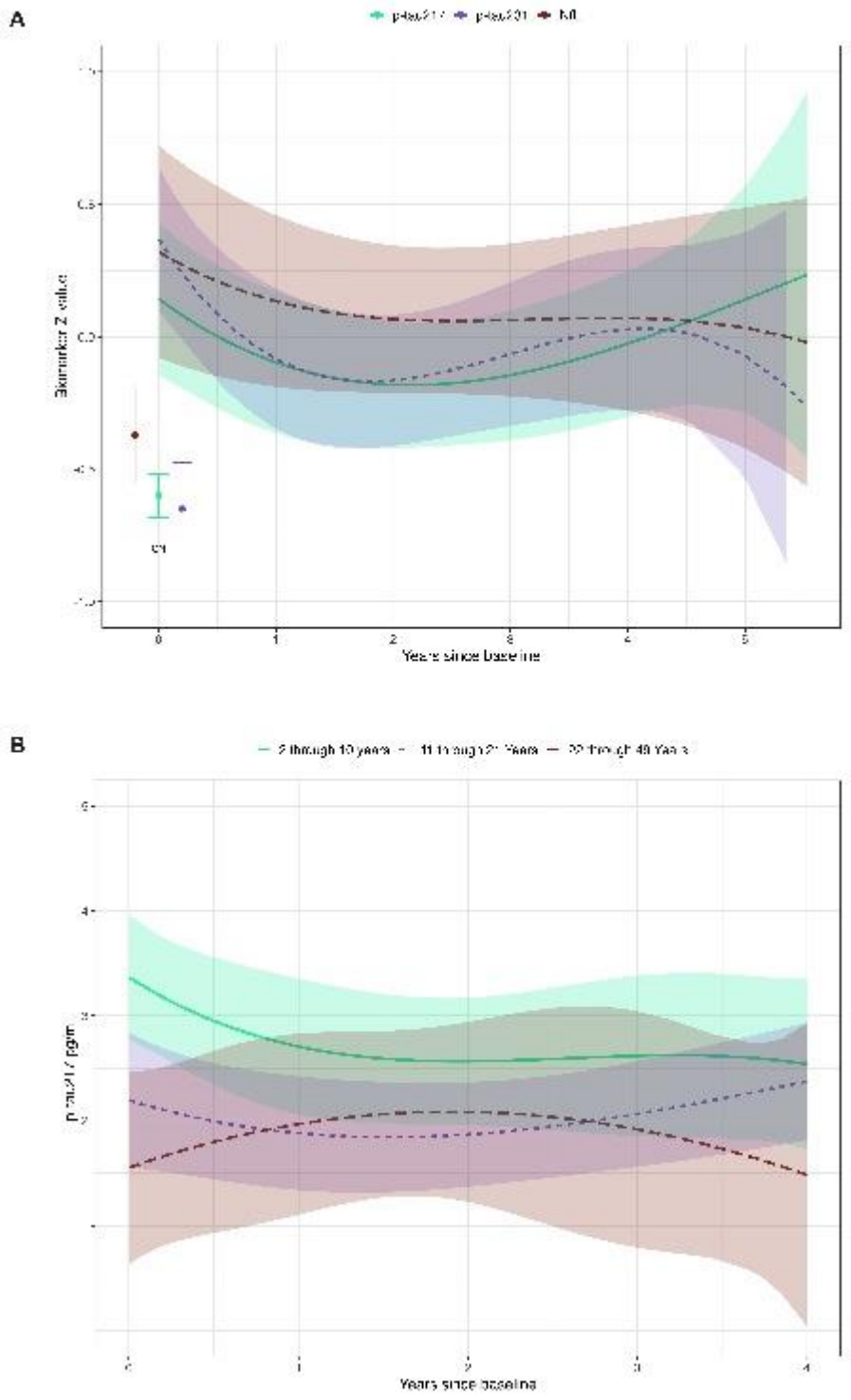
PLASMA P-TAU217 AS A BIOMARKER OF SEVERITY AND DISEASE PROGRESSION IN NIEMANN-PICK DISEASE TYPE C, A TANGLE PATHOLOGY WITHOUT AMYLOIDOSIS.

POSTERS: I01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Fernando Gonzalez-Ortiz[1], Kaj Blennow[1], Thomas Karikari[2], Tormod Fladby[3], Bjørn-Eivind Kirsebom[4], Frances Platt[5], Dawn Shepherd[5], Danielle Te Vruchte[5]
[1]Gothenburg University, Psychiatry And Neurochemistry, Göteborg, Sweden, [2]Gothenburg University, Psychiatry And Neurochemistry, Gothenburg, Sweden, [3]Akerhus University Hospital, Neurology, Oslo, Norway, [4]Akerhus University Hospital, Neurology, Lørenskog, Norway, Norway, [5]Oxford Univeristy, Lysosomal And Sphingolipid Disorders, Oxford, United Kingdom

Aims: Niemann-Pick disease type C (NPC) is a genetic condition primarily characterized by the accumulation of cholesterol and sphingolipids within cellular compartments, leading to neurodegeneration and cognitive impairment. Unlike Alzheimer's disease (AD), NPC does not exhibit amyloid β (Aβ) plaques. However, both conditions present neurofibrillary tangles (NFT) of hyperphosphorylated tau. Moreover, NFT in AD and NPC have the same pattern of phosphorylation and seem to be almost identical. Plasma p-tau correlations with amyloid deposition, established either by PET or CSF positivity, have led to the idea that p-tau reflect amyloid pathology more than tau. Amid of this speculation, we decided to investigate the role of plasma p-tau217 in NPC.
Methods: We measured plasma p-tau217 in a multicentre cohort (n=180), consisting of healthy controls (n=60), NPC patients (n=60) and AD patients (n=60). Furthermore, we investigated plasma p-tau217 associations with age, annual severity increment score (ASIS) and magnitude of lysosomal dysfunction in NPC and compared levels in NPC and AD.
Results: Plasma p-tau217 was significantly higher in the NPC group compared to controls (2.52 pg/ml ±1.93 and 1.02 ± 0.34, respectively, $p<0.001$, AUC: 0.85). P-tau217 levels correlated inversely with age at baseline ($R= -0.57$, $p<0.001$) and positively with longitudinal increases in lysosomal enlargement and ASIS ($R=0.26$, $p<0.001$ and $R=0.46$, $p<0.001$, respectively). Mean concentrations of plasma p-tau217 in AD were higher than levels in the NPC group (2.97 pg/ml ±1.30 and 2.52 pg/ml ±1.93, respectively).


a
<0.0001
Plasma p-tau217, pg/ml
12
9
6
3
0
HC
NPC
b
Differential Diagnoses
Controls versus NPC
Sensitivity%
100
80
60
40
20
0
0
20
40
60
80
100
100% - Specificity%
Plasma p-tau217 AUC = 84.9%
(95% CI: 78.4% - 91.4%)
c
0.0015
Plasma p-tau217, pg/ml
NPC
AD
d
0.3016
0.3161
0.3604
Plasma p-tau217, pg/ml
NPC
AD (A+T-)
AD (A+T+)



Conclusions: Our findings indicate that plasma p-tau217 can reflect tau pathology independently of brain amyloid. However, joint amyloid and tau pathologies, as in AD, have stronger effects on this marker. High

levels of plasma p-tau217 in NPC were associated with disease severity and rapid progression, supporting its use as a prognostic/monitoring marker.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1341 / #936

Poster Topic: *Theme I: Lysosomal Storage Diseases / I02. Therapeutic Targets, Mechanisms for Treatment*

INFLAMMATION AND AUTOPHAGY DYSFUNCTION IN METACHROMATIC LEUKODYSTROPHY: MTOR AS A NOVEL THERAPEUTIC TARGET?

POSTERS: I02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Daniel Erskine[1], Zoe Catchpole[1], Annabelle Eleana Hartanto[1], Tetsushi Kataura[2], Kate Madden[1], Viktor Korolchuk[2]
[1]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Biosciences Institute, Newcastle upon Tyne, United Kingdom

Aims: Metachromatic leukodystrophy (MLD) is a rare lysosomal storage disorder characterised by the accumulation of sulfated cerebrosides (sulfatide) that underlies the striking white matter degeneration that underlies cognitive and motor impairment in MLD. The aim of the present study was to investigate disease mechanisms in MLD, with a view to developing novel therapies for patients for whom gene therapy is not indicated.
Methods: *Post-mortem* tissue was obtained from the globus pallidus and dentate nucleus of MLD cases (N=5) and age-, sex- and ethnicity- matched controls for discovery proteomics analysis, combined with histological validation. Pathways identified from the neuropathology study were then further studied by exposing HMC3 microglial cells and MLD fibroblasts to sulfatide *in vitro* and characterising the cellular phenotype. Drugs based on pathways identified from the neuropathology were then tested in MLD fibroblasts to determine whether they rescue the phenotype.
Results: Discovery proteomics identified up-regulation of inflammatory pathways and the mTOR nutrient-sensing pathway in MLD cases. Imunoblotting of MLD tissue identified accumulation of autophagosomes, consistent with deficient autophagy in the context of mTOR activation. Sulfatide exposure led to changes in HMC3 microglia consistent with activation, including morphological changes and increased production of reactive oxygen species. Screening of the mTOR inhibitor, rapamycin, in MLD fibroblasts is on-going.
Conclusions: These findings suggest that MLD is characterised by widespread inflammation and deficient autophagy, both potentially resulting from activation of the mTOR pathway as a result of lysosomal dysfunction. As mTOR inhibition has been demonstrated to attenuate inflammation and white matter loss in the related condition, Krabbe disease, these findings may indicate mTOR is a key mechanistic target in ameliorating lysosomal storage disorders characterised by accumulated sphingolipids.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1342 / #1258

Poster Topic: *Theme I: Lysosomal Storage Diseases / I02. Therapeutic Targets, Mechanisms for Treatment*

THERAPEUTIC POTENTIAL OF HUMAN MICROGLIAL TRANSPLANTATION FOR THE TREATMENT OF SANFILIPPO SYNDROME (MPS-IIIA)

POSTERS: I02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Alina Lahian[1], Jean Paul Chadarevian[1], Johannes Schlachetzki[2], Jonathan Hasselmann[3], Sepideh Kiani Shabestari[1], Christina Tu[3], Lauren Le[3], Chris Glass[2], Jeffrey Esko[2], Philip Gordts[2], Hayk Davtyan[1], Mathew Blurton-Jones[1]
[1]University of California Irvine, Department Of Neurobiology And Behavior, Irvine, United States of America, [2]University of California, Department Of Cellular And Molecular Medicine, San Diego, United States of America, [3]University of California Irvine, Institute For Memory Impairments & Neurological Disorders, Irvine, United States of America

Aims: Sanfilippo Syndrome(MPSIIIA) is a devastating pediatric lysosomal storage disease that leads to progressive neurodegeneration and greatly shortened life span. MPSIIIA results from loss of function mutations in N-Sulphoglucosamine Sulphohydrolase(SGSH), a lysosomal enzyme critical for the degradation and recycling of heparan sulfate(HS) glycosaminoglycans(GAG). Recent evidence suggests that microglia express the highest levels of SGSH within the brain. Therefore, correction of SGSH mutations within microglia, or the transplantation of healthy microglia, could potentially increase levels of this enzyme, enhancing the degradation and clearance of HS-GAGs, and slowing or even preventing further neurodegeneration.
Methods: To explore the potential for human microglia transplantation, we generated a novel xenotolerant mouse model of MPSIIIa via CRISPR-deletion of SGSH. Following histochemical and biochemical validation, SGSH KO pups(P1-P2) were transplanted with saline or human iPSC-microglia progenitor cells. After 4months, mice were sacrificed, peripheral blood and liver collected and hemibrains dropfixed for immunohistochemical analysis and flash frozen for biochemistry and single nuclei RNA sequencing.
Results: Initial analysis of 4-month old SGSH-KO mice reveals a dramatic increase in lysosomal content, gliosis, lipid accumulation, and greatly elevated levels of nonreducing end heparan sulfates(HS-NRE). Remarkably, transplantation of human microglial progenitors significantly lowers lysosomal accumulation and suggests preliminary evidence of cross-correction by reducing lysosomal content within murine neurons adjacent to engrafted human microglia. Biochemical analysis further revealed that microglia transplantation partially restores enzymatic function leading to a significant reduction in disease-specific HS-NRE. Ongoing experiments will further examine mRNA and protein expression levels to elucidate the impact of human microglial transplantation on neuronal and other cell populations within the brain.
Conclusions: Taken together, these results provide the first evidence that iPSC-microglia could potentially be developed as a novel therapy for MPSIIIA and likely other lysosomal storage diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1343 / #1756

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J01. Disease Mechanisms, Pathophysiology*

EVIDENCE FOR APOER2-DAB1 PATHWAY DISRUPTION IN THE AMYGDALA IN SPORADIC ALZHEIMER'S DISEASE

POSTERS: J01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Christopher Ramsden[1], Mark Horowitz[1], Daisy Zamora[1], Dragan Maric[2]
[1]National Institutes of Health, Nia/lci/lpu, Bethesda, United States of America, [2]National Institute on Neurological Diseases and Strokes, Ninds/nih, Bethesda, United States of America

Aims: Neuropsychiatric symptoms are common early manifestations of sporadic Alzheimer's disease (sAD) that are associated with more rapid progression to severe dementia and death. Degeneration of the amygdala, a hub for emotional regulation and fear memory, may contribute to neuropsychiatric and cognitive manifestations of sAD. The ApoE receptor 2-Disabled homolog-1 (ApoER2-Dab1) pathway suppresses Tau phosphorylation as part of a multi-arm pathway that regulates cytoskeletal and synaptic integrity. Our group previously showed that multiple ApoER2-Dab1 components accumulate together with hyperphosphorylated Tau (pTau) in the hippocampus in mild cognitive impairment (MCI) and sAD cases. Here, we sought to assess whether ApoER2-Dab1 pathway components accumulate in amygdala in MCI and sAD.
Methods: Imunohistochemistry (IHC) was used to label ApoER2-Dab1 components in coronal amygdala sections from 30 rapidly autopsied cases spanning the clinicopathological spectrum of AD. IHC images were uploaded into HALO image analysis software (Indica Labs, Corrales, NM). Stain positive area was quantified and compared to a standard battery of neuropathological, cognitive, and neuropsychiatric endpoints. Multiplex-IHC was used to provide spatial and cytoarchitectural context for ApoER2-Dab1 pathway marker accumulation.
Results: Two ApoER2 ligands (ApoE and ApoJ) and five intraneuronal ApoER2 signaling partners (Dab1, pP85α$_{Tyr607}$,pLIMK1$_{Thr508}$, pTau $_{Ser202/Thr205}$ and pPSD95$_{Thr19}$) were higher in MCI and sAD cases than non-sAD controls and correlated with histological progression and cognitive and/or neurobehavioral manifestations of sAD. Multiplex-IHC revealed that Dab1, pP85α$_{Tyr607}$,pLIMK1$_{Thr508}$, pTau $_{Ser202/Thr205}$ and pPSD95$_{Thr19}$ accumulated together within MAP2-labeled dystrophic dendrites and soma of ApoER2-expressing neurons in the vicinity of ApoE/ApoJ-enriched extracellular plaques.
Conclusions: Findings add to growing evidence that ApoER2-Dab1 disruption contributes to pTau-related neurodegeneration in humans, and suggests that ApoER2-Dab1 disruption in amygdala may contribute to the neuropsychiatric manifestations of sAD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1344 / #2131

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J01. Disease Mechanisms, Pathophysiology*

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS IN DEMENTIA, OFTEN REVERSIBLE CONDITIONS

POSTERS: J01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Maria Roberta Vazzana[1], Antonia Nucera[2], Michela Papa[3]
[1]grande ospedale metropolitano, Urgency Medicine, reggio di calabria, Italy, [2]f. spaziani hospital, Urgency Medicine, frosinone, Italy, [3]moscati asl ce, General Medicine, aversa, Italy

Aims: Introduction:In the later stages of dementia some people with develops what's known as behavioural and psycological symptoms of dementia(BSPD). Symptoms of BPSD can include increased agitation, aggression,delusions,hallucinations, sleep disturbance and night-time waking.Behaviour changes could be caused by brain-related issues or from changes to someone's environment, health or medication.
Methods: Dementia is an umbrella term used to describe a group of symptoms that affect brains work. Many conditions, such as stroke, depression, infections, as well as normal ageing, can cause dementia-like symptoms.We decribe 120 patients than have been admitted in the emergency setting because of acute symptoms.We examinated the patients to see if they have any infection, pain constipation, depression or side-effects of their medicine that could be contributing to or causing the behavior change.
Results: :The mean age was 81, 68 women and 52 men. Hypertension was present in 96 and vascular changes in the brain were found in the neuroimaging. 78 patients had reversibile symptoms of dementia due to such conditions: urinary infection , hydrataion, costipation, fever and Covid-19 infection.
Conclusions: Conclusion:Dementia is always changing and unique for each person. Everyday life can be a stressful ordeal for a person with a dementia-related disorder. As the disease progresses, behaviors changes can occur .The pandemic worsened such situation. It is important in the acute setting to rule out any concomitant illness that can cause or worsen behavioral and psychological symptoms in dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1345 / #1445

Poster Topic: *Theme I: Lysosomal Storage Diseases / I02. Therapeutic Targets, Mechanisms for Treatment*

BRINGING COLOR TO ELECTRON MICROSCOPY SHOWED LIPID ACCUMULATIONS OF LYSOSOME IN LYSOSOMAL STORAGE DISEASE

POSTERS: I02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Hye Eun Lee[1], Minkyo Jung[2], Jae Hyeok Lee[3], Ji Young Mun[2]
[1]Kyungpook University, Division Of Biomedical Science, Dae, Korea, Republic of, [2]Korea Brain Research Institute, Neural Circuit, Daegu, Korea, Republic of, [3]Pusan National University Yangsan Hospital, Department Of Neurology, Yangsan, Korea, Republic of

Aims: In previous work, we showed iron accumulation was located in lysosome of patient derived cells with NBIA (Neurodegeneration with brain iron accumulation), and Lysosome's functional disorder in these cells was observed in activity test. Our current research aims to investigate ultrastructural changes of lysosomes in NBIA patient derived cell and lysosomal storage disorder.
Methods: We used mainly electron microscopy including Cryo-EM, Correlative light and electron microscopy, and 3DEM to investigate lysosomal structural changes. Correlative light-electron microscopy (CLEM) is a combination of light and electron microscopies, and thin lamella was made by Cryo-FIB for Cryo-tomography.
Results: In our results, patient's derived cells showed abnormal autophagy, mitochondria or excess lipid by confocal microscopy. Ultrastructure analysis by transmission electron microscopy (TEM) showed abnormal vesicles and shorten mitochondria. Specially, lipid or protein accumulations were shown in specific lysosome including lamellar structures through Correlative light and electron microscopy (CLEM) and Cryo-CLEM and tomography.
Conclusions: Those data showed the functional and structural changes in lysosome induced lysosomal disorders, which suggested how related lysosome's function and specific protein or lipid accumulations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1346 / #2088

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J01. Disease Mechanisms, Pathophysiology*

MULTIPLE LIMBIC PROTEINOPATHIES CORRELATE TO PSYCHOTIC AND HYPERACTIVE BEHAVIOURAL SYMPTOMS: DATA FROM THE ABBIATEGRASSO BRAIN BANK

POSTERS: J01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Giulia Negro[1], Valentina Medici[2], Michele Rossi[2], Xhulja Profka[2], Annalisa Davin[3], Riccardo Ferrari[3], Valeria Terzoli[2], Arcangelo Ceretti[2], Mauro Ceroni[2], Antonio Guaita[4], Tino Poloni[2]
[1]University Milano-Bicocca, Neurology, School Of Medicine And Surgery, Monza, Italy, [2]Golgi-Cenci Foundation, Neurology-neuropathology And Abbiategrasso Brain Bank, Abbiategrasso, Italy, [3]Golgi-Cenci Foundation, Neurobiology And Neurogenetics, Abbiategrasso, Italy, [4]Golgi-Cenci Foundation, Research Center For Brain Aging And Related Diseases, Abbiategrasso, Italy

Aims: Psychotic and hyperactive behavioural symptoms are the most considerable challenges in the clinical-therapeutic management of patients with dementia. The limbic system is primarily responsible for emotional processes strictly related to behaviour, and the presence of neuroinflammation could exacerbate behavioural symptoms. In our series of pathologically defined demented patients, we investigate the correlation of multiple limbic lesions with the aforementioned behavioural symptoms and microglial activation in specific limbic regions.
Methods: Twenty-four subjects from the Abbiategrasso Brain Bank underwent serial neurological and neuropsychological evaluations. At death, they all had a diagnosis of major neurocognitive disorder. According to the donation program, their brains underwent a complete vascular and degenerative neuropathological characterization. Further, microglial activation was assessed in four limbic regions (hippocampus, amygdala, gyrus cinguli, orbitofrontal cortex) through a semi-quantitative method. The Fisher's exact test and the Mann-Whitney test were used for statistical analysis.
Results: Clinical diagnosis includes Alzheimer's Disease (AD; n=10), multiple etiologies (n=8), Lewy body disease (n=2), vascular dementia (n=2) and frontotemporal lobar degeneration (n=2). Additional unexpected neuropathology was found in 19 cases, including Lewy Type Synucleinopathy (LTS), and TDP-43 pathology (TDP). Sixteen cases had psychotic and hyperactive behavioural symptoms; 12 of them exhibited additive limbic pathology (1 LTS; 8 TDP-43; 3 TDP-43/LTS). The presence of multiple limbic proteinopathies (LTS and/or TDP-43 pathology) significantly correlates with psychotic and hyperactive symptoms ($p = 0.032$), the latter also significantly correlates with microglial activation in the dentate gyrus, amygdala and orbitofrontal cortex. Moreover, multiple limbic proteinopathies significantly correlate with microglial activation in the hippocampus.
Conclusions: Frequently, limbic LTS and TDP-43 lesions are concomitant suggesting a possible synergistic role of these proteinopathies, promoting neuroinflammation, causing limbic dysfunction and influencing the clinical phenotype.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1347 / #2420

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J01. Disease Mechanisms, Pathophysiology*

DYSREGULATED RIBOSOME GENE EXPRESSION AND ASTROCYTE-DOPAMINERGIC NEURONAL SIGNALING IN THE PREFRONTAL CORTEX OF ELDERLY MAJOR DEPRESSIVE DISORDER PATIENTS.

POSTERS: J01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Ashlesh Patil[1], Ansh Malik[2], Gunjan Sharma[2], Satyendra Tripathi[3], Vishwajit Deshmukh[4]
[1]AIIMS Nagpur India, Physiology, Nagpur, India, [2]AIIMS Nagpur, Mbbs Student, Nagpur, India, [3]AIIMS Nagpur, Biochemistry, Nagpur, India, [4]AIIMS Nagpur, Anatomy, Nagpur, India

Aims: Aging is known to be associated with major depression (MDD), it is not yet fully understood how depression may differ in older patients. This bioinformatic study aims to identify dysregulated genes in the prefrontal cortex focusing on two age groups: working-age individuals and senior individuals.
Methods: For this bioinformatic study, we utilized the GSE208338 dataset obtained from the Gene Expression Omnibus (GEO) database. The dataset contains gene expression data obtained from post-mortem brain tissue of dorsolateral prefrontal cortex. Four groups were compared, including working-age individuals with MDD, senior individuals with MDD, working-age healthy controls, and senior healthy controls. Gene pathway analysis and protein-protein interaction analysis of differentially expressed genes were investigated.
Results: We found that 190 genes were up/downregulated by at least 1.2 log fold times in senior healthy controls as compared to working-age healthy controls ($p<0.05$). Additionally, 33 genes were up/downregulated by at least 1.2 log fold times in senior MDD as compared to working-age MDD. Among these, 6 genes (TMEM176A, FZD, FBXO5, VIM, EPHX1, SP1005) were increased in senior MDD compared to working-age MDD, while 7 genes (ADCK5, S100A1, COL4A4, PWP1, PKNOX2) were decreased in senior MDD compared to working-age MDD but not in senior healthy controls compared to working-age healthy controls. Protein-protein interaction analysis showed dysfunctional ribosome biogenesis and astrocyte-dopaminergic neuron signaling.
Conclusions: This study suggests that senior individuals with depression may differ from working-age depressed individuals. Dysregulation of S100 proteins and ribosomal gene expression has been observed in older patients on electroconvulsive therapy or antipsychotic drugs, indicating that the treatment of depression or the disease itself may be altering the genes. Additionally, the astrocyte-dopaminergic system, which is implicated in depression, worsens in senior depressed individuals.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1348 / #1496

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J02. Therapeutic Targets, Mechanisms for Treatment*

THE REGULATION OF MICROGLIAL POLARIZATION BY INHIBITION OF TOLL-LIKE RECEPTOR 2

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Kyoung Ja Kwon[1,2], Seol-Heui Han[2], Ryeong-Eun Kim[1]
[1]Konkuk University, Neuroscience, Seoul, Korea, Republic of, [2]Konkuk University Medical Center, Neurology, Seoul, Korea, Republic of

Aims: Neuroinflammation holds a vital role in neurodegenerative diseases and neuropsychiatric disorders and that microglia and astrocytes chiefly modulates inflammatory responses in the central nervous system (CNS). Toll-like receptors (TLRs), is critical in innate immune responses, regulation in microglia can be a potential therapeutic strategy for neurological disorders. In this study, we examined the protective effects of GSP1-111, a novel synthetic peptide for inhibiting TLRs signaling, on neuroinflammation and depression-like behavior.
Methods: In this regard, we examined 1) the mRNA expression of inflammatory mediators including iNOS, IL-1b, TNFa, TGFb and COX-2, 2) nitric oxide (NO) production, 3) the protein expression of TLR2 and TLR4 in the BV2 microglial cells and the brain of LPS-injected mice, and 4) depressive-like behaviors in the mice.
Results: GSP1-111 decreased TLR2 expression and remarkably reduced mRNA expression of inflammatory M1-phenotype markers, including tumor necrosis factor (TNF)-a, interleukin (IL)-1b, and IL-6, while elevating that of M2 phenotype markers, Arg-1 and IL-10. In vivo GSP1-111 administration significantly decreased depression-like behavior induced by lipopolysaccharide (LPS) in forced swim test and significantly reduction brain levels of M1-specific inflammatory cytokines. GSP1-111 could prevent depression-like behavior by inhibiting TLR2.
Conclusions: Our results suggest that TLR2 pathway is a promising therapeutic target for depression, and GSP1-111 could be a novel therapeutic candidate for various neurological disorders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1349 / #958

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J02. Therapeutic Targets, Mechanisms for Treatment*

L-DOPA ADDICTION, PATHOLOGICAL GAMBLING AND COCAINE ADDICTION: A COMMON MULTIDISCIPLINARY REHABILITATION APPROACH.

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Giovanni Albani[1,2], Elena Gabutti[3], Patrizia Padula[3], Annalisa Caretti[4], Raffaella Critelli[4], Elisa Bacchetta[4], Patrizia Morandi[4], Valentina Pauselli[4], Michela Soia[4], Mauro Croce[3], Chiara Crosalenz[4]
[1]Clinical and Research Institute Auxologico Italiano, Parkinson's Disease Centre, Verbania, Italy, [2]Gravedon Hospital, Neurorehabilitation, Gravedona COMO, Italy, [3]Association, Myway, Verbania, Italy, [4]ASL VCO, Serd, Verbania, Italy

Aims: Cocaine addiction, gambling and dopaminergic dysregulation syndrome in patients with Parkinson's disease, despite their clinical diversity, contain neurobiological circuits in common which allow us to adopt a perspective of shared rehabilitation strategy.
Methods: In this project, we propose a multidisciplinary rehabilitative approach for 30 patients affected of cocaine addiction, pathological gambling and l-dopa addiction in people with Parkinson's disease,through a psychoeducational path combined with 12 neuromodulation sessions through transient current dirrect stimulation (TDCS) with 20 minutes of anodic right/cathodic left stimulation on the dorsolateral prefrontal cortex The selection criteria for the various categories of patients were: for cocaine addiction and for pathological gamblers diagnosis of according to DSM 5 criteriaand active addiction ; for patients with Parkinsons ' s disease a positive Quiprs Questionnaire score for Dopamine dysregulation syndrome and a Levodopa Equivalent Daily Dosage over 600 mg/die. The psychoeducational path consists in focusing on the most dangerous individual trigger situations without implementing the addictive behavior, replacing it withpersonal and social resources. The integrated method is based on the Cognitive-Behavioral Therapy approach and in particular the exposure with prevention of the response (Exposure/Prevention) in imagination.
Results: All three categories of patients reported a high frequency of non-motor symptoms (Patients with Parkinson's disease) and clinical symptoms related to craving.
Neuromodulation treatment was terminated by all patients without side effects with a decrement of craving sintomatology.
Conclusions: Parkinson's disease patients affected by dopaminergic dysregualtion syndrome , pathological gamblers and cocaine addicters may show similar clinical picture concerning craving symptomatology, which may be considered a clinical aim to reduce addiction behavior. Neuromodulation combined with psychoeducational effect may be proposed as approach .

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1350 / #1614

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J02. Therapeutic Targets, Mechanisms for Treatment*

NEURODEGENERATION-ASSOCIATED PSYCHIATRIC SYNDROMES (NAPS): METHODOLOGY FOR INVESTIGATING THE FACTOR STRUCTURE OF PSYCHIATRIC SYNDROMES ASSOCIATED WITH NEURODEGENERATIVE DISEASE

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Juan Pablo Cajiga[1], Claudine Narayan[1], Yedili Genao Perez[1], Masood Manoochehri[1], Colin Stein[1], Megan Barker[2], Alyssa De Vito[1,3], Yunglin Gazes[4], Jennifer Manly[4], Adam Brickman[4], Corinne Sejourne[5], Jeannie Ake[6], Hannah Silverman[7], Edward Huey[1,3]
[1]Brown University, Department Of Psychiatry And Human Behavior, Providence, United States of America, [2]The University of Queensland, Queensland Brain Institute, Brisbane, Australia, [3]Butler Hospital, Memory And Aging Program, Providence, United States of America, [4]Columbia University, Department Of Neurology, Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York City, United States of America, [5]McGill University, Department Of Psychology, Quebec, Canada, [6]University of North Carolina at Chapel Hill, Program On Aging, Chronic Illness, And Long Term-care; Cecil G. Sheps Center For Health Services Research, Chapel Hill, United States of America, [7]University of California, San Francisco, School Of Medicine, San Francisco, United States of America

Aims: The aim of this study is to determine underlying factor structures of psychiatric syndromes associated with the degeneration of specific brain networks in humans with ADRD.
Methods: We pursue this objective through the collection of neuropsychiatric assessments from patients and their caregivers including: Structured Clinical Interview for DSM-5 Research Version, DSM-5 Cross-Cutting Measures, NPI, GDS, and SCL_90R. Specific aims include: 1. Identifying psychiatric factors previously recognized in other patient groups and discover additional factors specific to these patients. We will use multiple group factor analysis to assess the similarity of the factor structure between a test group (n=300) of mild AD and a generalizability group including diverse neurodegenerative diseases (n=300; MCI, bvFTD, PPA, DLB, HD, PDD). We will utilize the most informative items from this factor analysis to create a new instrument that is tailored to patients diagnosed with ADRD. 2. Replicating and expanding upon associations between specific brain networks and neuropsychiatric factors previously observed in patients with penetrating traumatic brain injury. These analyses will be performed on neuropsychiatric symptoms (NPS) and MRI data collected from our test and replication groups, focusing on patients with mild AD and NPS. 3. Comparing the effectiveness of three measures of NPS (DSM-5 Cross-Cutting, NPI, GDS) in explaining the variance in sMRI regional volume and the outcomes of integrative MRI analyses in networks related to NPS factors.
Results: Anticipated outcomes include the identification of brain regions associated with specific psychiatric symptoms, which will provide insights into potential targets for symptom treatment, especially anatomically-based treatments, among individuals with neurodegenerative disorders.
Conclusions: This study will enhance our understanding of the neuroanatomy of psychiatric symptoms in patients with neurodegenerative illnesses and help develop new treatments for these symptoms.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1351 / #1819

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J01. Disease Mechanisms, Pathophysiology*

FUNCTIONAL MOVEMENT DISORDERS - A MOSAIC OF NON-STEREOTYPICAL MANIFESTATIONS

POSTERS: J01. DISEASE MECHANISMS, PATHOPHYSIOLOGY

Darshana Vijaywargiya[1], Tinatin Chabrashvili[2]
[1]SUNY Upstate Medical University, Neurology, Syracuse, United States of America, [2]SUNY Upstate Medical University, Neurology And Neuroscience, Syracuse, United States of America

Aims: Functional movement disorders (FMD) are complex neuropsychiatric conditions with a motor-dominant phenotype. The objective of this case report is to present a case that started with neuromuscular symptoms and evolved as a FMD, a potentially novel FMD phenotype combining movement and neuromuscular presentations including somatic symptoms and psychiatric diagnoses.
Methods: In July 2022, a 24-year-old male enlisted in the military while deployed in the Middle East, developed a constellation of symptoms including urinary retention, progressive bilateral lower extremity weakness and paresthesias causing walking difficulties (without falls) requiring use of a cane by November 2022. Around mid-November 2022, he started manifesting involuntary, jerky movements in head, neck and extremities. Neurological exam revealed non-stereotypical, hyperkinetic, choreiform movements of head, neck and extremities, upper greater than lower, appearing randomly, suppressible on distraction and exaggerated on direct observation and testing of individual muscles. Gait was normal based, irregular amplitude, slow marching type with normal speed and cadence. On subsequent visits, while the aforementioned movements decreased, additional movements like low amplitude finger tapping, neck jerking similar to shivering, lip smacking, irregular hand movements appeared. None of these movements were associated with an urge to move.
Results: Normal MRI of the neuraxis, EMG, EEG, ceruloplasmin, metabolic, urological work-up. Negative heavy metal screen, connective tissue panel, lyme, and sickle cell screens. Whole exome sequencing with mitochondrial DNA testing revealed no pathological genetic variants. KF rings were not detected on ophthalmologic exam. He was diagnosed with FMD after extensive workup. On subsequent visits, abnormal movements resolved with physical therapy coupled with cognitive behavioral therapy.
Conclusions: This case exemplifies the importance of functional movement disorders as a differential while evaluating non-stereotypical, inconsistent movements associated with neuromuscular phenotypes.

P1352 / #711

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J02. Therapeutic Targets, Mechanisms for Treatment*

SUB THALAMIC NUCLEUS VERSUS GLOBUS PALLIDUS INTERNUS: EFFECTIVE TARGET FOR REDUCING DEPRESSION AFTER DEEP BRAIN STIMULATION

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Tulika Gupta, Rafika Munawara
Post Graduate Institute of Medical Education and Research, Anatomy, Chandigarh, India

Aims: Background: Deep Brain Stimulation of the subthalamic nucleus (STN) or Globus Pallidus Internus (GPi) is a standard treatment for Parkinson's disease, with both regions exhibiting comparable treatment effectiveness. Post-treatment neuropsychiatric side effects includes severe depression. Loss of serotonergic neurons is thought to be the primary cause of depression. Identification of a region with lesser number of serotonergic neurons may reduce these side effects. There is a lack of molecular evidence comparing the choice of STN and GPi in this regard. This study aimed to quantify the number of serotonergic neurons and semi-quantify the serotonin levels in the STN and GPi.
Methods: The STN and GPi regions were studied histologically in 15 human brain specimens; ethical clearance was taken at the time of body donation. Serotonergic neurons were identified immunohistochemically using tryptophan hydroxylase 2 antibody. Semi-quantification of the Immunoreactivity was performed by calculating the histo-score.
Results: The number of immunopositive cells was, 80 in the STN and 16 in the GPi, per 10 high power fields. GPi had a significantly lesser number of serotonergic neurons than STN. Three types of neurons were observed. In the STN, large cells were concentrated in the center and small cells in the periphery. While in GPi only small neurons were present. Two patterns of serotonergic granule distribution were observed; the majority of the cells had a fine granular pattern. In STN, variability in the number of Serotonergic neurons and in the histo-score was observed more in the cells in the medial half of the nucleus, than in the lateral half.
Conclusions: GPi could be a safer target region, for considerably lowering the incidence of post-DBS depression.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1353 / #514

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J02. Therapeutic Targets, Mechanisms for Treatment*

5-HT2A AND 5-HT2C DUAL INVERSE AGONIST FOR THE TREATMENT OF PSYCHOSIS IN DEMENTIA.

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Kohei Jino[1], Ken Koda[1], Nozomi Takai[1], Takuya Oguma[2], Kana Hyakkoku[1], Ken-Ichi Kusakabe[2], Naotaka Horiguchi[1]
[1]Shionogi & Co., Ltd., Neuroscience, Drug Discovery & Disease Research Laboratory, Osaka, Japan, [2]Shionogi & Co., Ltd., Laboratory For Medicinal Chemistry Research, Osaka, Japan

Aims: People with dementia experience psychosis, which is a distressing factor for both patients, their family, and caregivers. Pimavanserin is the only drug approved for the psychosis associated with Parkinson's disease, but it has also demonstrated efficacy for dementia-related psychosis in clinical trials. Pimavanserin is known as a 5-HT_{2A} receptor inverse agonist. However, it also has suboptimal affinity to 5-HT_{2C} receptor. Based on its clinical outcomes, we hypothesized that the antipsychotic effect of pimavanserin has been exerted by simultaneous inhibition of both 5-HT_{2A} and 5-HT_{2C} receptors. The objective of the study is to verify the hypothesis from engagements with those targets and non-clinical behavioral models.
Methods: MK-801 (NMDA receptor antagonist) induced locomotor hyperactivity in Wistar rats (6 or 7-weeks-old) was conducted, evaluating antipsychotic effect. The receptor occupancy study and microdialysis study (medial prefrontal cortex, dopamine) were performed to assess with 5-$HT_{2A/2C}$ receptors.
Results: Pimavanserin exhibited a dose-dependent efficacy in a rodent psychobehavioral model. At effective doses, saturated occupancy for 5-HT2A receptors and increased DA flux were observed, indicating engaging both receptors. On the other hand, doses occupying only 5-HT2A receptor did not reduce MK-801 induced hyperactivity in rats. In addition, no significant efficacy was observed when SB242084, a selective 5-HT_{2C} inhibitor, was administered alone, albeit DA flux increased.
Conclusions: We demonstrated that simultaneous inhibition of both 5-HT_{2A} and 5-HT_{2C} are pivotal to reduce MK-801 induced hyperactivity in rats. Our findings highlight that a 5-HT2A and 5-HT2C dual inverse agonist would be a promising therapy mitigating dementia-related psychosis.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1354 / #1867

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J02. Therapeutic Targets, Mechanisms for Treatment*

POSITIVE AND NEGATIVE VALENCE EMOTIONAL SYSTEMS IN NEURODEGENERATIVE DISEASE (PAVES): METHODOLOGY FOR INVESTIGATING MECHANISMS AND NEUROANATOMY OF NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE AND RELATED DEMENTIA

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Claudine Narayan[1], Juan Pablo Cajiga[1], Colin Stein[1], Nicholas Balderston[2], Madeleine Sharp[3], Yedili Genao Perez[1], Masood Manoochehri[1], Luke Hearne[4], Megan Barker[5], Alyssa De Vito[1,6], Yunglin Gazes[7], Jennifer Manly[7], Adam Brickman[7], Corinne Sejourne[8], Hannah Silverman[9], Jeannie Ake[10], Edward Huey[1,6]
[1]Brown University, Department Of Psychiatry And Human Behavior, Providence, United States of America, [2]University of Pennsylvania, Department Of Psychiatry, Philadelphia, United States of America, [3]McGill University, Department Of Neurology And Neurosurgery, Montreal Neurological Institute, Montréal, Canada, [4]The University of Queensland, Queensland Neurostimulation Centre, Spring Hill, Australia, [5]The University of Queensland, Queensland Brain Institute, Brisbane, Australia, [6]Butler Hospital, Memory And Aging Program, Providence, United States of America, [7]Columbia University, Department Of Neurology, Taub Institute For Research On Alzheimer's Disease And The Aging Brain, New York City, United States of America, [8]McGill University, Department Of Psychology, Quebec, Canada, [9]University of California, San Francisco, School Of Medicine, San Francisco, United States of America, [10]University of North Carolina at Chapel Hill, Program On Aging, Chronic Illness, And Long Term-care; Cecil G. Sheps Center For Health Services Research, Chapel Hill, United States of America

Aims: This study investigates the impact of neurodegeneration on emotional systems by using the Research Domain Criteria (RDoC) Paradigms as categorized by the National Institute of Mental Health, with a particular emphasis on the Negative Valence (NV) and Positive Valence (PV) Systems and their relevance to Alzheimer's disease and related dementias (ADRD). Applying these RDoC paradigms will help us gain a deeper insight into the development of neuropsychiatric symptoms (NPS) in neurodegenerative disease.
Methods: RDoC behavioral tasks spanning both NV and PV systems are administered to participants with a diagnosis of mild (CDR=1) AD, bvFTD, svPPA, or HD, and age matched controls. NV tasks include: Behavioral Approach Task (fear), NPU-Threat Task (anxiety), and Cold Pressor Task (pain processing). PV tasks include the Probabilistic Learning Task (reward learning) and a Habit Learning Task. We will analyze data derived from these tasks in conjunction with neuropsychiatric and imaging data collected from the broader Neurodegeneration-Associated Psychiatric Syndromes (R01AG062268) project. Our analytical framework encompasses correlations between our RDoC paradigm, MRI findings, and NPS outcomes, as well as an integrative assessment of behavioral and MRI data.
Results: We hypothesize that individuals with neurodegenerative diseases will have impaired processing within the PV and NV domains, displaying correlations with NPS and regional brain atrophy. We anticipate that the degeneration of the vmPFC will be associated with low NV scores, internalizing NPS (such as anxiety and depression), and apathy. Furthermore, we predict that degeneration in NV Circuit Elements will be linked to high NV and Internalizing NPS.
Conclusions: Our project represents a comprehensive examination of NPS mechanisms in order to advance our understanding of these crucial aspects of ADRD and inform the development of novel treatments to enhance patients' quality of life.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1355 / #1605

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J02. Therapeutic Targets, Mechanisms for Treatment*

EVALUATION OF PHARMACOLOGICAL SAFETY AND MECHANISM OF ACTION OF AN ANTIPARKINSONIAN PEPTIDE.

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Gabriela Pinheiro[1], Isabela Guedes[2], Victória Dos Santos[2], Danilo Rodrigues De Oliveira[1], Jair Goulart[1], Márcia Renata Mortari[3]
[1]University of Brasilia, Institute of Biological Sciences, Department Of Physiological Sciences, Laboratory Of Neuropharmacology, Asa Norte, Brasília, Brazil, [2]University of Brasilia, Physiological Sciences, Brasilia, Brazil, [3]Institute of Biological Science, Department Of Physiology, Brasília, Brazil

Aims: The present study aims to evaluate the toxicity, pharmacological security, and mechanism of action of Occidentalina-1202, a wasp venom peptide with antiparkinsonian and neuroprotective effects.
Methods: The experimental design for the toxicity evaluation consisted on a 14-day and 30-days observation period in the acute and chronic models respectively. The peptide was administrated in three different doses (4mg/kg, 20 mg/kg and 40mg/kg) once in the acute model and 1x/day in the chronic model, and the mice were subjected to the Open Field test. At the end of the observation period, animals were euthanized and had brain, liver, lungs, kidney, and heart collected. The organs were weighted and measured, and further processed for preparation of histology slides. To access the mechanism of action, synaptosomes were prepared from cerebral cortices, the binding assay was performed with H^3-GABA, H^3-Glutamate, and a range of six different concentrations of the peptide.
Results: In the evaluation of the histology slides, no alterations were observed in any of the tissues analyzed, in any of the groups (vehicle, Diazepam, 4mg/kg, 20 mg/kg and 40mg/kg). No pronounced weight loss was observed in the animals during the observation period (both acute and chronic model), as well as in the weight and volume of the organs. Regarding food and water consumption in the chronic model, no alterations were detected. The binding assay showed a 15% competition with H^3-Glutamate in the 10nM peptide concentration. The peptide did not show competition with H^3-GABA.
Conclusions: These findings suggest that Occidentalina-1202 is safe to treat Parkinson's disease, being a potential therapeutic alternative and that the peptide might compete with Glutamate. This study was funded by FAPDF, CNPq and CAPES.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1356 / #1895

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J03. Drug Development, Clinical Trials*

QUALITATIVE INTERVIEWS FOR CONCEPT ELICITATION IN CAREGIVERS OF PATIENTS WITH DEMENTIA RELATED APATHY

POSTERS: J03. DRUG DEVELOPMENT, CLINICAL TRIALS

Stella Karantzoulis[1], Betsy Williams[1], Karli Heuer[1], Jianbin Mao[2], Gary Globe[2], Emily Ruzich[1], Rahul Sasane[2]
[1]IQVIA, Patient Centered Solutions, New York, United States of America, [2]Cerevel Therapeutics, Heor, Cambridge, United States of America

Aims: Diagnostic criteria for dementia-related apathy (DRA) includes diminished initiative, diminished interest, and diminished emotional expression/responsiveness. The development of existing instruments measuring DRA did not involve patients nor caregivers. This study aims to fill this void by characterizing the patient experience with DRA using 1:1 concept-elicitation interviews with caregivers of patients with DRA. Patients with dementia were not interviewed given their anosognosia.
Methods: Caregivers of patients with clinically significant DRA and with mild/moderate dementia were recruited through advocacy groups, clinician referral, and social media. Physician confirmation of DRA diagnosis was required; study materials were IRB approved. Caregiver interviews were conducted by trained interviewers using a semi-structured discussion guide; interviews were recorded and transcribed with caregiver permission, and transcripts were coded and analyzed. Caregivers were asked open-ended questions to characterize the patient's experience with DRA. Concepts for DRA were presented to caregivers during the interview for feedback.
Results: Fifteen caregivers (n=11 females; mean age=52.9 years; n=6 spouses as caregivers) of patients with DRA (n=6 females; mean age=75.6 years; n=9 moderate dementia, n=6 mild dementia) were interviewed. Most caregivers described lack of motivation, lack of interest, being inactive/sedentary (n=14 each), losing interest rapidly mid-activity (n=13), withdrawing/isolating socially (n=12), and reduced communication, lack of initiative, neglecting instrumental activities of daily living, lack of emotions (n=11 each) as features of DRA. Reported impacts included sleeping a lot (n=11), decreased physical activity, reduced meaningful intimacy (n=9 each), reduced communication (n=8), daytime immobility (n=7), and less interaction with environment (n=7).
Conclusions: No new concepts were identified during these interviews, thus confirming aspects of apathy from the conceptual model developed from literature and clinician interviews.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1357 / #373

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J02. Therapeutic Targets, Mechanisms for Treatment*

LINK BETWEEN POST-TRAUMATIC STRESS DISORDER (PTSD) AND MEDIA EXPOSURE IN INDIVIDUALS OVER 65.

POSTERS: J02. THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT

Anne-Julie Vaillant-Ciszewicz, Laura Lantermino, Alice Cuni, Cassandra Quin, Olivier Guérin
CHU DE NICE, Geriatrics, NICE, France

Aims: Post-Traumatic Stress Disorder (PTSD) is underdiagnosed in the elderly. The clinical expression of the disorder and its prevalence after the age of 65 are challenging to identify in the scientific literature. Currently, there is also no validated screening tool available for this population. Some studies suggest a connection between PTSD and media exposure on PTSD symptoms, but no conclusive findings have been reached to date. The objective of this study is to identify signs of anxiety in residents/patients of nursing homes and long-term care facilities who are exposed to news (continuous news channels, newspapers, etc.) and the potential link with psychological symptoms suggestive of PTSD according to DSM-5 criteria in adults.
Methods: The multicenter exploratory study conducted by the Hospital of Nice (5 nursings homes/long-term care facilities) has obtained approval from the Research Ethics Committee. Fifty inclusions were conducted from December 2022 to September 2023. The first step of our methodology involves identifying patients through the rating of the "Anxiety" item on the Neuropsychiatric Inventory (NPI). Clinical psychologists leading the project then conduct a non-directive interview with the included resident/patient, following the signing of informed consent. The emotional impact of the news on the individual is assessed. If positive responses are obtained, the Traumatic Check List-Specific clinical scale (PCL-S) is administered.
Results: The results are currently being processed and will be presented at the conference.
Conclusions: This study will help determine whether news from the past 24 months (such as the Ukraine War, food shortages, etc.) reactivates traumatic experiences in nursing home/long-term care facility residents. Additionally, it aims to provide an overview of significant life events among residents (with and without cognitive impairments).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1358 / #625

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J03. Drug Development, Clinical Trials*

AN OVERVIEW STUDY ON PARKINOL TOXICITY

POSTERS: J03. DRUG DEVELOPMENT, CLINICAL TRIALS

Raafat Abdeldayem
Mansoura university, Toxicology, Mansoura, Egypt

Aims: Antiparkinsonian drugs are known to be substances of abuse. This is true both in abusers of other substances and in chronic schizophrenics, the latter being infrequent abusers of other drugs The aim of the study is to determine the extent of the spread of this drug among hospital patients under study
Methods: 924 cases of different signs of poisoning, admitted the poison units of the hospitals under study along the last six years. Five ml of blood are taken without anticoagulant under precautions to prevent contamination. Each sample was placed in labelled sterile polypropylene tube and sealed immediately.1 µl of each extracted sample was injected into GC-MSD (Hewlett Packard 6890 series) of FID (Flame Ionization detector) and examine in Wiley library
Results: Twenty six Parkinson cases were detected by GC/MS of characteristic peak at specific retention time (12.21 min) is appeared and the compatible ion fragments (98, 55,218) from Wiley library are obtained and indicated that the compound is benzhexol.
Conclusions: GC/MS is today the method of choice for systematic toxicological analysis in clinical and forensic toxicology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1359 / #1456

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

PATHWAY ALTERATIONS AND BIOMARKERS FOR NEUROPSYCHIATRIC SYMPTOMS IN OLDER PEOPLE WITH COGNITIVE DECLINE AND ALZHEIMER'S DISEASE

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Julius Popp[1,2], Miriam Rabl[1], Loïc Dayon[3,4], Christopher Clark[1]
[1]University of Zurich, Department For Psychiatry, Psychotherapy And Psychosomatics, Zurich, Switzerland, [2]Lausanne University Hospital, Old Age Psychiatry, Department Of Psychiatry, Lausanne, Switzerland, [3]Nestlé Research, Nestlé Institute Of Food Safety & Analytical Sciences, Lausanne, Switzerland, [4]Ecole Polytechnique Fédérale de Lausanne, Institut Des Sciences Et Ingénierie Chimiques, Lausanne, Switzerland

Aims: Neuropsychiatric symptoms (NPS) are common in older people with cognitive decline and are associated with worse long-term outcomes. The contribution of systemic and central nervous system (CNS) pathophysiological alterations to the etiology of NPS is not well understood. Furthermore, no biomarkers for early detection of these alterations, and for prediction of further disease progression are available to date.
Methods: Using hypothesis-free untargeted proteomics in a cohort of longitudinally followed-up older people with normal cognition and with cognitive impairment, we identified plasma protein biomarkers predictive of NPS persisting over time and investigated biological pathway alterations underlying NPS. Using targeted approaches, we addressed associations of neuroinflammatory markers and cortisol and DHEAs with NPS and related cognitive decline. Additionally, we related the identified alterations with regional brain volumetry.
Results: We found 15 altered plasma proteins levels in participants with NPS. These proteins additionally predicted both persisting NPS and cognitive decline at follow-up visits. In CSF, gene ontology enrichment showed abundance alterations of proteins related to cell adhesion, immune response, and lipid metabolism, among others, in relation to NPS. The observed associations were independent of the presence of Alzheimer's disease (AD) pathology. NPS were associated with distinct inflammatory profiles in serum and CSF. Furthermore, CSF cortisol predicted persisting NPS. The strongest correlations between regional brain volumes and NPS severity were found for the right temporal lobe, third ventricle, frontal lobe, and right hippocampus.
Conclusions: Our results provide evidence for specific molecular alterations and volumetric changes in NPS. These are at least in part independent of the presence of AD pathology. Blood-based biomarkers may help to identify patients with NPS persisting over time, which may facilitate clinical decision and developing of targeted interventions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1360 / #509

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

MACROSCALE STRUCTURAL COVARIANCE NETWORK REVEALS THREE DISTINCT SUBTYPES AND ABNORMAL PATTERNS OF NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE CONTINUUM

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Jiwei Jiang[1], Kun Zhao[2], Jun Xu[1]
[1]Beijing Tiantan Hospital, Capital Medical University, Neurology, Beijing, China, [2]Biomedical Engineering School of Biological Science and Medical Engineering Beihang University, Radiology, Beijing, China

Aims: The current diagnosis of neuropsychiatric symptoms (NPS) highly depends on the clinical scale assessments, affected by the emotions and educational levels of caregivers. This study aimed to identify the subtypes of NPS by using a regional radiomics similarity network (R2SN), and to characterize the abnormality patterns associated with the clinical and multimodal imaging features, and progression of each subtype.
Methods: An individual-level R2SN is constructed for N=550 {healthy controls (HCs)=63, patients without NPS among AD continuum (nNPS)=111, patients with NPS=376}. The R2SN profiles of patients with NPS were clustered into three subtypes using nonnegative matrix factorization. The patterns of brain alterations, clincial manifestations, multimodal neuroimaging, gene expression and clinical progression in each subtype were evaluated.
Results: Patients with NPS were clustered into three goups, severe NPS (sNPS, n=187), moderate NPS (moNPS, n=87), and mild NPS (miNPS, n=102). Significant differences were observed among three subtypes with respect to the following: 1) clinical measures (Patients with sNPS exhibited lower BMI and scores in the MMSE, MoCA and MNA, but higher scores in the NPI, ADL, CBI, and PSQI than nNPS (P<0.05 for all), while there was no significant difference in the MMSE and MoCA scores between patients with miNPS and nNPS.); 2) multimodal neuroimaging (Significant differences in the lateral occipital cortex, inferior temporal gyrus, medioventral occipital cortex, fusiform gyrus, and insular gyrus of the altered morphological connectivity, brain volumes, cortical thickness, and cCBF were found among three subtypes.); 3) the rate of clinical progression was faster in sNPS within 9.87± 3.28 months; 4) enriched genes for inorganic ion transmembrane transport and synaptic transmission.
Conclusions: Identification of NPS subtypes based on brain connectomes and a full understanding of heterogeneity could help clinical early diagnosis and intervention in AD continuum.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1361 / #372

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

THE POTENTIAL OF MEASURING CONSCIOUS STATES VIA EEG CLOSED EYES RECORDINGS AS A DIAGNOSTIC MARKER OF ALZHEIMER'S DISEASE

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Yuan Ma[1], Gaku Yoshikawa[1,2], Jeffrey Keith Spaneas Bland[1]
[1]K. K. FOVE, Development Division, Tokyo, Japan, [2]Japan Advanced Institute of Science and Technology, ., Tokyo, Japan

Aims: We aim to diagnose Alzheimer's disease (AD) via electroencephalogram (EEG) signals employing the *integrated information theory*, a concept that measures conscious states (in Phi values) based on the amount of mutual information across elements in a system. As a pilot study, this work presents the potential of Phi values calculated by EEG signals obtained from the prefrontal cortex.
Methods: We employed 26 copies of EEG data (13 AD and 13 healthy control) recorded by two electrodes, Fp1 and Fp2. Participants were resting with closed eyes during the data collection. We transformed the first 60s of pre-processed EEG amplitude into Phi values, compared two groups by t-test, and examined the predicting accuracy by the ROC Analysis.
Results: The 13 Phi values of the AD group (M = 3.05, SD = 1.06) compared to the 13 Phi values of the healthy control group (M = 4.17, SD = 0.9) demonstrated significantly lower values, $t(24) = -2.9$, p = 0.008. The ROC analysis revealed an AUC of 0.81, indicating reasonably practical discrimination of the Phi values between the two groups (the ROC curve, see Figure
1).

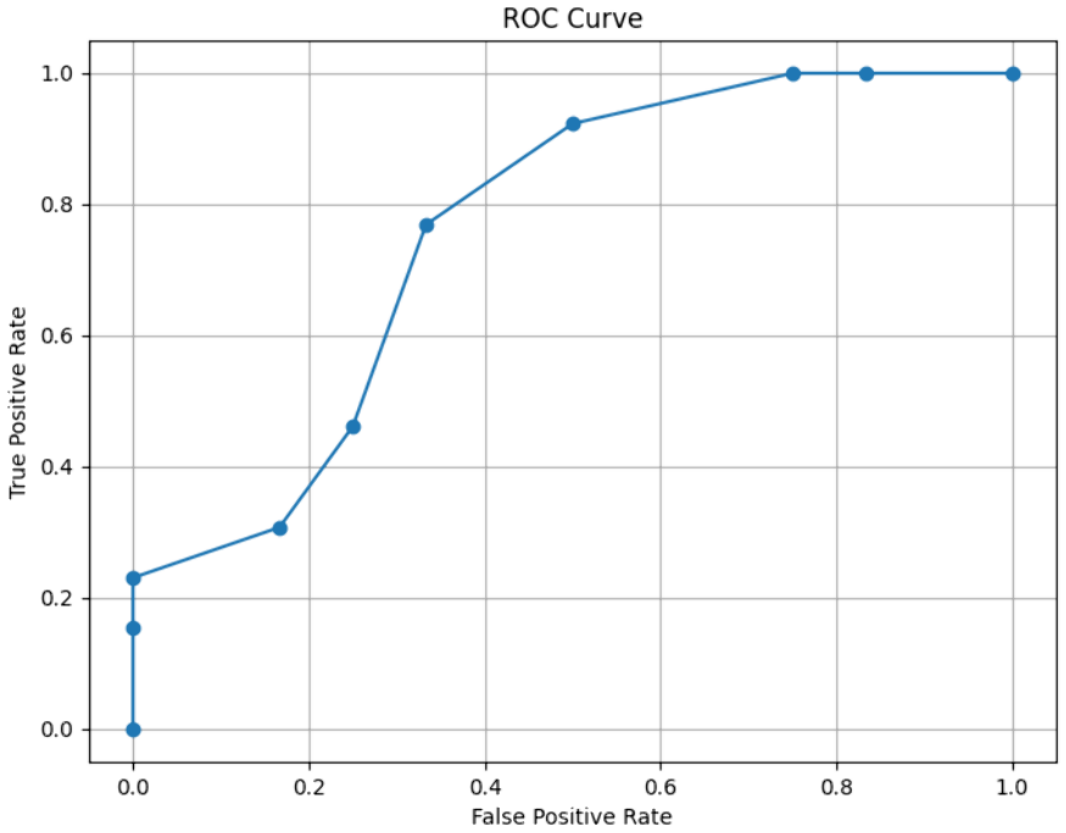


Figure. 1. The ROC curve.

Conclusions: This study found good potential for the Phi value calculated from the mutual information of two EEG electrodes allocated on the prefrontal cortex, contributing a new EEG-based biomarker to diagnosing AD. Our future work will focus on improving the Phi values in predicting accuracy by increasing the complexity of electrode combinations and specifying the EEG frequency domains.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1362 / #2185

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

THE PHENOCOPY SYNDROME – A SEPARATE OR CONTINUOUS ENTITY ALONG WITH FRONTOTEMPORAL DEMENTIA?

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Diana Mortágua, Diana Rafaela
Centro Hospitalar e Universitário de Coimbra, Psychiatry, Coimbra, Portugal

Aims: To present and discuss evidence on the phenocopy syndrome of the behavioral variant of frontotemporal dementia (bvFTD) and its relationship to neurodegenerative disorders.
Methods: Literature review;case description.
Results: Frontotemporal dementia (FTD) is one of the most important causes of early-onset dementia. In the mid-2000, a different group of patients was described, presenting clinical characteristics compatible with bvFTD, without the typical neuroimaging findings and progression over time. These were considered to present a mimetic, or phenocopy, syndrome of bvFTD. Since the term was coined, a substantial body of evidence has allowed to gain some insight that allows to differentiate “true” from phenocopy bvFTD. Although clinically speaking both entities are initially indistinguishable, longitudinally, the phenocopy syndrome shows little or no decline in functioning over time. Besides, phenocopies present with normal brain imaging, or small abnormalities that remain stable over time. Regarding etiology, a group of patients positive to C9Orf72 (most frequent mutation in bvFTD) show slow progression of deficits over time, similar to phenocopies without associated neurodegenerative pathology; besides, patients with this mutation also present with psychiatric pathology more frequently than the bvFTD group and have a higher burden of psychiatric morbidity in their close relatives, once again resembling “idiopathic” phenocopies. Milder forms of Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder can remain “compensated” throughout adulthood and only later reach medical attention.
Conclusions: Recently, both these studies and similar findings regarding ADHD and synucleinopathies in adulthood have led to the hypothesis of a continuous between neurodevelopmental and neurodegenerative disorders, accounting for the difficulties in establishing definite boundaries between neurodegenerative disorders as well, although while etiology remains, in most cases, undefined, this is still the matter of much debate and a source of controversy.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1363 / #1610

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

DECREASED LEVELS OF NPTX2 IN LATE-LIFE DEPRESSION

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Johanna Nilsson[1], Bjørn-Eivind Kirsebom[2], Nikias Siafarikas[3], Kaja Nordengen[3], Lene Pålhauge[3], Stephanie Knudtzon[2], Per Selnes[3], Henrik Zetterberg[1,4,5,6,7], Kaj Blennow[1,4], Ann Brinkmalm[1,4], Tormod Fladby[3]
[1]Gothenburg University, Department Of Psychiatry & Neurochemistry, Molndal, Sweden, [2]Department of Neurology, University Hospital of North Norway, Neurology, Tromsø, Norway, [3]Akerhus University Hospital, Department Of Neurology, Lørenskog, Norway, Norway, [4]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [5]UCL London, Uk Dementia Research Institute, London, United Kingdom, [6]Clear Water Bay, Hong Kong Center For Neurodegenerative Diseases, Hong Kong, China, [7]Wisconsin Alzheimer's Disease Research Center, University Of Wisconsin School Of Medicine And Public Health, Madison, United States of America

Aims: The best correlate to cognitive decline in Alzheimer's disease (AD) is synaptic degeneration. Identifying biomarkers capable of quantifying synaptic degeneration that can be used as prognostic biomarkers and to track cognitive decline would be valuable. We have developed several assays for synaptic proteins, including synucleins, neuronal pentraxins, SNAREs, and neurogranin, in CSF for evaluation as potential biomarkers. So far NPTX2 in particular has shown the highest promise in neurodegenerative diseases as a biomarker of cognitive decline but less work has been done in neuropsychiatric diseases.
Methods: Seventeen synaptic proteins were quantified in the Norweigan Dementia Disease Initiation cohort including predementia Alzheimer's disease (AD, n=134), Parkinson's disease with MCI (PD, n=12), late-life depression with normal AD biomarkers (LLD, n=18), and healthy controls (HC, n=41). Stratification of the predementia Alzheimer's disease cases into A/T/N stage was performed using ELISA-determined CSF amyloid beta 42/40 ratio, phosphorylated-tau181, and total-tau. For quantification, micro-high-performance liquid chromatography-mass-spectrometry (triple quadrupole) was used. For group comparisons, linear models adjusted for age and sex were used.
Results: NPTX2 displayed decreased levels in LLD ($p<0.05$) compared to HC as well as at early stages of predementia AD (A+/T-/N- MCI, $p<0.001$) and PD MCI ($p<0.01$) (Figure). The other biomarkers such as 14-3-3 zeta/delta and neurogranin displayed increased levels in late stages of predementia AD (A+/T-/N- MCI, $p<0.001$) and decreased levels in PD MCI (neurogranin only, $p<0.001$), but no changes in the LLD group compared to HC.
Conclusions: NPTX2 is a promising biomarker of cognitive decline not only in neurodegenerative diseases but also in neuropsychiatric diseases such as LLD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1364 / #1826

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J03. Drug Development, Clinical Trials*

EVALUATING PARTICIPANT BURDEN: ELECTRONIC PATIENT-REPORTED OUTCOME ASSESSMENT COMPLETION TIME IN CLINICAL TRIALS FOR PARKINSON'S DISEASE

POSTERS: J03. DRUG DEVELOPMENT, CLINICAL TRIALS

Laura Khurana, Jessica Emerson
Clario, Ecoa Clinical Science And Consulting, Philadelphia, United States of America

Aims: Patient-reported outcomes (PROs) that measure quality of life and symptom impacts are becoming more important in clinical trials of treatments for Parkinson's Disease (PD). Given the existing symptom and disease burden in PD, participant burden needs to be thoughtfully considered when incorporating PROs into trials. The objective of this analysis was to explore whether PROs present a higher burden to participants with PD as compared to participants without PD by leveraging metadata from an electronic PRO (ePRO) to examine time to completion. The Beck Depression Inventory – Second Edition (BDI-II) was selected; it is a 21-question PRO measure of depression severity, and is commonly used in trials across many different disease areas.
Methods: Operational ePRO metadata from 1 PD trial and 11 non-PD trials were analyzed to determine time to complete the BDI-II. A total of 4806 records were analyzed; 101 records from the PD trial and 4705 records from non-PD trials. Each record represented one completion of the BDI-II on Clario's ePRO device.
Results: The analysis revealed a significant difference whereby participants in PD trials took significantly longer to complete the BDI-II than non-PD trial participants (t=-7.40, p<.001). Mean completion time for the BDI-II was 318s (5.3min) among participants in PD trials and 159s (2.65min) among non-PD trial participants.
Conclusions: This analysis suggests that clinical trial participants with PD take more time to complete the electronic version of the BDI-II than those without PD. This should be considered during protocol design, as the threshold for participant burden in PD trial participants may be lower than for other trial participants. We recommend that this analysis be replicated with other PROs to determine the extent to which these results are generalizable.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1365 / #704

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

EXPLORING IMMERSIVE VIRTUAL REALITY FOR COGNITIVE MONITORING IN HOME CARE: INSIGHTS AND RECOMMENDATIONS FROM EXPERT EVALUATION

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Angelo Cedric Panganiban[1], Richelle Ann Juayong[1], Jaime Caro[1], Veeda Michelle Anlacan[2]
[1]University of the Philippines Diliman, Department Of Computer Science, Quezon City, Philippines, [2]University of the Philippines Manila, Department Of Neuroscience, Manila City, Philippines

Aims: Mild Cognitive Impairment (MCI) represents a transitional phase preceding younger onset dementia. To expedite early detection of MCI, cognitive function monitoring through long-term routine evaluations in home-care could be implemented and supplement standardized clinical procedures. However, this approach should be meticulously tailored to accommodate specific characteristics of the target population and their unique living environments. Immersive Virtual Reality (VR) presents an innovative solution that could simulate personalized and controlled environments to benefit the target population. **Objectives**: The objectives of this exploratory study were to gather preliminary insights and recommendations concerning the usability of the developed VR prototype, and solicit expert opinions regarding its potential utility as a means of assessing cognition based on user performance during gameplay.
Methods: Methods: Upon acquiring satisfactory VR user experience from alpha testing, the researchers invited four experts from the Alzheimer's Disease Association of the Philippines (ADAP) to experience the prototype. The researchers arranged a two-day demonstration of the VR prototype followed by an online focus group discussion.
Results: Results: The domain experts appreciated the prototype's design, noting its suitability for older persons with some adjustments to enhance safety. They also recognized the prototype's potential for cognitive measurement with suggestions on expanding the range of assessments in future iterations.
Conclusions: Conclusion: This research represented an initial exploration to utilize immersive VR-based interventions for monitoring cognitive function in home-care. It intended to lay the groundwork for future developments and improvements in immersive VR tools. As VR technology continues to evolve, older persons could benefit from this emerging technology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1366 / #1477

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

THE ASSOCIATION BETWEEN AMYLOID STATUS AND SYMPTOMS OF DEPRESSION AND ANXIETY OVER TIME IN SUBJECTIVE COGNITIVE DECLINE; THE SCIENCE PROJECT

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Calvin Trieu[1,2,3], Argonde Van Harten[1,2], Mardou Van Leeuwenstijn[1,2], Lior Kroeze[1,2], Jarith Ebenau[1,2], Inge Verberk[1,2,3], Sietske Sikkes[1,2,4], Sander Verfaillie[5,6], Elsmarieke Van De Giessen[5], Charlotte Teunissen[3], Wiesje Van Der Flier[1,2]
[1]Amsterdam Neuroscience, Neurodegeneration, Amsterdam, Amsterdam, Netherlands, [2]Amsterdam UMC, Alzheimer Center Amsterdam, Neurology, Amsterdam, Netherlands, [3]Amsterdam UMC, Department Of Clinical Chemistry, Amsterdam, Netherlands, [4]Vrije Universiteit Amsterdam, Faculty Of Behavioural And Movement Sciences, Amsterdam, Netherlands, [5]Amsterdam UMC, Department Of Radiology & Nuclear Medicine, Amsterdam, Netherlands, [6]Amsterdam UMC, Department Of Medical Psychology, Amsterdam, Netherlands

Aims: This study investigates the longitudinal association between amyloid status and depressive/anxiety symptoms in individuals with subjective cognitive decline (SCD), while also exploring potential modifying roles of personality traits and education.
Methods: We included 329 individuals with SCD from the SCIENCe cohort (follow-up: 3.80±2.10), including 88 amyloid-positive (66.2±7.0) and 241 amyloid-negative participants (61.4±7.5). Amyloid status was determined by amyloid PET/CSF biomarkers according to visual read or established cut-points. Depressive/anxiety symptoms were assessed using the Geriatric Depression Scale (GDS), Center for Epidemiological Studies-Depression (CES-D), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). We used linear mixed models to assess the association between amyloid status and depressive/anxiety symptoms over time, and its interaction with neuroticism (Dutch Personality Questionnaire), somatization, (Four-Dimensional Symptom Questionnaire), and education (Dutch Verhage scale).
Results: In univariate analyses amyloid status was not associated with GDS, CES-D and HADS-A at baseline or over time. Using a three-way interaction model, we found that neuroticism modified the association between amyloid status and GDS over time ($p<0.10$), with a stronger association in individuals with lower neuroticism (β:0.10±0.08), than in individuals with higher neuroticism (β:-0.03±0.12). Similarly, somatization modified the association between amyloid status and CES-D over time ($p<0.05$), with a stronger association in individuals with lower somatization (β:0.65±0.23), compared to individuals with higher somatization (β:-0.08±0.29). Additionally, education levels modified the association between amyloid status and CES-D & HADS-A over time ($p<0.05$; $p<0.10$), with stronger associations in individuals with lower education (β:0.75±0.34; β:0.34±0.16), compared to individuals with higher education (β:0.14±0.23; β:-0.04±0.10).
Conclusions: Neuroticism, somatization and education modify the association between amyloid status and depressive/anxiety symptoms over time. This emphasizes the importance of considering individual characteristics when examining the association between amyloid status and depressive/anxiety symptoms in individuals with SCD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1367 / #354

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

IMPAIRED INSIGHT AND OVERESTIMATION OF ABILITY AS PREDICTORS OF BRAIN CHANGES ACROSS TIME IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Jacob Wilkins[1,2], Li Su[1,2,3], Carlos Muñoz-Neira,[1,2,3]
[1]Sheffield Institute of Translational Neuroscience, Artificial Intelligence And Computational Neuroscience Group, Sheffield, United Kingdom, [2]University of Sheffield, School Of Medicine And Population Health, Sheffield, United Kingdom, [3]University of Cambridge, Old Age Psychiatry Research Group, Cambridge, United Kingdom

Aims: Impaired insight can be understood clinically as a loss of ability to appropriately recognise one's own disease status. The study aimed to examine how the character of insight changes with disease stage and assess whether baseline levels of impaired insight can predict rate of brain atrophy across a period of 30 months in a cohort of subjects consisting of: subjective memory complaint (SMC), mild cognitive impairment (MCI), Alzheimer's disease (AD) and cognitively healthy controls (CN).
Methods: Data from 794 eligible participants was extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. Insight levels were estimated using self-administered and informant responses to the Measurement of Everyday Cognition (ECog). Impairment was further categorised into overestimation or underestimation of ability. Brain atrophy rates were estimated for the whole brain and subregions associated with early atrophy in AD disease course. Atrophy rates were measured by change in brain volume calculated from 3 Tesla brain scans undertaken within 30 months.
Results: Insight impairment worsened with disease stage, from minor failures of insight in CN and SMC to more pronounced impairment in MCI and AD. Overestimating ability was significantly correlated with increased whole-brain atrophy rates ($p<0.001$) independent of general cognitive decline. Overestimation of ability exhibited significant correlations with increased atrophy in specific regions of the brain: the medial temporal lobe, fusiform gyrus, and hippocampus.
Conclusions: The present results suggest a significant correlation between overestimation of ability and increased rates of subsequent brain atrophy, highlighting insight as a possible neuropsychological prognostic marker. This is particularly seen in regions of the brain such as the hippocampus. However, further study into the phenomenon of insight and its progression over the disease course is required before predictive ability can be fully assessed.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1368 / #1321

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

RELATIONSHIP BETWEEN BRAIN ATROPHY AND NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Hyon Ah Yi[1], Hyung Lee[1], Hae Won Kim[2], Kyung Sook Won[2]
[1]Keimyung University School of Medicine, Neurology, DAEGU, Korea, Republic of, [2]Keimyung University School of Medicine, Nuclear Medicine, DAEGU, Korea, Republic of

Aims: Neuropsychological symptoms(NPS) are commonly found in Alzheimer's disease(AD) and believed to appear in middle or late stages of AD. However, NPS can be found in early AD and the anatomical localizations of NPS are not completely understood. We aimed to investigate the relationship between structural brain changes and NPS, and between congition and NPS in cognitively impairment patients(CI).
Methods: We enrolled 50 controls, 49 mild cognitive impairment(MCI) and 64 mild to moderate AD. All participants underwent brain MRI, neuropsychological evaluations including Neuropsychiatric inventory(NPI), and amyloid PET. NPI score was classified into 1)NPI-behavioral score(NPI-behav), which included agitation/aggressiveness, disinhibition, irritability and aberrant motor behavior, 2)NPI-psychosis, included delusions and hallucinations, 3)mood disturbance(NPI-mood), included depression, anxiety, sleep, appetite and apathy 4)euphoria. All of them were scored using NPI. We evaluated subcortical change with FIRST.
Results: ANOVAs, adjusted for age, sex and education, showed that NPI-total and NPI-mood scores differed between groups with a tendency to be severe from controls to MCI and further to AD. Comparing controls and cognitively impaired patients(CI) showed lower NPI-total, -behav, -psychosis and mood scores in controls besides euphoria. Correlation analyses revealed that there was significant negative correlation between all of NPI scores except euphoria with MMSE scores. There were correlations between cortical thickness of parts of the lobes and NPI scores besides euphoria after adjusting for age, education and MMSE($p<0.05$). For subcortical analysis, the lower volumes of caudate nucleus and putamen were negatively correlated with NPI-behav and NPI-psychosis, euphoria was related to the lower volumes of hippocampus and amygdala.
Conclusions: NPS were related to the cognitive deterioration and volume loss of focal subcortical regions in early AD and MCI. Our results support previous suggestion of disrupted frontal-subcortical circuit as the mechanisms of NPS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1369 / #1190

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J04. Imaging, Biomarkers, Diagnostics*

IDENTIFYING DISTINCT CLINICAL PHENOTYPES THROUGH MULTIMODAL ANALYSIS IN PATIENT WITH "TYPICAL" AMNESTIC ALZHEIMER'S DISEASE

POSTERS: J04. IMAGING, BIOMARKERS, DIAGNOSTICS

Hussein Zalzale[1], Pamela Lukasewicz Ferreira[1], Bruna Bellaver[1], Guilherme Povala[1], Guilherme Negrini[1], Peter Lemaire[1], Marina Scop-Meidros[1], Francieli Rohden[1], Cristiano Schaffer Aguzzoli[1], Carolina Soares[2], Joao Pedro Ferrari-Souza[1], Douglas Teixeira Leffa[1], Sarah Abbas[3], Dana Tudorascu[4], Nesrine Rahmouni[5], Cécile Tissot[5], Jenna Stevenson[6], Joseph Therriault[5], Stijn Servaes[5], Nicholas Ashton[7], Kaj Blennow[8], Henrik Zetterberg[9], Thomas Karikari[4], Sang Son[10], Helmet Karim[1], Pedro Rosa-Neto[5], Chang Hyung Hong[10], Hyun Rho[10], Oscar Lopez[11], Victor Villemagne[12], Ann Cohen[12], William Klunk[4], Tharick A Pascoal[1]
[1]University of Pittsburgh, Psychiatry, PITTSBURGH, United States of America, [2]University of Pittsburgh, Psychiatry, Pittsburgh, United States of America, [3]3501 Forbes Avenue, Psychiatry, Pittsburgh, United States of America, [4]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America, [5]Translational Neuroimaging Laboratory, Mcgill University Research Centre For Studies In Aging, Alzheimer's Disease Research Unit, Douglas Research Institute, Montréal, Canada, [6]McGill University, Neurology And Neurosurgery, Montreal, Canada, [7]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience & Physiology, Göteborg, Sweden, [8]Gothenburg University, Psychiatry And Neurochemistry, Göteborg, Sweden, [9]Sahlgrenska University Hospital, Clinical Neurochemistry Laboratory, Mölndal, Sweden, [10]Ajou University School of Medicine, Psychiatry, Suwon, Korea, Republic of, [11]University of Pittsburgh School of Medicine, Department Of Neurology, Pittsburgh, United States of America, [12]University of Pittsburgh School of Medicine, Department Of Psychiatry, Pittsburgh, United States of America

Aims: To uncover distinct clinical phenotypes within "typical" Alzheimer's disease (AD) based on cognitive and neuropsychiatric markers, track their longitudinal progression, and identify their corresponding pathological and neuroanatomical correlates.
Methods: We employed K-modes clustering on 2483 cognitively impaired (CI) individuals across the AD spectrum, excluding atypical AD and other CI etiologies, from five cohorts: TRIAD, ADNI, BICWALZS, OASIS-III, and Pittsburgh. Cluster-specific clinical and pathological profiles were established through comparison with 2670 cognitively unimpaired (CU) participants across plasma biomarkers (Ptau-181, Ptau-217, GFAP, Nfl, AB42/40 ratio) and neuroimaging (amyloid and tau PET, MRI-derived degeneration maps). Symptom trajectories were assessed using longitudinal follow-up, revealing whether the phenotypes represent sequential or parallel disease forms. Proportional Cox hazards models quantified functional decline rate using CDR-SB, and longitudinal symptom rate of change were also computed for each phenotype.
Results: We identified five distinct clinical phenotypes: pure amnestic syndrome, global cognitive impairment without NPS, global cognitive impairment with NPS, CI with predominant affective symptoms, and CI with predominant hyperactive symptoms (**Figure 1**). Each phenotype displayed a unique neuropathological and neurodegeneration topographical profile (**Table 2, Figure 2**). Three-year longitudinal data showed that these phenotypes represent parallel rather than sequential disease forms (**Figure 3**). The phenotypes exhibited significantly different rates of functional decline, as well as varied rates of change in cognitive symptoms (**Figure 4**).

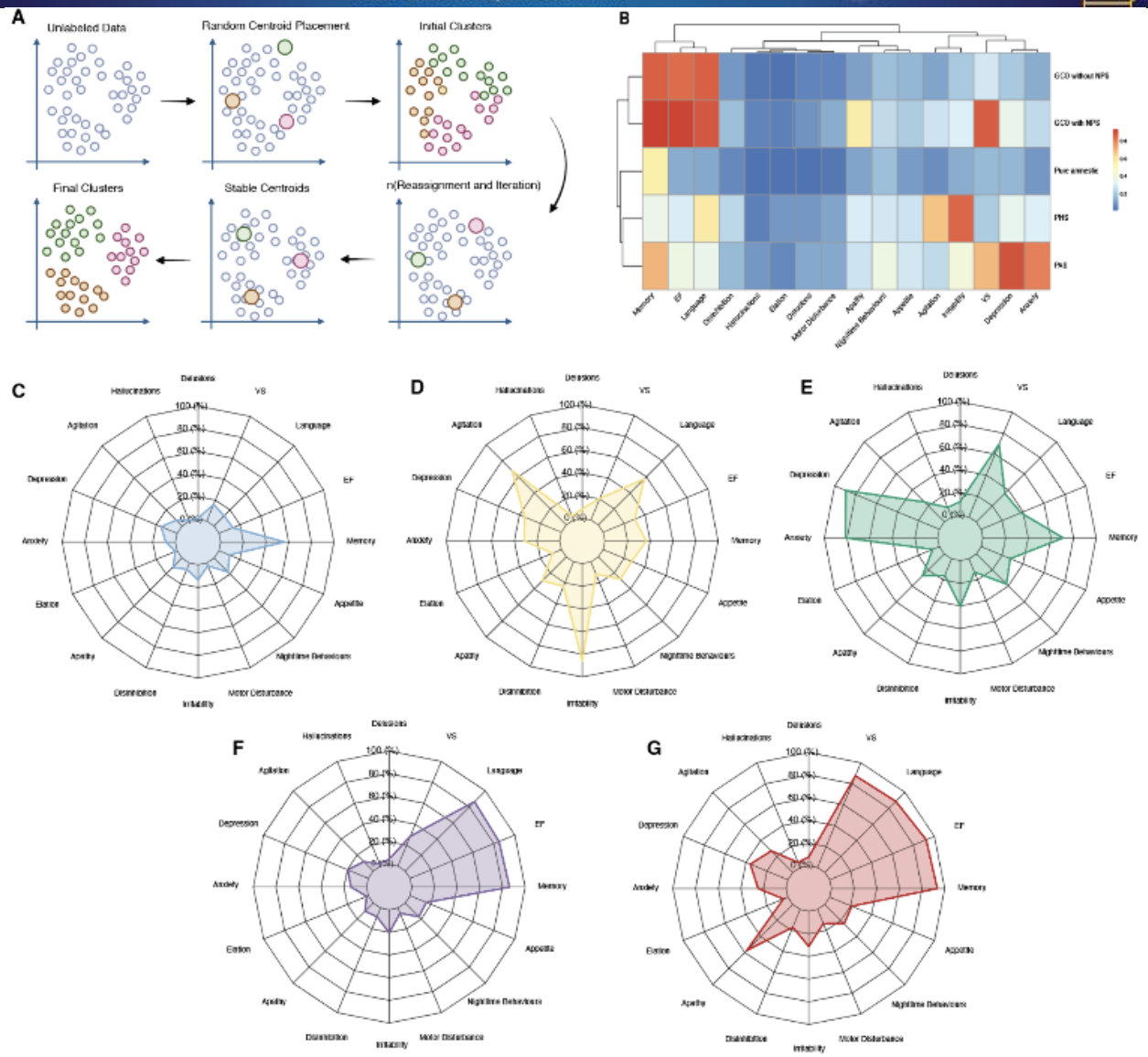


Figure 1: Identification of Five Distinct AD Phenotypes via K-Modes Clustering. A: Iterative K-Modes Process for Stable Phenotype Detection. **B:** Heatmap and Dendrogram Illustrating Cluster Formation and Symptom Prevalence. **C-G**: Radar Charts Depicting the Five Identified Phenotypes: **C**) Purely Amnestic Syndrome, **D**) CI with Predominant Hyperactive Symptoms, E) CI with Predominant Affective Symptoms, **F**) GCD Without NPS, and **G**) GCD With NPS.

	Total	Pure Amnestic	GBD without NPS	CI with Predominant Hyperactive	CI with Predominant Affective	GBD with NPS
Cohort						
ADNI	1622 (69.6)	493 (72.4)	618 (79)	115 (64.2)	143 (46.9)	253 (66.1)
BICWALZ	413 (17.7)	110 (16.2)	73 (9.34)	38 (21.2)	103 (33.8)	89 (23.2)
ADRC	221 (9.48)	36 (9.4)	66 (8.4)	20 (11.2)	51 (16.7)	36 (9.4)
TRIAD	74 (3.18)	5 (1.31)	25 (3.2)	6 (3.35)	8 (2.62)	5 (1.31)
Sex						
Female	1171 (47.1)	348 (46.3)	324 (47.2)	80 (38.8)	195 (54.6)	224 (46.7)
Male	1310 (52.9)	404 (53.7)	362 (52.8)	126 (61.2)	162 (45.4)	256 (53.3)
Age	73.1 (7.8)	71.9 (7.7)	74.7 (7.7)	71.5 (7.5)	71.8 (7.8)	73.6 (7.9)
Education years	14.4 (4.4)	15.4 (3.9)	14.7 (3.7)	15 (4.3)	12.5 (5.5)	13.4 (4.9)
APOE4 Carrier	1069 (48.7)	294 (45.6)	391 (52.6)	68 (40.5)	283 (40.6)	201 (56.3)
Diabetes	109 (3.3)	37 (4.93)	23 (3.35)	6 (2.91)	23 (3.35)	20 (4.15)
Hypertension	458 (18.4)	117 (15.6)	83 (12.1)	40 (19.4)	131 (36.7)	87 (18.0)
Diagnosis						
MCI	1640 (70.4)	603 (88.5)	449 (63.8)	153 (85.5)	207 (67.9)	178 (46.5)
AD	690 (29.6)	78 (11.5)	283 (36.2)	26 (14.5)	98 (32.1)	205 (53.5)
CDR SOB	2.5 (2)	1.5 (1.2)	2.6 (2)	2 (1.4)	2.6 (2.1)	3.9 (2.4)
			Plasma Biomarkers			
Aβ 42/40 ratio	-0.05(1.38)	0.08 (1.68)	-0.15(1.26)	0.07(1)	-0.14(1.34)	-0.06 (1.31)
Ptau-217	1.27 (2.3)	1.06(1.85)	1.62(2.29)	0.3(1.95)	1.12(2.35)	2.1(2.84)
Ptau-181	0.22 (0.77)	0.11(0.79)	0.36(0.77)	0.04(0.53)	0.15(0.59)	0.33(0.88)
NFL	0.12(0.85)	-0.05(0.81)	0.36(0.94)	-0.02(0.73)	0.04(0.73)	0.28(0.96)
GFAP	0.86(1.51)	0.59 (1.42)	1.18(1.6)	0.48(1.26)	0.84(1.63)	1.27(1.36)
			Neuroimaging			
Amyloid PET	0.84(1.39)	0.51(1.3)	1.17(1.43)	0.31(1.29)	0.51(1.3)	1.2(1.34)
Tau PET	0.58 (1.99)	0.47(1.77)	0.82(2.18)	0.44(1.88)	0.09(0.54)	0.79(2.61)
WMH	0.64 (2.03)	0.35 (1.36)	1.16(2.81)	-0.08(0.59)	-0.02(0.68)	1.16 (2.81)

Table 2: Comparison of multiple demographic variables, Plasma biomarkers, and neuroimaging biomarkers between the three discovered phenotypes

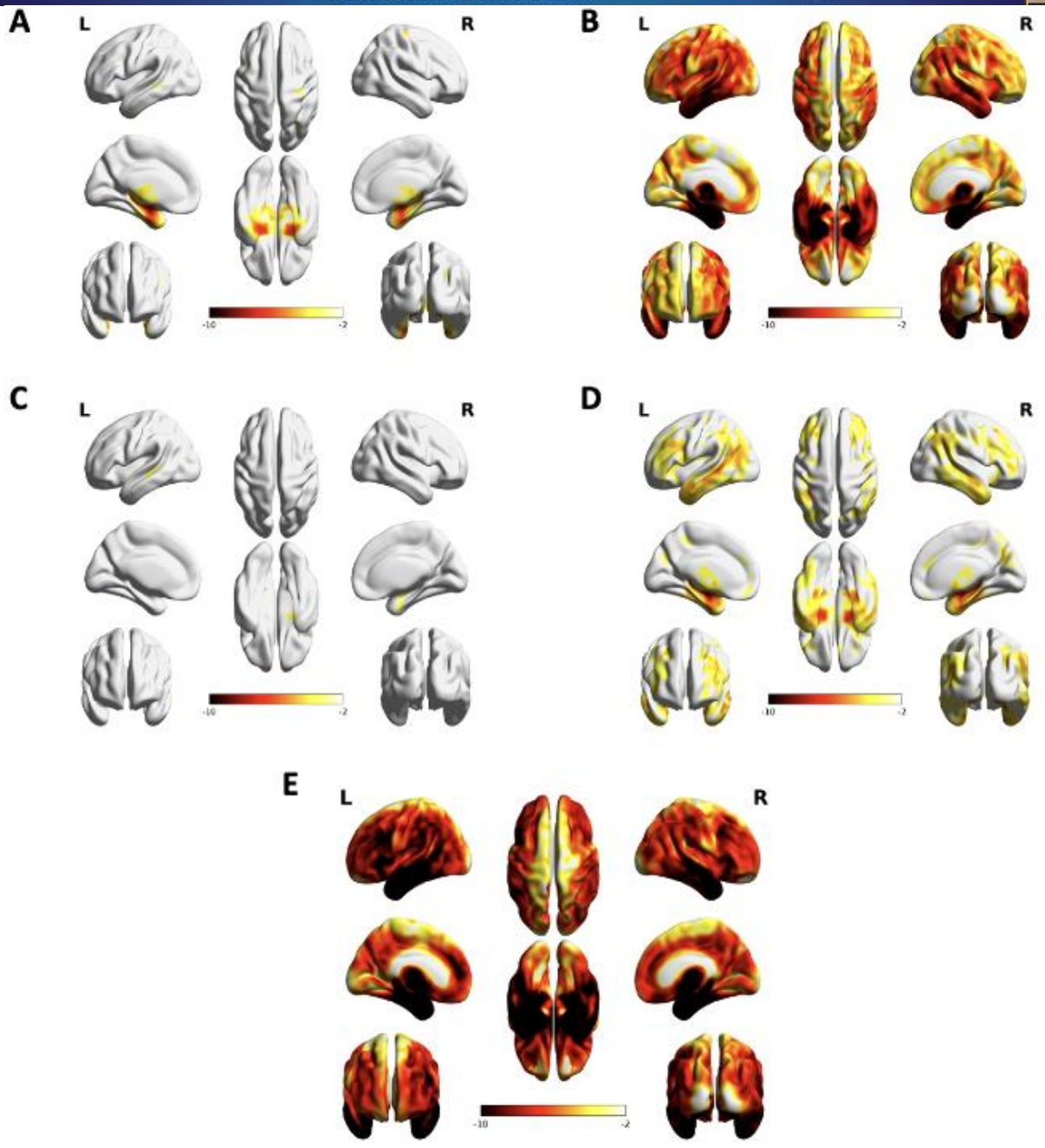


Figure 2: 3D Degeneration Maps for Each Clinical Phenotype, Derived from Average Cognitively Unimpaired Baselines

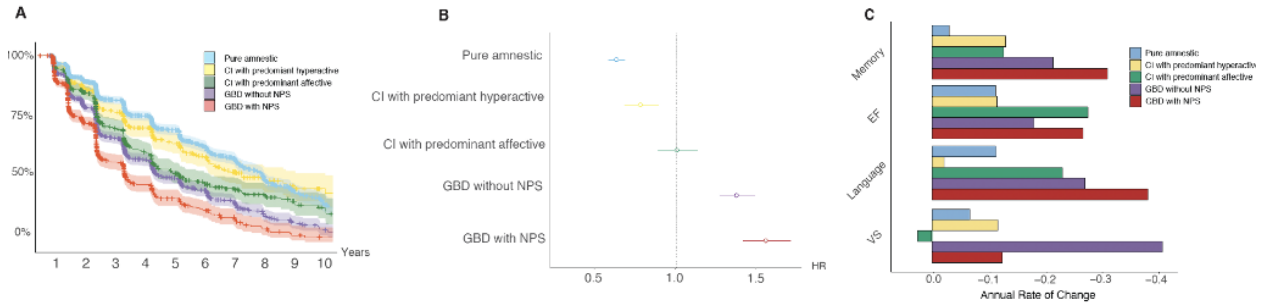


Figure 4: Longitudinal Analysis of the Five Identified Phenotypes. **A**: Survival curves over a 10-year period, controlled for sex, age, and diagnosis using a Proportional Cox Hazards model. **B**: Hazard ratios for each cluster, adjusted for relevant factors, in comparison to the broader CI population for predicting cognitive decline. **C**: Annual rate of symptom progression across the four cognitive domains within each cluster.

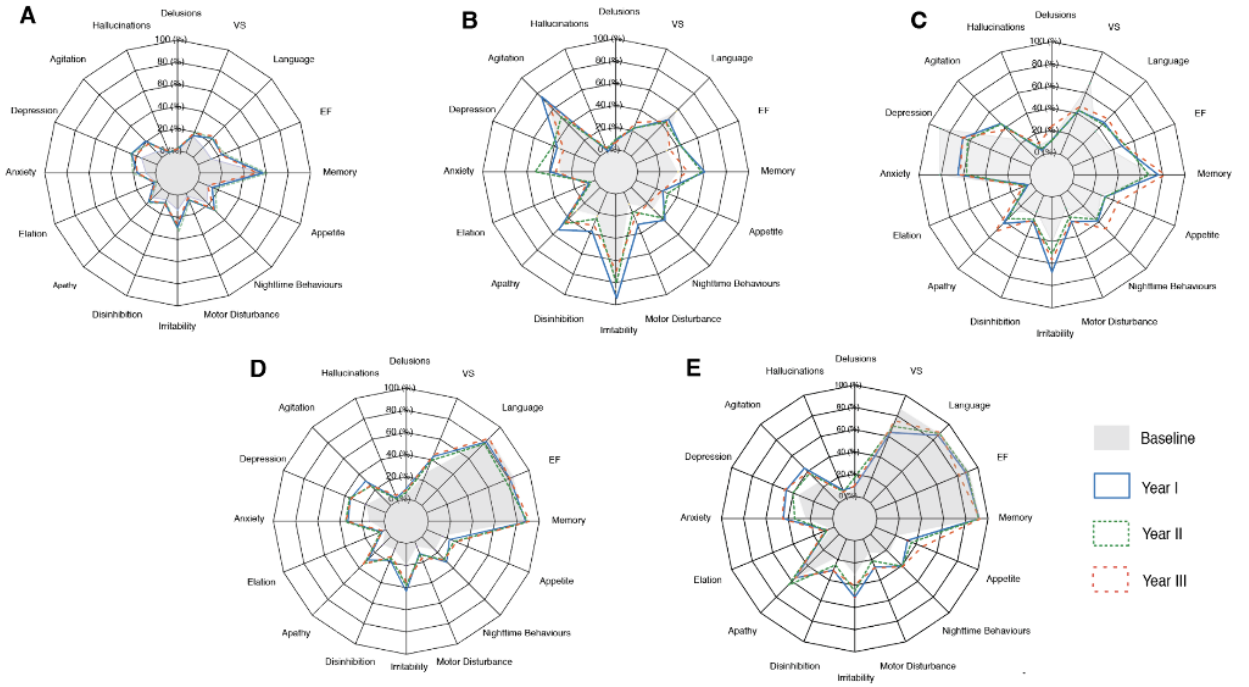


Figure 3: **Longitudinal Radar Chart of Symptom Prevalence Within Each Cluster at Baseline and Annual Follow-Ups (Years 1, 2, 3)**. Subtypes: **A**) Purely Amnestic Syndrome, **B**) CI with Predominant Hyperactive Symptoms, **C**) CI with Predominant Affective Symptoms, **D**) GBD Without NPS, **E**) GBD With NPS. Symptom Structure Within Each Cluster Remains Consistent Over Time.

Conclusions: Our results suggest the existence of robust and replicable sub-phonotypes in "typical" AD by revealing with divergent neuropathological profiles and clinical characteristics. These results highly the importance of personalized medicine to provide a more tailored dementia care in the context of the emerging AD treatments.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1370 / #505

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J05. Genetics, Epidemiology*

CHAIN MEDIATION ANALYSIS OF THE EFFECTS OF NUTRITION AND COGNITION ON THE ASSOCIATION OF APOLIPOPROTEIN E ALLELE 4 WITH NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE

POSTERS: J05. GENETICS, EPIDEMIOLOGY

Jiwei Jiang, Wenyi Li, Jun Xu
Beijing Tiantan Hospital, Capital Medical University, Neurology, Beijing, China

Aims: Apolipoprotein E (*APOE*) is the most recognized risk gene for cognitive decline and clinical progression of late-onset Alzheimer's disease (AD); nonetheless, its association with neuropsychiatric symptoms (NPSs) remains inconclusive. To investigate the association of *APOEε4* with NPSs and explore nutritional status and cognition as joint mediators of this association.
Methods: Between June 2021 and October 2022, patients with amnestic mild cognitive impairment (aMCI) or AD were recruited from the Chinese Imaging, Biomarkers, and Lifestyle Study. NPSs were assessed using the Neuropsychiatric Inventory, while global cognition and nutritional status were evaluated using the Mini-Mental State Examination (MMSE) and Mini-Nutritional Assessment (MNA), respectively. Simple mediation and multiple chain mediation models were developed to examine the mediating effects of the MNA and MMSE scores on the relationship between *APOEε4* and specific neuropsychiatric symptom.
Results: Among 310 patients, 229 (73.87%) had NPSs, and 110 (35.48%) carried APOEe4. Patients with APOEe4 were more likely to have hallucinations (P=0.014), apathy (P=0.008), and aberrant motor activity (P=0.018). MNA and MMSE scores mediated the association between APOEe4 and hallucinations (17.97% and 37.13%, respectively), APOEe4 and apathy (30.73% and 57.72%, respectively), and APOEe4 and aberrant motor activity (17.82% and 34.24%), respectively. Chain-mediating effects of MNA and MMSE scores on the association of *APOEe4* with hallucinations, apathy, and aberrant motor activity after adjusting for confounding factors were 6.84%, 11.54%, and 6.19%, respectively.
Conclusions: Nutritional status and cognition jointly mediate the association between *APOEe4* and neuropsychiatric symptoms in patients with aMCI or AD. Considering the limitations of NPSs therapy in the AD continuum, this study offers novel valuable insights into the role of targeted nutritional interventions in reducing the negative effect of *APOEe4* on the onset and development of NPSs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1371 / #370

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J05. Genetics, Epidemiology*

COMPETING RISK ANALYSIS OF THE ASSOCIATION BETWEEN DEMENTIA AND THE RISK OF MAJOR DEPRESSIVE DISORDER IN TAIWAN: A NATIONWIDE POPULATION-BASED COHORT STUDY

POSTERS: J05. GENETICS, EPIDEMIOLOGY

Chih-Ching Liu[1], Chien-Hui Liu[2]
[1]College of Medical and Health Science, Asia University, Department Of Healthcare Administration, Taichung, Taiwan, [2]National Yang Ming Chiao Tung University, Institute Of Biomedical Informatics, Taipei, Taiwan

Aims: Major depressive disorder (MDD) and dementia are both major contributors to the global burden of disease. Despite existing literature on the association between dementia and the risk of MDD, there is a lack of a nationwide longitudinal cohort study that considers the competing risk of death. Therefore, this cohort study assessed the association between dementia and the risk of MDD over an 11-year period in population-based settings of Taiwan, accounting for death as a competing risk.
Methods: We conducted a population-based retrospective cohort study based on Taiwan's National Health Insurance Database. We identified 80,108 patients diagnosed with dementia in 2009–2010 and matched them with patients without dementia by sex, age, and year of diagnosis to assess the relative risk of MDD. All patients were followed until they received a diagnosis of new onset MDD, their death, or the end of 2019. Cause-specific hazards models were used to estimate adjusted hazard ratios (aHRs).
Results: Our results showed the incidence density of MDD was higher in patients with dementia than in patients without dementia (12.77 vs. 4.69 per 1000 person-years), with an aHR of 2.47 (95% CI: 2.35–2.59). Also, the association between dementia and MDD was observed in the strata of follow-up periods. Among them, the association was strongest within 1-year of follow-up, then reduced rapidly but persisted over follow-up of more than 10 years.
Conclusions: This study found an association between dementia and the risk of MDD. Our findings suggest the need to identify MDD in patients with dementia.

P1372 / #568

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J06. Cell, Molecular and Systems Biology*

TFINDER: A PYTHON WEB TOOL PREDICTING NEURODEGENERATIVE-LINKED TRANSCRIPTION FACTOR BINDING SITES

POSTERS: J06. CELL, MOLECULAR AND SYSTEMS BIOLOGY

Julien Minniti
CNRS UMR 7275 Institut de Pharmacologie Moléculaire et Cellulaire, Biologie Cellulaire & Moléculaire Du Vieillissement Cérébral Normal & Pathologique, Valbonne, France

Aims: Transcription factors (TFs) bind to the regulatory regions of genes and regulate their expression. Dysregulation or mutations of TFs lie at the core of neurodegenerative diseases pathophysiology. Notable among these TFs are p53, a key regulator of apoptosis; NFkB, involved in the neuroinflammatory response; and the less-documented Parkin, which has a neuroprotective function against Alzheimer's disease, Parkinson's disease, and glioblastoma development. Experimental validation of TF-regulated genes typically involves ChIP and EMSA assays. However, identifying Transcription Factor Binding Sites (TFBSs) in-silico is a fundamental step. Many tools recover regulatory regions but lack user-friendliness. TFBS analysis leans heavily on databases, often lacking data about recent TFBS. Consequently, databases fail to uncover unpublished TFBSs, and some tools require payment. TFinder offers an all-encompassing solution. It allows users to retrieve regulatory regions by providing only the gene name and promptly search for TFBSs, irrespective of their database status. TFinder is fast, accessible, user-friendly and open source.
Methods: We investigated the regulation of TP53, PSEN1, PSEN2, CCNA2, CCNB1, SNCA, and GBA at the protein and mRNA levels under conditions of Parkin overexpression or knockout using Western Blot and RT-qPCR. TFinder expedited the extraction of these genes' promoter regions and identified Parkin-recognized TFBSs, particularly GCCGGAG. We cross-referenced TFinder-predicted TFBSs with validated ones from promoter activity assays, EMSA, and ChIP.
Results: TFinder efficiently extracted the sequences and pinpointed TFBSs, which we subsequently validated functionally. Our findings indicate that Parkin directly and transcriptionally regulates TP53, PSEN1, PSEN2, CCNA2, CCNB1, SNCA, and GBA.
Conclusions: TFinder is a powerful and user-friendly tool for discovering TFBSs. It proves to be a valuable time-saving resource, especially for studying non-referenced TFs.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1373 / #1956

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J07. Animal Models*

CONSEQUENCES OF PATHOGENIC TAU EXPRESSION IN MOUSE LOCUS COERULEUS

POSTERS: J07. ANIMAL MODELS

Anuradha Korukonda, Jake Atallah, David Weinshenker
Emory University, Department Of Human Genetics, Atlanta, United States of America

Aims: During early stages of Alzheimer's disease (AD), patients often suffer from prodromal symptoms such as anxiety, depression, agitation, and sleep disturbances prior to the onset of cognitive impairment. Incidentally, the brainstem noradrenergic locus coeruleus (LC) is the first structure to develop hyperphosphorylated 'pretangle' tau pathology in the brain, and norepinephrine (NE) influences several of these physiological processes. It is critical to evaluate if early tau accumulation in the LC and the manifestations of prodromal behaviors are causally linked. We thus developed a translationally-relevant tau mouse model that recapitulates the 'LC first' phenomena commonly observed in humans.
Methods: Adult male and female tyrosine hydroxylase (TH)-Cre mice (3 months) underwent intra-LC infusions with a Cre-dependent adeno-associated virus expressing EYFP or P301S mutant human tau (n=5-8/group). 3 months post-infusion, mice underwent behavioral tests to assess sleep latency, locomotor activity, compulsivity, stress-induced anxiety-like behavior, and association memory deficits. Following behavioral tests, brain sections comprising the LC and hippocampus were immunostained with TH to assess for LC integrity, AT8 to detect pretangle tau, NE transporter (NET) to evaluate NE fiber intensity in projection regions, and GFAP and IBA1 as neuroinflammatory markers. Immunoreactivity (IR) was calculated as a measure of fluorescence via ImageJ.
Results: At 3 months, hyperphosphorylated tau was detected in cell bodies and somatodendritic compartments of LC neurons. These mice showed hypersomnia or decreased latency to fall asleep, anxiety-like behavior, and deficits in contextual memory. In tandem, tau accumulation in the LC provoked robust astrocyte inflammatory responses in the LC and dentate gyrus, without significantly affecting NET or TH levels.
Conclusions: Tau pathology in the LC contributes to manifestations of prodromal symptoms. Further studies will address molecular mechanisms underlying tau-mediated LC dysfunction in early AD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1374 / #2063

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J07. Animal Models*

VALIDATING PINK1-/- RATS AS SUITABLE MODELS FOR EXPLORING THE IMPACTS OF GLUCOCEREBROSIDE DYSREGULATION ON NON-MOTOR DEFICITS IN PARKINSON'S DISEASE

POSTERS: J07. ANIMAL MODELS

Mary Kritzer, Markus Riessland, Taylor Russo, Kelly Ng, Elliot Paimany
Stony Brook University, Department Of Neurobiology And Behavior, Stony Brook, United States of America

Aims: Dysregulation in lipid metabolism in Parkinson's disease (PD) is associated with increased risk and/or greater severity of non-motor deficits, including autonomic dysregulation, neuropsychiatric symptoms and cognitive deficits. Our objective is to validate rats with knockout of the PTEN-induced putative kinase1 gene (*Pink1*-/-) as models for exploring PD-relevant lipid pathologies and their roles in predicting, contributing to and/or mitigating non-motor deficits in PD.
Methods: Male and female control and *Pink1*-/- rats were behaviorally tested every two months from 3-12 months old on tasks measuring cognition/memory, affect/anxiety and motor function. This was interleaved with ECG analysis and assessments of glucocerebroside (GluCer) extracted from animals' fur and measured in dot blot assays using an antibody specific for GluCer (Glycobiotech).
Results: Male *Pink1*-/- rats developed significant object recognition memory deficits (Novel Object Recognition, Object Location, Object-in-Place) by 5 months old. *Pink1*-/- females showed little memory impairment but did show significant deficits in sensorimotor gating and worsening anxiety, e.g., in elevated plus maze, from 3 months on. *Pink1*-/- rats of both sexes also had significantly increased heart rates and significantly reduced heart rate variability. These and all non-motor impairments were expressed months before the onset of motor signs. Finally, significantly increased GluCer levels were seen in *Pink1*-/- males from 3 months of age on. However, in females no significant effects of the *Pink1*-/- genotype on GluCer were seen.
Conclusions: Our data show that *Pink1*-/- rats develop prodromal, non-motor deficits in multiple domains; emulate male susceptibility to cognitive deficits, female vulnerability to affective disturbance and sex differences in GluCer dysregulation similar to those observed in PD. Together, these findings identify *Pink1*-/- rats as well suited for deeply exploring the impacts of brain lipid metabolism in PD in sex-specific ways.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1375 / #300

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J07. Animal Models*

SHORT-TERM HIGH-FAT DIET FEEDING INDUCES COGNITIVE DECLINE, AGGRESSIVENESS AND ANXIETY-LIKE BEHAVIOR IN ADULT ZEBRAFISH (DANIO RERIO)

POSTERS: J07. ANIMAL MODELS

Victor Luna Picolo, Andreza De Bem
Universidade de Brasília, Physiology, Brasília, Brazil

Aims: Obesity is a high- prevalence (13% of adult population in 2016), global health concern defined by a high body mass index (BMI). Several comorbidities are associated, including some affecting central nervous system (CNS), i.e. neurodegenerative diseases, cognitive deficit and psychobehavioral disturbs. Zebrafish has raised as a versatile and cheap model widely used to study human diseases, including obesity and neurological diseases. Therefore, our objective is verify the impact of a high-fat diet on the central nervous system (CNS) using well- stablished behavioral tests.
Methods: Animals was feed according with three dietary groups. The standard diet group (SD) received only 7.5 mg/fish of dry food, while the high-fat diet groups received 5 mg/fish dry food plus 7.5 (HFD-7.5) or 15 mg/fish (HFD-15) of chicken egg yolk. Dietary fat content (w/w) was approximately 6.5%, 16.9% and 21.1%, respectively. After two weeks of diets ingestion, behaviors were assessed.
Results: Both HFD groups had obesogenic effects, indicated by increase on BMI, abdominal length and body weight compared with SD group. We show a HFD ingestion induced aggressive and anxiety-like behavior on zebrafish, as measured by mirror-induced aggression and novel tank diving test, respectively. Also, the higher concentration of HFD (HFD-15) elicited cognitive deficit on inhibitory avoidance test while sociability was unaffected, as determined by the social preference test.
Conclusions: Our results are in accordance with evidences in obese human and rodent models, suggesting similar effects of fat intake. Therefore, we highlight the unexplored potential of zebrafish to elucidate this study field.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1376 / #2944

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

CARE GIVER BURDEN IN DEMENTIA

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Sai Teja, Karthik Vinay Mahesh
PGIMER, Neurology, chandigarh, India

Aims: Our Aim was to study the clinical profile of patients presenting with major neurocognitive disorder and to study care giver burden.
Methods: All confirmed cases attending neurology and psychiatry outpatient department or admitted inpatients and fulfilling inclusion criteria was included instudy. Total sample size includes 91.
• Written informed consent would beobtained
• Detailed history as well as neurological examination was carried out in all patients eligible forstudy • Severity of dementia is assessed by Dementia ratingscale
• Care giver burden is assessed by family burden interview Pai andKapoor
Results: The current study included 91 patients with a mean (SD) age of presentation is 63.36 (8.73) Males constituted 54 patients (59.3%) and females 37 (40.7%).
Among subtypes of Major neurocognitive disorder most common was FTD group 40 (44%) followed by AD 22 (24.2%), VD 10(11%), CBS 6 (6.6%), and least CJD 4(4.4%).
Among primary caregivers' spouses constituted 39, children including both son and daughter constituted 40 members
The mean (SD) MMSE was 11.78 (9.47) in our group and the Mean (SD) MOCA score is 9.59.
The family burden score assessed by the Pai and Kapur scale is 6.93(5.03) with a maximum score of 23
The highest Burden was noted in the financial domain and disruption of family routine activities.
Caregiver burden was maximum in CJD with a score of 11 (4.16) followed by FTD 7.88(5.65) and VD 7.20(3.71) with the least in AD 4.68(4.24) group.
Conclusions: Caregiver burden was maximum in Major Neurocognitive disorder with higher neuropsychiatric symptoms like CJD followed by FTD, vascular dementia, with the least burden in AD. Financials and disruption of routine family activities lead to a major burden for caregivers compared to the physical and emotional component

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1377 / #877

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

IMPACT OF CAREGIVER BURDEN ON SLEEP PATTERNS AND CIRCADIAN RHYTHMS OF THE HEART RATE IN SPOUSAL CAREGIVER OF COGNITIVE IMPAIRMENT PATIENTS: A FITBIT-BASED STUDY

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Shin Young Park[1], Jung Been Lee[2], Taek Lee[2], So Yeon Jeon[3]
[1]Chungnam National University Hospital, Daejeon, Republic of Korea, Department Of Psychiatry, Daejeon, Korea, Republic of, [2]Sun Moon University, Division Of Computer Science And Engineering, Asan, Korea, Republic of, [3]Chungnam National University Hospital, Psychiatry, Daejeon, Korea, Republic of

Aims: Numerous studies have established associations between caregiver burden and various aspects of circadian rhythms (heart rate, sleep pattern), primarily relying on subjective measures. In this study, we examined the impact of caregiver burden on spousal caregivers (SCGs) and their circadian rhythms, utilizing Fitbit technology.
Methods: A total of 49 SCGs participated in the study(mean age of 71.9±6.3 years). Participants underwent clinical assessments, including the Pittsburgh Sleep Quality Index (PSQI) and Zarit Burden Interview (ZBI), to evaluate global cognition. They also wore daily activity trackers(Fitbit) for 14 consecutive days.
Results: Elevated ZBI scores in SCGs with cognitive impairment were associated with earlier wake times($p=0.003$), increased daytime sleep($p=0.018$), and reduced nocturnal sleep duration($p=0.002$) based on Fitbit data. This trend was consistent among all patient spouses, regardless of cognitive impairment, and ZBI scores linked to reduced overall sleep duration($p=0.021$) and time in bed(TIB, $p=0.022$). However, no significant relationship was found between ZBI scores and sleep efficiency or PSQI scores. Furthermore, higher ZBI scores were associated with reduced circadian rhythm amplitude($p<0.001$) and goodness-of-fit($p<0.001$).
Conclusions: These findings emphasize the significant impact of caregiver burden on sleep pattern and circadian rhythms of heart rate, suggesting that PSQI may overestimate sleep quality compared to actigraphy. Many SCGs may experience unrecognized sleep disturbances, highlighting the need for interventions. Additionally, cosinor analysis indicates that higher ZBI scores are associated with more static activity(reduced amplitude) and irregular fluctuations in sleep duration, rest periods, and activity times(reduced GoF).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1378 / #1367

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

PRELIMINARY EVIDENCE OF BURDEN EFFECT ON BRAIN MORPHOMETRY IN INFORMAL CAREGIVERS OF PATIENTS WITH ALZHEIMER'S DISEASE

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Giulia Quattrini[1], Claudio Singh Solorzano[1], Roberto Gasparotti[2], Francesca Morganti[3], Orazio Zanetti[4], Cristina Festari[1], Michela Pievani[1]
[1]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Laboratory Of Alzheimer's Neuroimaging And Epidemiology, Brescia, Italy, [2]University of Brescia, Neuroradiology Unit, Brescia, Italy, [3]University of Bergamo, Department Of Human And Social Sciences, Bergamo, Italy, [4]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, U.o. Alzheimer, Brescia, Italy

Aims: Informal caregivers (iCG) of patients with Alzheimer's disease (AD) generally experience burden and stress; however, whether these chronic conditions have an effect on the brain is unclear. Stress may have neurotoxic effects on brain regions modulating behavior and distress such as the anterior hypothalamus, hippocampus, amygdala, and prefrontal cortex. In this study, we tested the association between caregiver burden and stress and brain morphology in iCG of AD patients.
Methods: Twenty iCG (age=52.6±9.1 years, 90% females) underwent clinical evaluation, including the Zarit Caregiver Burden Interview (ZBI) and the Perceived Stress Scale (PSS), and 3T MRI exam. Structural 3D T1-weighted images were processed using FreeSurfer v7.2.0 to assess cortical thickness and subcortical volumes (mean prefrontal cortex thickness, mean volumes of the hypothalamus, hippocampus, amygdala, and their subregions). Spearman correlations were conducted between ZBI, PSS and MRI measures controlling for age.
Results: A negative correlation emerged between ZBI score and the anterior hypothalamic volume (whole, *rho*=-0.648, *p*=.003; left, *rho*=-0.540, *p*=.017; right, *rho*=-0.649, *p*=.003). No significant correlations emerged between PSS and MRI features.
Conclusions: Our preliminary results showed an association between iCG burden and lower volume of the anterior hypothalamus. Further studies are needed to clarify the possible mechanisms underlying these associations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1379 / #627

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

"IF I KEEP CALM AND USE A SOFT VOICE AND SMILE AND LOOK AT HIM … IT WORKS MUCH BETTER"

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Dympna Casey, Barbara Whelan, Priscilla Doyle, Niamh Gallagher, Siobhán Smyth
University of Galway, School Of Nursing And Midwifery, Galway, Ireland

Aims: A carer education programme was developed as part of a pilot comprehensive resilience-building psychosocial intervention (CREST) for people with dementia living in the community. The aim of the programme was to enable carers to respond more confidently to the needs of the person with dementia, to provide them with an opportunity to focus on their own health needs and to meet other carers and share experiences. We explore the carers' experience of the programme consisting of six weekly 2-hour sessions with each week covering a different topic.
Methods: Qualitative group and individual interviews were conducted with the carers during the education programme and at the end of the CREST intervention. Attendance rates were recorded and evaluation forms completed by carers at the end of each session. Qualitative data were analysed using thematic analysis and descriptive statistics used for quantitative data.
Results: Nine carers completed the intervention with an average of 91% attendance (range: 67-100%). Evaluations were very positive with all agreeing that the content of each session was helpful and met their expectations. A key motivation to participate was to gain more knowledge and understanding about dementia and learning communication strategies were particularly useful. The support and learning that carers got from other group members, the social interaction and the emphasis on self-care were important elements of the programme.
Conclusions: Carers of people with dementia need good support to enable them to manage the demands of caregiving. The carer education programme of the CREST intervention helped to support carers to manage stresses through better communication strategies, to build a support network of other carers and to focus on their own needs to better enable them in their role.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1380 / #1097

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

THE CAREGIVER BURDEN OF DEMENTIA

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Wei-Pin Hong[1], Ming-Chyi Pai[2]
[1]National Cheng Kung University Hospital, Department Of Neurology, Tainan City, Taiwan, [2]Medical College and Hospital, National Cheng Kung University, Neurology (behavioral Neurology), Tainan, Taiwan

Aims: Dementia causes considerable caregiver burden to caregivers. In this study, our first aim is to qualify the caregiver burden and the second aim is to reveal the need of caregivers in different types of dementias and different stages.
Methods: Each patient with dementia coming to visit dementia clinic in National Cheng Kung University Hospital, Tainan, one of the medical centers in Taiwan has comprehensive survey and records of dementia from the first visiting and the after follow-up, including basic demographic data, cognitive function, Zarit burden interview scale, and Neuropsychiatric inventory scale, etc. We enrolled the patients with dementia in recent 5 years. The patients were categorized into Alzheimer's disease, Lewy body dementias, vascular dementias, and other type of dementia according to the diagnosis and clinical dementia rating. Subjective cognitive decline, mild cognitive impairment, and patients living in long-term care facilities were excluded. Analysis of variance is as a statistical method.
Results: The results are under organization and analysis recently. It will be revealed during the AD/PD 2024 conference.
Conclusions: Caregivers burden may damage the health of caregivers and decrease the quality of care in patients with dementia. To understand the needs of caregivers in different types of dementia is essential. Strategies of dementia care should modify for different dementia cases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1381 / #258

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

DEVELOPMENT AND PSYCHOMETRIC EVALUATION OF FAMILY CAREGIVERS' HARDINESS SCALE: A SEQUENTIAL-EXPLORATORY MIXED-METHOD STUDY

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Lida Hosseini[1], Hamid Sharif Nia[2], Mansoureh Ashghali Farahani[1]
[1]Iran university of medical science, Nursing And Midwifery School, Tehran, Iran, [2]Mazandaran University of Medical Sciences, School Of Nursing And Midwifery Amol, Amol, Iran

Aims: Caring for patients with Alzheimer's disease is a stressful situation.Caregivers need to have their hardiness empowered to provide proper and appropriate care to these older adults. Few studies have been conducted to assess the hardiness of caregivers of patients with AD. Presumably, one reason for this knowledge gap is the lack of a proper scale to evaluate hardiness in this group.This study was conducted to develop a reliable and valid Family Caregivers' Hardiness Scale (FCHS).
Methods: This study is a cross-sectional study with a sequential-exploratory mixedmethod approach. The concept of family caregivers' hardiness was clarified using deductive content analysis, and item pools were generated. In the psychometric step, the samples were 435 family caregivers with a mean age of 50.26 (SD ± 13.24). The data were gathered via an online form questionnaire. The items of the FCHS were evaluated using face and content validity. Then, the factor structure was determined and confirmed using exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) followed by convergent and divergent validity, respectively. Finally, scale reliability, including stability, and internal consistency were evaluated.
Results: The finding revealed that FCHS consists of five factors, namely, "Religious Coping" (5 items), "Self-Management" (6 items), "Empathic Communication" (3 items), "Family Affective Commitment" (3 items), and "Purposeful Interaction" (4 items) that explained 58.72% of the total variance. The results of CFA showed a good model fit. Reliability showed acceptable internal consistency and stability.
Conclusions: The concept of hardiness in Iranian family caregivers is a multidimensional concept that is most focused on individual-cultural values, emotional family relationships, and social relationships. The designed scale also has acceptable validity and reliability features that can be used in future studies to measure this concept in family caregivers.

P1382 / #515

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

HARDINESS IN FAMILY CAREGIVERS DURING CARING FROM PERSONS WITH ALZHEIMER DISEASE: A DEDUCTIVE CONTENT ANALYSIS STUDY

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Lida Hosseini[1], Hamid Sharif Nia[2], Mansoureh Ashghali Farahani[1]
[1]Iran university of medical science, Nursing And Midwifery School, Tehran, Iran, [2]Mazandaran University of Medical Sciences, School Of Nursing And Midwifery Amol, Amol, Iran

Aims: This study was designed to describe the experiences of family Caregivers' hardiness in caring for Alzheimer's Patients.
Methods: The deductive content analysis method was performed between April 2020 and February 2021 in one of the teaching hospitals in Iran. Fourteen family caregivers of Alzheimer's patients were selected using purposive and snowballing sampling and the data were collected by semi-structured interviews. After that, data were analyzed using Elo and Kingas steps.
Results: The results of this study showed that based on the experiences of family caregivers, the family caregivers' hardiness in caring for Alzheimer's patients is a feature of cognitive ability to deal with stressful care situations and consists of five dimensions of commitment, control, challenge, communication and culture with 22 generic categories that they were nested into this five dimension.
Conclusions: Family caregivers' hardiness is a trait related to the individual and environmental factors, and the prevailing social and cultural conditions affect the individual's perception and experience of hardship and threats, as well as his/her understanding of protective factors and how to use them. Therefore, hardiness should not be interpreted as a simple approach regardless of culture.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1383 / #516

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

DEVELOPMENT AND VALIDATION OF CARE STRESS MANAGEMENT SCALE IN FAMILY CAREGIVERS FOR PEOPLE WITH ALZHEIMER: A SEQUENTIAL EXPLORATORY MIXED-METHOD STUDY

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Lida Hosseini[1], Hamid Sharif Nia[2], Mansoureh Ashghali Farahani[1]
[1]Iran university of medical science, Nursing And Midwifery School, Tehran, Iran, [2]Mazandaran University of Medical Sciences, School Of Nursing And Midwifery Amol, Amol, Iran

Aims: Considering all the emotional and fnancial costs imposed on the families of Alzheimer's patients, stress from caring is an issue that cannot be ignored and plans need to be developed to help these caregivers to manage the care properly. The current study was designed to develop a valid and reliable care stress management scale for family caregivers of patients with Alzheimer's
Methods: This study is a methodological study with a sequential-exploratory mixed-method approach that was performed in two-phase: develop the caring stress management scale and evaluate the psychometric properties of the scale. In the frst phase, 14 semi-structured face-to-face interviews were performed with family caregivers of patients with Alzheimer's. The interviews were transcribed immediately and an item pool with 275 items was prepared. After removing the duplicate or overlapping code, the initial format of the caring stress management scale (CSMS) was designed. In the second step, the items of the CSMS were evaluated using face and content validity. After that, the construct validity was evaluated using exploratory factor analysis, confrmatory factor analysis, and convergent and divergent validity respectively. Finally, the reliability was assessed by stability and internal consistency. The sample size was 435 and data was gathered via an online form questionnaire.
Results: This study designed the CSMS with two factors including emotional-focused coping (4 items) and problemfocused coping (4 items) that explained 51.00% of the total variance. The results of the confrmatory factor analysis showed a good model ft. Furthermore, the internal consistency and stability of this scale were acceptable.
Conclusions: The results showed that the care stress management scale has two factors in Iranian family caregivers and it is valid and reliable and can be used by therapists and researchers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1384 / #2071

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

EXPLORING THE IMPACT OF FAMILY SUPPORT GROUP CAREGIVING PROGRAM AT DEMENTIA CARE CENTERS ON FAMILY CAREGIVERS: A CASE STUDY OF A SOUTHERN REGIONAL HOSPITAL

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Chia Hui Hsiao, Yuan-Han Yang
Kaohsiung Municipal Ta-Tung Hospital, Neurology, Kaohsiung, Taiwan

Aims: This study explores the impact of the Family Support Group Caregiving Program provided by dementia care centers on family caregivers. It aims to determine if the program positively affects aspects of family caregivers, such as caregiving burden, stress, knowledge, skills, attitudes, and quality of life.
Methods: The study used the 'SCZBI-12 Caregiver Burden Scale,' a structured questionnaire from a dementia care center at a regional hospital in the south. It involved 15 family caregivers who participated in six sessions of the Family Support Group Caregiving Program. To evaluate the program's impact on caregivers' well-being, pre- and post-program questionnaires were administered. The pre-test was conducted before the caregivers' first session at the center, while the post-test followed program completion. Data analysis was carried out using SPSS 22.0 software, including paired tests to compare pre- and post-program results.
Results: Statistical analysis of 15 valid samples revealed a significant decrease in caregiver burden following participation in the Family Support Group Caregiving Program at the dementia care center. The burden score dropped from 3.08 before the program to 2.24 after the program, showing a significant difference ($P < 0.001$). This represents a notable 27% reduction in burden. These findings underscore the program's effectiveness in reducing caregiver burden among family caregivers.
Conclusions: In summary, dementia care centers' Family Support Group Caregiving Program effectively reduces caregiver burden and stress, improves knowledge and skills, and enhances attitudes and overall quality of life for family caregivers. These programs equip caregivers with professional expertise, offer emotional and social support, and ultimately strengthen their caregiving abilities and well-being. Therefore, it is recommended that relevant organizations continue to offer and develop such programs to enhance dementia care and improve the lives of family caregivers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1385 / #901

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

CAREGIVING BURDEN FOR SPOUSES OF PATIENTS WITH COGNITIVE IMPAIRMENT: EFFECTS ON SERUM HOMOCYSTEINE LEVEL

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Ho Young Jeong[1], Jeong Lan Kim[1,2], So Yeon Jeon[1,2]
[1]Chungnam National University Hospital, Department Of Psychiatry, Daejeon, Korea, Republic of, [2]Chungnam National University College of Medicine, Department Of Psychiatry, Daejeon, Korea, Republic of

Aims: Spousal caregivers (SCG) are predisposed to an elevated risk of cognitive decline and cardiovascular diseases. Identifying potential biomarkers for these adverse health outcomes is of utmost importance. Homocysteine is a promising biomarker associated with both cardiovascular diseases and dementia risk. This study aimed to scrutinize the correlation between caregiver burden and homocysteine levels in SCGs of individuals with cognitive impairment.
Methods: Between May 2020 and December 2022, clinical evaluations and blood tests were conducted on SCGs and care-recipients attending the Chungnam National University Geriatric Neuropsychiatric Clinic. The study encompassed a cohort of 98 spousal caregivers. Caregiver burden was quantified utilizing the Zarit Burden Interview, and blood assays were performed subsequent to overnight fasting.
Results: Linear regression analysis, controlling for variables such as age, sex, and care-recipient's clinical diagnosis, unveiled a significant positive correlation between spousal caregiver burden and homocysteine levels ($\beta = 0.280$, $t = 2.652$, $p = 0.010$). This positive correlation persisted ($p = 0.018$) even after adjusting vascular risk score and APOE ε4 positivity as covariates. Notably, even after the exclusion of SCGs caring for cognitively normal individuals (n = 8), the positive correlation remained significant ($p = 0.019$).
Conclusions: Our findings indicate that the caregiver burden in SCGs of patients with cognitive impairments might amplify homocysteine levels, potentially exacerbating the risk of cognitive decline or instigating cardiovascular diseases. Consequently, screening for homocysteine levels in spousal caregivers could be instrumental in initiating early interventions, mitigating negative health outcomes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1386 / #296

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

TEMPORAL RELATIONSHIPS IN DEMENTIA FAMILY DYADIC COMMUNICATION: SEQUENTIAL ANALYSIS

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Sohyun Kim
University of Texas at Arlington, College Of Nursing And Health Innovation, Arlington, United States of America

Aims: This study examines the temporal relationships between antecedent family caregiver facilitative communication and subsequent care recipient communication during 75 in-home care video observations.
Methods: We conducted a secondary analysis using timed-window analysis of 5, 10, 15, 20, 25, and 30 seconds to examine the likelihood of relationships between dyadic communication patterns. We utilized 95% confidence intervals, p-values, and Yule's Q statistics.
Results: Care recipient engaging nonverbal communication was more likely to occur within all time windows after caregiver facilitative verbal and nonverbal communication (range: OR = 1.41 – 1.76, p < .001, Yule's Q = 0.170 – 0.274). Care recipient engaging verbal communication was more likely to occur within the 25- and 30-second windows after caregiver facilitative verbal communication (range: OR = 1.15 – 1.18, p = .027 – .039, Yule's Q = 0.069 – 0.082). Conversely, care recipient challenging verbal communication was less likely to occur within all time windows after caregiver facilitative verbal communication (range: OR = 0.73 – 0.83, p < .001 - .027, Yule's Q = -0.095 – -0.155). Care recipient neutral communication was less likely to occur within all time widows after caregiver facilitative verbal communication (range: OR = 0.70 – 0.80, p <.001 - = .036, Yule's Q = -0.114 – -0.178). Care recipient neutral communication was less likely to occur within all time widows except the 25-second window after caregiver facilitative nonverbal communication (range: OR = 0.68 – 0.85, p =.002 - .036, Yule's Q = -0.079 – -0.188).
Conclusions: Caregiver facilitative communication was associated with more likely subsequent care recipient engaging communication and less likely challenging and neutral communication. These findings will guide in educating family caregivers on engaging individuals living with dementia in their daily care.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1387 / #1098

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

THE LONG-TERM IMPACT OF ALZHEIMER'S DISEASE DIAGNOSTIC DISCLOSURE ON THE PSYCHOLOGICAL WELL-BEING OF INFORMAL CAREGIVERS: A PRELIMINARY STUDY

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Claudio Singh Solorzano[1], Cristina Bonomini[2], Sandra Rosini[2], Michela Pievani[1], Cristina Festari[1]
[1]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Laboratory Of Alzheimer's Neuroimaging And Epidemiology, Brescia, Italy, [2]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Alzheimer Unit, Brescia, Italy

Aims: The disclosure of an Alzheimer's Disease (AD) diagnosis is an acute stress event for informal caregivers (iCGs). The present preliminary study explores the posttraumatic stress symptoms (PTSS) related to disclosure and their relationship with iCGs' psychological well-being.
Methods: The study included 39 iCGs (mean age=56) of mild-to-moderate AD patients. Participants completed the Impact of Events Scale (IES) retrospectively, considering the moment of AD disclosure, and filled out the Zarit Burden Interview (ZBI), State-Trait Anxiety Inventory (STAI-Y1-2), Beck Depression Inventory–II (BDI-II), and Revised Scale of Caregiving Self-efficacy (RSCSE). iCGs were classified as subclinical or mild-severe PTSS according to an IES cut-off of 26. Mann-Whitney U tests were used to compare subclinical vs. mild-severe PTSS groups on the above scales. Partial Spearman correlations were used to test the association between scales, controlling for the duration of the caregiving role (mean years=3).
Results: Compared to iCGS with subclinical PTSS (n=20), iCGs with mild-severe PTSS (n=19) reported higher levels of caregiver burden (ZBI: z=-2.853, *p*=0.004), anxiety (STAI-Y1: z=-2.815, *p*=0.005; STAI-Y2: z=-2.772, *p*=0.006), and depressive symptoms (BDI-II: z=-2.969, *p*=0.003) and lower levels of self-efficacy in controlling disturbing thought about their caring role (RSCSE-CUT subscale: z=-2.123, *p*=0.033). Moreover, higher levels of intrusive thoughts (IES-intrusion subscale) were associated with greater distress experience (ZBI: r=-0.460, *p*=0.004; STAI-Y1:r=0.340, *p*=0.037; BDI-II: r=0.494, *p*=0.002) and the presence of negative thoughts on their caregiving experience (RSCSE-CUT subscale: r=-0.328, *p*=0.044), while levels of avoidance (IES-intrusion subscale) were only associated with anxiety.
Conclusions: These findings suggest that disclosure of an AD diagnosis might be a traumatic experience for iCGs and may increase their vulnerability for subsequent poor mental health. Future research should deepen these findings and develop strategies to reduce the detrimental effects of the disclosure moment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1388 / #1774

Poster Topic: *Theme J: Psychiatric Symptoms in Neurodegenerative Diseases / J07. Animal Models*

ASSESSING THE COGNITIVE EFFECTS OF METHYLPHENIDATE IN A RAT MODEL OF SPORADIC ALZHEIMER'S DISEASE USING A HOME-CAGE-BASED APPROACH

POSTERS: J07. ANIMAL MODELS

Davor Virag[1], Jan Homolak[1,2], Ana Babić Perhoč[1], Ana Knezovic[1], Jelena Osmanovic Barilar[1], Melita Salkovic-Petrisic[1]
[1]University of Zagreb School of Medicine, Department Of Pharmacology And Croatian Institute For Brain Research, Zagreb, Croatia, [2]Medical Microbiology and Hygiene, Universitätsklinikum Tübingen, Interfaculty Institute Of Microbiology & Infection Medicine | cluster Of Excellence - Controlling Microbes To Fight Infection, Tübingen, Germany

Aims: Epidemiological and animal studies have highlighted an Attention Deficit Hyperactivity Disorder (ADHD)-like phenotype as a risk factor for later development of Alzheimer's disease (AD), with some smaller clinical studies in AD patients showing a potentially beneficial effect of methylphenidate (MPH) treatment. ADHD-related behavioural characteristics have been found in some AD animal models, such as the rat model of AD induced by intracerebroventricular streptozotocin (STZ). We aimed to investigate the effect of oral MPH on cognitive performance in this model.
Methods: Three-month old male Wistar rats (n=40) were injected intracerebroventricularly with citrate buffer (control/CTR) or STZ (3 mg/kg) split in two doses 48 hours apart after which MPH therapy was initiated daily in a dual-bottle dosage regimen (4 and 10 mg/kg) for 6 weeks to half of CTR and STZ groups. Cognitive ability was assessed in the classical Novel Object Recognition (NOR) test at 2, 4, and 6 weeks after STZ. Baseline and 6-week continuous measurement of cognitive performance was performed in an operant conditioning task using VlaDiSlav, a custom home cage apparatus.
Results: At 2 weeks, STZ demonstrated worse performance than CTR (NOR), but this deficit was ameliorated by MPH. No change in NOR were observed at 4 and 6 weeks between the groups. Learning curves in continuous testing using VlaDiSlav show a severely diminished learning rate in STZ group, however, STZ+MPH learning rate was similar to CTR values.
Conclusions: VlaDiSlav continuous measurement gives insight into the learning process suggesting that STZ induced a severe learning deficit that might be normalized by MPH treatment. These findings also highlight the benefits of supplementing conventional behavioural testing with continuously operating, automatised, programmable home cage-based devices.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1389 / #700

Poster Topic: *Theme K: Patient Care and Support / K01.a. Dementia and Cognitive Dyfunction: Caregiver support*

DEMENTIA IDENTIFICATION AND CARE MANAGEMENT IN VALUE-BASED INSURANCE PROGRAM

POSTERS: K01.A. DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT

Zaldy Tan, Nabeel Qureshi, Erica Spivack, Nancy Sicotte
Cedars-Sinai Medical Center, Neurology, Los Angeles, United States of America

Aims: To assess the impact of a dementia care program on a value-based Medicare population.
Methods: In a large multi-specialty medical group practice, we identified patients enrolled in a value-based insurance program (Medicare Advantage) using the EPIC electronic health record (EHR). Patients were eligible to enroll in a care coordination program if they had an ICD-10 diagnosis of ADRD in the EHR problem list and/or past medical history, or currently taking an FDA-approved medication for ADRD. A study-assigned nurse practitioner (NP) identified the patient's medical, behavioral, and psychosocial needs using the novel CEDARS-6 dementia care tool to formulate and share a care plan with the patient's primary care provider. To evaluate patient and caregiver health status, we assessed patient behavior (NPI-Q), caregiver stress [Modified Caregiver Strain Index (MCSI)], and caregiver depression (PHQ-9) at baseline and at one year.
Results: We enrolled 195 (33.1%) of eligible patients, with non-responders to the invitation accounting for the majority (75%) of non-enrollees. The average age of enrollees was 81.3 (SD=9.16), 64.6% were female, and 81.2% identified English as their primary language. At baseline, patients scored an average NPI-Q Severity score of 10.40 (6.87), and an average NPI-Q Distress score of 13.80 (10.54). Preliminary data show decreases of 1.4 and 1.1 in NPI-Q Severity and Distress scores, respectively ($p>0.05$). Caregivers scored an average PHQ-9 score of 5.65 (5.28) and MCSI score of 10.62 (7.01). Preliminary data show decreases of 0.8 and 1.2 in PHQ-9 and MCSI, respectively ($p>0.05$).
Conclusions: PLWD proactively enrolled in a dementia care program have high baseline rates of behavioral issues and their caregivers have elevated depression and stress scores. It is important to track the longitudinal effects of the CARES dementia program on these measures.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1390 / #2161

Poster Topic: *Theme K: Patient Care and Support / K01.b. Dementia and Cognitive Dyfunction: Mobile applications, social networks*

THE BDSC-MCI PROJECT: BEHAVIORAL FINDINGS OF AN ECOLOGICAL TEST OF SPATIAL NAVIGATION

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

Davide Cammisuli, Gianluca Castelnuovo
Catholic University of the Sacred Heart, Department Of Psychology, Milan, Italy

Aims: Spatial abilities are involved in everyday tasks such as wayfinding and learning the layout of a new environment. Particularly, spatial orientation (SO) mainly relies on egocentric/body-oriented navigation, allocentric/world-related navigation and path integration. Behavioral reports of SO can be provided by wearable bodies with sensors able to detect posture and movement beyond physiological parameters, such as those developed by Comftech, the Howdy Senior, a class II medical device that processes and trasmits data to a devoted smarthphone application. In this research, we aimed to detect impaired SO in a sample of patients with MCI due to AD when compared with healthy older adults and individuals with subjective cognitive decline.
Methods: 25 healthy controls, 25 individuals with SCI, and 26 patients with MCI *due to* AD were tested by a naturalistic task (The Detour Navigation Test-modified version, DMT-mv) in an urban area of Milan (Italy). Thanks to the use of Howdy Senior device, gait parameters in the ecological task were recorded. Specifically, 'Time' (number of minutes to complete the pre-established route), 'Latitude', 'Longitude', 'Altitude', 'Speed' (estimated by an integrated accelerometer for calculating steps variability), and 'Direction' were recordered. Moreover, a GPX tracking of participants' body movements were registered, too. Anova with post-hoc tests was performed among groups on these measures.
Results: Patients with MCI due to AD showed significant differences on Time and Speed variables than the other groups ($p<0.001$). GPX tracking also demonstrated a lower adherence of the return walk, calculated as higher "wrong turns" and "moments of hesitation" of the DNT-mv.
Conclusions: Patients with MCI due to AD present with gait impairment when they are requested to lear new paths of a novel environement through a continuous and non-invasive monitoring device.

P1391 / #954

Poster Topic: *Theme K: Patient Care and Support / K01.b. Dementia and Cognitive Dyfunction: Mobile applications, social networks*

USING IOT TECHNOLOGY AND POSITIONING SYSTEM TO ASSIST IN THE CARE AND MONITORING OF THE DAYCARE CENTER FOR DEMENTIA

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

Wen Chien Hsieh
Kaohsiung Municipal Ta-Tung Hospital, Soical Work, Kaohsiung, Taiwan

Aims: In order to respond to the needs of the dementia elderly and their families in the community, Kaohsiung Municipal Ta-Tung Hospital cooperated with the Kaohsiung City Government, social administration and education system to officially open the Full-Love Daycare center in 2016 which located in elementary school; although it has successfully model for Taiwan, till now it also faces difficulties after its operation dilemma: (1) Space dilemma(2) Difficulties in caring manpower.(3) Limited participation of family members.
Methods: Using the integrated long-term care system for internal(staff) and external(families) users, divided into positioning system, smart measurement, institution management and family services:(1) Intelligent positioning system for accurate positioning and safe moving .(2) Smart measurement: introduce IoT technology, use the Bluetooth function of the physiological measurement equipment, and automatically transmit to the hospital outpatient system, and the doctor.(3) Institutional management structure: Using color-based visual management, the system will pop up a reminder window.(4) Family service structure: this function is connected with LINE.
Results: The result included:
1. The number of get-lost dementia elders declined from 3-7 per year to 0. 2. The error rate of transcription of measurement records declined from 3.4% to 0% 3. The on-time completion rate and completeness rate of the assessment records are 100%. 4. Information import of staff satisfaction 100%. 5. The overall satisfaction of family members of integrated long-term care system is 100%.
Conclusions: Long-term care is the global care trend in the future, and the elderly with dementia are increasing year by year. How to make the elderly with dementia receive dignified care requires the dedication of health care institutions. Changes in technology can create an efficient and dignified care model, and can also reduce the burden on family members.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1392 / #1306

Poster Topic: *Theme K: Patient Care and Support / K01.b. Dementia and Cognitive Dyfunction: Mobile applications, social networks*

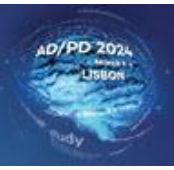
DOVE: AN APP TO REDUCE GETTING LOST INCIDENTS IN PEOPLE WITH COGNITIVE IMPAIRMENT, PART I

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

Ming-Chyi Pai[1], Yang-Cheng Lin[2], Ray-Bing Chen[3], Chi-Hsiang Chu[4], Jing-Jy Wang[5], Cai-Ying Jhou[1], Chih-Han Chang[6], Wei-Pin Hong[1]
[1]Medical College and Hospital, National Cheng Kung University, Neurology (behavioral Neurology), Tainan, Taiwan, [2]National Chung Kung University, Industrial Design, Tainan, Taiwan, [3]National Chung Kung University, Department Of Statistics And Institute Of Data Science, Tainan, Taiwan, [4]Tunghai University, Department Of Statistics, Taichung, Taiwan, [5]National Chung Kung University, Nursing, Tainan, Taiwan, [6]National Chung Kung University, Biomedical Engineering, Tainan, Taiwan

Aims: As spatial navigation impairment is frequently seen in people with dementia, and may result in unexpected injury or life threatening conditions, we designed an APP called DOVE to reduce incidents of getting lost (GL) or missing.
Methods: People with cognitive impairment or their caregivers were encouraged to join the DOVE and install it on mobile, including mild cognitive impairment (MCI), Alzheimer dementia (AD), Lewy body dementia (LB) and other dementia. Demographic, clinical status, the scenarios of GL/missing, and the consequences were collected. We inquired previous incidents and requested the users to report each new incident.
Results: From 1 Feb 2023 to 13 Sep 2023, 488 incidents of GL or missing were uploaded to cloud databank. Among them, GL occurred more often in CDR 0.5 group (104 vs 75) while missing more often in CDR 1.0 group (235 vs 74). Before joining the DOVE, the average occurrence of GL or missing of the patients was 1.54 times. The figure dropped to 0.10 after they joined the DOVE. Based on the individuals who have never experienced GL/missing, people diagnosed having AD with CDR 1.0 or more have an increased risk of GL (OR 3.20) compared with those having non-AD and CDR 0.5.
Conclusions: The marked reduction in GL/missing after the users joined the DOVE may be thanks to more attention paid by caregivers. Most of the users, however, did not report through their mobile APP until been inquired by clinicians in the clinic. More efforts must be put on to improve active reporting. We will provide safety guide and education materials for the users in the future and the beneficial effect on newly diagnosed patients is expected to be promising.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com



P1393 / #718

Poster Topic: *Theme K: Patient Care and Support / K01.b. Dementia and Cognitive Dyfunction: Mobile applications, social networks*

EFFECTIVENESS OF WALKING PRESCRIPTION USING MOBILE HEALTH TECHNOLOGY FOR THE OLDER ADULTS WITH COGNITIVE IMPAIRMENT: A RANDOMIZED CONTROLLED STUDY

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

Hee Jung Kim, Yun Jung Hwang, Jee Eun Park, Dong Young Lee
Seoul National University College of Medicine, Psychiatry, Seoul, Korea, Republic of

Aims: This study aims to verify the effectiveness and feasibility of walking prescription using mobile health (mHealth) technology for older adults with cognitive impairment.
Methods: Sixty older adults with mild cognitive impairment or mild dementia who visited the memory clinic were enrolled (76.1±5.4 years; female, 56.7%). They were randomly assigned into three groups: group A was prescribed the goal of daily steps based on their telemonitored activity using a smart band; group B only wore a smart band without a prescription; group C took a monthly education to encourage their walking. We investigated the changes in daily steps (primary outcome), cognitive function, physical status, and depressive symptoms from baseline to post-intervention (12-week) and to follow-up (24-week). We examined the linear mixed effect models with factors of group, time, and their interaction. Post-hoc analyses using paired t-tests were also conducted.
Results: For group A, there was a significant group x time interaction effect on daily steps both at 12-week and 24-week (β [SE] = 2205.88 [672.34], p = .001; β [SE] = 2194.63 [884.33], p = .015), whereas, group B showed increased numbers of steps only at 12-week but not at 24-week. Group C showed a continuous decrease in daily steps during the study period. Among the secondary outcomes, cognitive function measured by the Mini-Mental State Examination (MMSE) was significantly different according to groups and times. Groups C showed a significant decrease in cognitive function both at 12-week and 24-week, however, group A and B showed stationary MMSE scores during 24 weeks.
Conclusions: Our findings suggest that walking prescription using mHealth technology is effective for increasing physical activities and for maintaining cognitive health in older adults with cognitive impairment.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1394 / #522

Poster Topic: *Theme K: Patient Care and Support / K01.b. Dementia and Cognitive Dyfunction: Mobile applications, social networks*

DEVELOPMENT OF A WEARABLE DEVICE AIMED AT CHANGING THE COGNITIVE FUNCTIONS OF OLDER ADULTS BY MASTICATORY BEHAVIOR CHANGE

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

Ma. Therese Sta. Maria[1,2], Yoko Hasegawa[1], Yukina Miyazaki[3], Tatsuya Suzuki[3], Ryo Takehara[3], Shogo Yoshimura[1], Kazuhiro Hori[1], Yumie Ono[4], Kensuke Yamamura[5], Takahiro Ono[6]
[1]Niigata University Graduate School of Medical and Dental Sciences, Division Of Comprehensive Prosthodontics, Niigata, Japan, [2]Faculty of Dentistry, Manila Central University, Department Of Prosthodontics, Caloocan, Philippines, [3]Graduate School of Science and Technology, Meiji University, Electrical Engineering Program, Kawasaki, Japan, [4]Meiji University, Department Of Electronics And Bioinformatics, School Of Science And Technology,, Kawasaki, Japan, [5]Niigata University Graduate School of Medical and Dental Sciences, Division Of Oral Physiology, Niigata, Japan, [6]Osaka Dental College School of Dentistry, Department Of Geriatric Dentistry, Osaka, Japan

Aims: Although there have been various reports on the relation between cognitive function and mastication, the effect of the habit of chewing well on cognitive function is not yet clear. Therefore, to clarify whether cognitive function is affected by changes in masticatory behavior, we conducted a clinical trial on older adults and attempted to create an algorithm that effectively improves cognitive function.
Methods: We enrolled 50 healthy older adults, aged 65 years and over, who were randomly allocated into intervention and control groups. The intervention group used a chewing counter (biteScan®, SHARP) with an algorithm that promotes positive masticatory behavior change during each meal for one month, while the control group ate meals without a chewing counter. Cognitive function, masticatory behavior, and body composition were evaluated twice, once at the initial visit and once 30 days later. We evaluated whether changes in masticatory behavior affect cognitive function in older adults using two-way ANOVA and post hoc tests.
Results: In older adults, even if the number of chews increased significantly in the intervention group using the chewing counter compared to the control group, their body composition did not change. In addition, the intervention group of older adults also scored significantly higher than the control group in the memory task at the follow-up evaluation. Functional near-infrared spectroscopy (fNIRS) measured brain activity during a cognitive task and found increased cortical activity in the dorsolateral prefrontal cortex in the group using the chewing counter.
Conclusions: These results suggest that using a chewing counter that promotes positive masticatory behavior change may be an effective way to change mastication behavior and may alter cognitive functions related to memory.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1395 / #2304

Poster Topic: *Theme K: Patient Care and Support / K01.b. Dementia and Cognitive Dyfunction: Mobile applications, social networks*

DIGITALLY SUPPORTED LIFESTYLE PROGRAM TO PROMOTE BRAIN HEALTH AMONG OLDER ADULTS- LETHE PILOT TRIAL: STUDY DESIGN AND PROGRESS

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

Anna Rosenberg[1], Helena Untersteiner[2], Anna Giulia Guazzarini[3], Jeroen Bruinsma[4], Matteo Colombo[3], Rik Crutzen[4], Ana Diaz[5], Vassilis Loukas[6,7], Hannes Hilberger[8], Simone Huber[8], Miia Kivipelto[9,10,11,12,13,14,15,16,17,18], Jenni Lehtisalo[1], Dimitrios Fotiadis[6,7], Jyrki Lötjönen[19], Mattia Pirani[3], Bianca Buchgraber-Schnalzer[8], Sten Hanke[8], Francesca Mangialasche[17,18], Patrizia Mecocci[3], Elisabeth Stoegmann[2], Tiia Ngandu[1]
[1]Finnish Institute for Health and Welfare, Population Health Unit, Helsinki, Finland, [2]Medical University of Vienna, Department Of Neurology, Vienna, Austria, [3]Institute of Gerontology and Geriatrics, University of Perugia, Department Of Medicine And Surgery, Perugia, Italy, [4]Care and Public Health Research Institute at Maastricht University, Department Of Health Promotion, Maastricht, Netherlands, [5]Alzheimer Europe, Alzheimer Europe, Luxembourg City, Luxembourg, [6]Foundation for Research and Technology - Hellay, FORTH-BRI, Biomedical Research Institute, Ioannina, Greece, [7]University of Ioannina, Department Of Materials Science And Engineering, Ioannina, Greece, [8]University of Applied Science at FH Joanneum, Institute Of Ehealth, Graz, Austria, [9]University of Eastern Finland, Institute Of Clinical Medicine/ Neurology, kuopio, Finland, [10]Karolinska Institutet, Division Of Clinical Geriatrics, Centre For Alzheimers Research, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden, [11]Fingers Brain Health Institute, Stockholms Sjukhem, Stockholm, Sweden, [12]Karolinska University Hospital, Theme Inflammation And Aging, Solna, Sweden, [13]Imperial College London, Ageing Epidemiology Research Unit (age), School Of Public Health, Faculty Of Medicine, London, United Kingdom, [14]University of Eastern Finland, Institute Of Public Health And Clinical Nutrition, Kuopio, Finland, [15]Imperial College London, Ageing Epidemiology Research Unit, London, United Kingdom, [16]University of Eastern Finland, Institute Of Clinical Medicine, Neurology, Kuopio, Finland, [17]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, Division Of Clinical Geriatrics, Center Of Alzheimer Research, Stockholm, Sweden, [18]Karolinska University Hospital, Theme Inflammation And Aging, Stockholm, Sweden, [19]Combinostics Ltd, Combinostics Ltd, Tampere, Finland

Aims: Due to socio-demographic changes, the dementia prevalence is increasing. The current lack of treatments that can halt cognitive deterioration, highlights the importance of dementia prevention. The landmark FINGER study showed that a multidomain lifestyle intervention has significant cognitive benefits in non-demented elderly. The LETHE pilot trial is testing an updated FINGER intervention, that is delivered in parts through digital tools that were co-designed with an Advisory Board comprising individuals at risk for or living with cognitive impairment or dementia.
Methods: The LETHE pilot study is a 24-month randomized controlled feasibility study conducted in Austria, Finland, Italy, and Sweden. Participants (aged 60-77 years) at risk for dementia but without significant cognitive impairment are enrolled. Participants are randomized 1:1 to intervention and control group. Participants in the intervention group participate in tailored in-person and digital intervention activities in six lifestyle domains (physical activity, nutrition, cognitive activity, cardiovascular risk factors, social engagement, and relaxation). In contrast, participants in the control group have exclusively access to educational content related to the aforementioned domains. Both study groups are equipped with Fitbit smartwatches for passive data collection. The primary outcomes of the study are feasibility and change in risk of dementia.
Results: At this stage, all clinical sites completed recruitment. Overall, 315 people were invited to screening visits. Of these 159/315 (50.4%) met the eligibility criteria and attended baseline visits,

eventually 156 participants were randomized. For the intervention group, both digital and face-to-face intervention activities have already started. First study results are expected in 2025.

Conclusions: To make intervention programs accessible to the general population, digital tools are needed. The LETHE pilot study will therefore test the feasibility of a digitally supported lifestyle intervention for older people.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1396 / #960

Poster Topic: *Theme K: Patient Care and Support / K01.b. Dementia and Cognitive Dyfunction: Mobile applications, social networks*

SOCIAL SUPPORT IN DEMENTIA: A VALIDITY AND RELIABILITY STUDY OF PERSONAL RESOURCE QUESTIONNAIRE-2000 INDONESIA VERSION (PRQ-2000 INA) IN PEOPLE WITH DEMENTIA

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

Amelia Nur Vidyanti[1], Rizqa Nafiati[1], Galenisa Putri[1], Astuti Prodjohardjono[1], Christantie Effendy[2]
[1]Faculty of Medicine, Universitas Gadjah Mada, Department Of Neurology, Yogyakarta, Indonesia, [2]Faculty of Medicine, Universitas Gadjah Mada, Department Of Surgical Nursing, Yogyakarta, Indonesia

Aims: Social support may affect the clinical outcomes of people with dementia. However, the study investigating the relationship between social support and cognitive functioning in dementia is still lacking due to limited instrument to measure social support. The Personal Resource Questionnaire (PRQ2000) is an instrument used to assess perceived social support in a wide range of populations. We aimed to assess the validity and reliability of the PRQ2000 Indonesia version (PRQ2000-INA) in people with mild to moderate dementia.
Methods: This study was a cross-sectional study. We conducted forward-backward translation of the questionnaire. Confirmatory factor analysis (CFA) was used for the validity test. The reliability test was determined by using Cronbach's alpha value.
Results: The PRQ2000-INA has 15 questions which are divided into 3 factor dimensions of social supports. The results of CFA test from 75 respondents showed that all questions in each factor of PRQ2000-INA were valid and had an acceptable construct validity to measure social support. The Cronbach's alpha values for factor 1, factor 2, and factor 3 were 0.903, 0.918, and 0.940, respectively, indicating a reliable instrument.
Conclusions: In conclusion, PRQ2000-INA had a good validity and reliability to measure social support in people with mild to moderate dementia. Future study is needed to investigate the role of social support in cognitive functioning in people with dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1397 / #1057

Poster Topic: *Theme K: Patient Care and Support / K01.b. Dementia and Cognitive Dyfunction: Mobile applications, social networks*

PROJECT EWA – AI METHODS FOR EARLY AD/PD SYMPTOM DETECTION AND THE USE OF MOBILE TECHNOLOGIES FOR SCREENING

POSTERS: K01.B. DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS

Alfred Zimmermann[1], Eugen Ružický[2], Matej Škorvánek[3], Zuzana Képešiová[2], Nataliia Zozuk[4], Milan Rusko[5], Marián Trnka[5], Richard Malaschitz[1]
[1]AXON PRO Ltd., Ewa - Early Warning Of Alzheimer, Bratislava, Slovak Republic, [2]Pan-European University, Faculty Of Informatics, Bratislava, Slovak Republic, [3]P. J. Safarik University, University Hospital L. Pasteur, Košice, Slovak Republic, [4]Constantine the Philosopher University, Faculty Of Informatics, Nitra, Slovak Republic, [5]Slovak Academy of Sciences, Department Of Informatics, Bratislava, Slovak Republic

Aims: The aim of the project was to investigate the detection of symptoms of neurodegenerative diseases, especially AD and PD, by analysing the speech of the test subject. The results of the research were used to develop a mobile application in which a person names simple objects and activities that he or she sees in 40 consecutive images and describes a more complex scene within a 90-second time limit. The speech is then evaluated using AI methods and the result is communicated to the user in the app. The app also includes the option to participate in a longer-term tracking and cognitive training program.
Methods: The research part of the project established a methodology for identifying appropriate words and their associated images and established inclusion and exclusion criteria for participation in the project. This was followed by the recruitment of people diagnosed with AD and PD and the healthy control, which was in total over 1700 participants. The own developed ASR method was used to convert speech into text. Different types of acoustic, lexical and semantic parameters were extracted from the speech utterances to be used as an input vector for classifier. Different AI methods were also investigated for suitability for this task. The resulting classification was done by combining the results from the 6 AI methods.
Results: The classification results in the speech classification into one of four groups - healthy, AD, PD, unspecified disease, with the achieved relevance at the level of 90% specificity, 85% sensitivity and 93% accuracy. An application for long-term training of cognitive functions was also developed.
Conclusions: The developed application can serve as an excellent, inexpensive and easily accessible tool for screening the population for AD and PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1398 / #1583

Poster Topic: *Theme K: Patient Care and Support / K01.c. Dementia and Cognitive Dyfunction: Cognitive training*

FAMILIARIZATION SESSION MAY INCREASE TREATMENT SENSITIVITY: DATA FROM THE DEEP & FREQUENT PHENOTYPING STUDY IN PRODROMAL ALZHEIMER'S DISEASE USING CANTAB

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

John Bernstein[1], Emily Thorp[1], Nathan Cashdollar[1], Francesca Cormack[1], Jennifer Lawson[2], Vanessa Raymont[2], Simon Lovestone[3], James Rowe[4], Barbara Sahakian[5]
[1]Cambridge Cognition, N/a, Cambridge, United Kingdom, [2]University of Oxford, Psychiatry, Oxford, United Kingdom, [3]Johnson & Johnson, Research & Development, New Brunswick, United States of America, [4]University of Cambridge, Clinical Neurosciences, John Van Geest Centre For Brain Repair, Cambridge, United Kingdom, [5]University of Cambridge, Psychiatry, Cambridge, United Kingdom

Aims: Objectives: The Cambridge Automated Neuropsychological Assessment Battery (CANTAB) is a set of computerized cognitive tasks employed primarily in clinical trials. Prior work suggests that inclusion of a familiarization session (initial completion of a task prior to baseline assessment) may enhance treatment sensitivity by reducing the likelihood that increases in performance from baseline to follow-up testing sessions are due to practice/test familiarity. This study examined the utility of a familiarization session when employing commonly-administered CANTAB tasks in repeat testing designs.
Methods: Methods: Participants (n = 207, 57% male, mean age = 71.5) were individuals enrolled in a prodromal Alzheimer's Disease (AD) observational study. Participants completed measures examining reaction time (Reaction Time (RTI)), visual learning and memory (Paired Associates Learning (PAL)), working memory/executive functioning (Spatial Working Memory (SWM)) and sustained attention (Rapid Visual Processing (RVP)). Tests were completed at screening (familiarization), baseline (within one week of familiarization), 1-month, 2-month, 8-month and 10-month timepoints. Pearson correlation coefficients examined associations between subsequent time points for each task (e.g., familiarization vs. baseline, baseline vs. 1-month, etc.)
Results: Results: PAL and SWM performance at familiarization was only modestly correlated with performance at baseline (r = .45 and r = .44, respectively); however, correlations between subsequent time points for these tasks was moderate to strong (r ranges = .55 to .83 and .74 to .76, respectively), suggesting a potential benefit of familiarization session inclusion. RTI and RVP performance was strong across timepoints (r ranges = .84 to .89 and .70 to .93, respectively).
Conclusions: Conclusions: A familiarization session is useful in limiting practice effects on several CANTAB tasks, including the PAL and SWM. CANTAB tasks show good stability over a ten-month period and are suitable for longitudinal geriatric clinical trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1399 / #2164

Poster Topic: *Theme K: Patient Care and Support / K01.c. Dementia and Cognitive Dyfunction: Cognitive training*

THE BDSC-MCI PROJECT: IMPLEMENTATION OF A SPATIAL NAVIGATION VIRTUAL TRAINING IN INDIVIDUALS AT HIGH RISK OF DEVELOPING ALZHEIMER'S DISEASE

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

Davide Cammisuli, Gianluca Castelnuovo
Catholic University of the Sacred Heart, Department Of Psychology, Milan, Italy

Aims: Spatial navigation (SN) impairment in Alzheimer's Disease (AD), such as disorientation or even getting lost, is often overshadowed by the most ascertained episodic memory defect. However, deficits in spatial orientation appear early in the course of AD, and we already provided evidence of a specific deficit of pure path integration in genetic risk carriers. In this study, we aimed at ameliorating spatial navigation (SN) performance in higher risk subgroups (amyloid-positive MCI patients and APOE-e4 carriers) by combined sessions of computer-based cognitive remediation and virtual reality.
Methods: Three amyloid-positive MCI patients and two individual carrying the APOE-ε4 allele underwent a combined intervention of computer-based (CB) sessions of spatial memory tasks by the Erica© software (Giunti, Florence, Italy) and VR navigation sessions by the NeuroVirtual 3D software in order to improve spatial memory for landmarks location and mental frame syncing for supporting spatial scenarios. The intervention will last one month for a total of 12 sessions (3 days a week, 50 minutes *per* session). In the CB spatial memory task, the patient has to memorize a certain number of target figures and their position within a grid of variable dimensions. For the encoding phase of the NeuroVirtual 3D task, participants are instructed to memorize the position of an object in a virtual city. Then, in the retrieval phase, participants have to indicate the position of the object from another start position. Participants were tested after and before the training by the Corsi learning suvra-span. Results were analyzed by a Wilcoxon non-parametric test.
Results: Participants improved on the Corsi learning suvra-span ($p<0.05$).
Conclusions: We estimate the impact of the present rehabilitation training in terms of SN amelioration in senior citizens at higher risk, with relevant implications for independent spatial orientation in everyday activities.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1400 / #2046

Poster Topic: *Theme K: Patient Care and Support / K01.c. Dementia and Cognitive Dyfunction: Cognitive training*

RESTING STATE BRAIN NETWORKS ACTIVITY AND ASSOCIATION WITH TRANSFER OF COGNITIVE TRAINING GAINS

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

Sofia Faraza[1], Martin Dyrba[2], Dominik Wolf[3,4], Florian Fischer[3,4], Kristel Knaepen[5], Bianca Kollmann[3,6], Harald Binder[7], Andreas Mierau[5,8], David Riedel[5], Oliver Tüscher[3,6], Andreas Fellgiebel[3,4], Stefan Teipel[1,9]
[1]University Medical Center Rostock, Clinic For Psychosomatic Medicine And Psychotherapy, Rostock, Germany, [2]Deutsches Zentrum für Neurodegenerative Erkrankungen, Clinical Dementia Research, Rostock, Germany, [3]University Medical Center Mainz, Department Of Psychiatry And Psychotherapy, Mainz, Germany, [4]Center for Mental Health in Old Age, Center For Mental Health In Old Age, Mainz, Germany, [5]German Sport University Cologne, Institute Of Movement And Neurosciences, Cologne, Germany, [6]Leibnitz Institute for Resilience Research (LIR), Mainz, Mainz, Germany, [7]University of Freiburg, Institute Of Medical Biometry And Statistics (imbi), Faculty Of Medicine And Medical Center, Freiburg, Germany, [8]LUNEX International University of Health, Exercise and Sports, Department Of Exercise And Sport Science, Differdange, Luxembourg, [9]Deutsches Zentrum für Neurodegenerative Erkrankungen, Deutsches Zentrum Für Neurodegenerative Erkrankungen, Rostock, Germany

Aims: Age-related cognitive decline increases the need for cognitive interventions. Cognitive training is considered an effective non pharmacological intervention. Transfer of training gains to untrained tasks is a key indicator for the effectiveness of cognitive training. The underlying brain mechanisms need to be further investigated. We assessed functional connectivity determinants of transfer of training gains.
Methods: 181 healthy older adults (mean age:68 years) underwent a 4-week cognitive training across 3 sites. The control group consisted of 54 older adults. To evaluate transfer and training effects, participants underwent a neuropsychological assessment before and after the training. A second follow-up assessment was applied 12 weeks after the training. The training group was divided in subjects who had and who didn´t have successful transfer. We used composite scores representing working memory, memory and executive functions to assess transfer and training effects. Baseline resting-state functional magnetic resonance imaging was used to investigate functional connectivity of brain networks. We extracted brain resting state networks using Independent Component Analysis(ICA).
Results: We observed successful transfer of cognitive training gains in most of the participants. Our results demonstrated spatially restricted effects ($p < .01$ uncorrected) for the association of transfer of gains with the resting-state connectivity of brain networks.
Conclusions: Transfer of training gains in aging is possible. A strong association between transfer of gains and resting-state functional connectivity of networks was not identified.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1401 / #2389

Poster Topic: *Theme K: Patient Care and Support / K01.c. Dementia and Cognitive Dyfunction: Cognitive training*

WALKING PATTERNS, EQUILIBRIUM, COGNITIVE FUNCTION, AND INCIDENTS OF FALLS AMONG PARKINSON'S DISEASE PATIENTS IN NIGERIA

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

Temitope Farombi[1], Olufisayo Elugbadebo[2], Rufus Akinyemi[3], Adesola Ogunniyi[4]
[1]University of Ibadan, Chief Tony Anenih Geriatric Center, Ibadan, Nigeria, [2]University of Ibadan, Geriatric Psychiatry, Ibadan, Nigeria, [3]University of Ibadan, Institute Of Medical Research And Training, Ibadan, Nigeria, [4]University of Ibadan, Department Of Medicine, Ibadan, Nigeria

Aims: Background: Falls in Parkinson's disease (PD) patients were thought to result from failure of motor mechanism in the central nervous system. Recent studies showed possibke association between cognitive dysfunction, gait abnormality and fall in PD Patients. However, it is not clear if ti is an independent risk factor or if its effect on falls is associated with gait abnormality. We studied this possible association between cognitive impairment and fall rate in PD patients.
Methods: Materials and Methods: This descriptive study was conducted among PD patients at the University College Hospital, Ibadna. Diagnosed PD were assessed for risk factors and frequency of falls using Tinneti gait and balance test, Hoehn and Yahr severity scale, Unified Parkinson's Disease Rating Scale (UPDRS). Timed-Up and Go tests and modified Community Screening Instrument for Dementia (CSI'D').
Results: Seventy-eight PDs were screened using the above tools. Of these patients, 40.3% experienced falls since the onset of the disease, with 74.1% having > 2 fall episodes in the last one year. Disease duration was significantly longer in the fallers (p= 0.001), with significant difference in Tinetti Balance (p= 0.004), Hoehn and Yahr (p=0.001), UPDRS (p=0.001), Geriatric Depression Scale (p=0.050) and CSID score when compared to non- fallers (p=0.034). Daily life disabilty was the only independent predictor of fall after a multivariate logistic regression was modelled.
Conclusions: Conclusion: PD patients with cognitive impairment fell more when compared with cognitively intact PD patients. However, daily life disabilty was the only significant factor associated with fall in PD Patients. Improving cognition might not improve the fasll rate

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1402 / #375

Poster Topic: *Theme K: Patient Care and Support / K01.c. Dementia and Cognitive Dyfunction: Cognitive training*

ROCHE RATER ACADEMY: AN INNOVATIVE RATER TRAINING METHODOLOGY APPROACH IN NEUROSCIENCE TRIALS

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

Macarena Garcia Valdecasas Colell[1], Nathalie Pross[2], Enrique Gaspar[1], Ruth Croney[3], Jennifer Eyerman[1], Peter Deaton[3], Sara Inglis[3]
[1]F. Hoffmann-La Roche, Ltd., Roche Pharma Research And Early Development (pred), Basel, Switzerland, [2]F. Hoffmann-La Roche, Ltd, Roche Pharma Research, Basel, Switzerland, [3]F. Hoffmann-La Roche, Roche Pharma Research And Early Development (pred), Welwyn, United Kingdom

Aims: Roche Rater Academy (RRA) is a grass roots wide initiative that aims to improve scientific validity of clinical study endpoints in trials whilst increasing site productivity and improving rater training quality to ultimately improve the regulatory rigor of clinical trial submissions whilst supporting sites to upskill and diversify their qualified site raters.
Methods: A novel methodology was developed to select, calibrate, train and certify site rater's key for clinical endpoint data. The methodology is a holistic solution with fit for purpose training pathways designed to reduce site burden in tailored training to match rater's experience and enable upskilling of site raters reflective of their community. The solution embeds site feedback in an iterative approach to increase productivity by accelerating site start-up through a novel site centric approach to rater training, which removes previous bottlenecks in site activation and enrollment.
Results: With this innovative methodology we aim to improve Clinical Outcome Assessments data quality through gold standard rater training and certification pathways. RRA reduces site burden by tailored training to match rater's experience and accelerate study start up by removing bottlenecks in rater qualification. This will also develop a library of eCOA trainings which are more diverse in real clinical cases. The pilot study has been launched in AD and this model is scalable across indications in Neurodegenerative, Neuromuscular & Neuroimmunology trials.
Conclusions: The RRA is a novel approach to training and certifying site raters, which reduces rater related start up timelines by ∼25% and burden on study teams while enabling sites to upskill and diversify their site raters.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1403 / #229

Poster Topic: *Theme K: Patient Care and Support / K01.c. Dementia and Cognitive Dyfunction: Cognitive training*

ENHANCING COGNITIVE SKILLS IN HEALTHY INDIVIDUALS THROUGH FIDGET SPINNERS: AN INTERVENTIONAL STUDY

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

Yogesh Kumar, Ratandeep Biswas, Ruchi Rani
All India Institute of Medical Sciences Patna, Physiology, patna, India

Aims: 1) Assess the cognitive impact of consistent fidget spinner use. 2) Measure improvements in diverse cognitive functions. 3) Explore sustained effects after usage. 4) Investigate correlations with baseline cognitive abilities.
Methods: In this study, a cohort of 30 individuals characterized by good health was meticulously chosen. After establishing baseline scores through an array of cognitive function assessments, these participants underwent these evaluations both before and after a specific intervention – the daily utilization of fidget spinners – over a span of 9 days within three weeks. Following this intervention phase, a conclusive assessment was conducted. Subsequently, a follow-up evaluation was executed three weeks after discontinuation of fidget spinner usage.
Results: Significant enhancements were noted in scores of the digit symbol matching test, picture pairs test, multiple object track test, and fast choice test, both progressively over the study period and after the implementation of the fidget spinner intervention. Conversely, the matrix reasoning, fast reactions, and paced serial addition tests displayed nominal alterations. Importantly, a sustained effect was manifest in the follow-up scores, highlighting the persistence of these improvements in comparison to the baseline and end-assessment values.
Conclusions: While discernible changes were not observed in fluid intelligence and response speed, the practice of using fidget spinners elicited a consistent amelioration in processing speed, visual episodic memory, working memory, visuospatial attention, and inhibitory control. This phenomenon might be attributed to the demand for enhanced hand-eye coordination, allocation of attentional resources, and a reduction in spontaneous thought wandering imposed by fidget spinner usage. The findings underscore the potential benefits of regular fidget spinner engagement in augmenting diverse cognitive domains, thus holding promise for a wide spectrum of individuals.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1404 / #295

Poster Topic: *Theme K: Patient Care and Support / K01.c. Dementia and Cognitive Dyfunction: Cognitive training*

IMPROVING HUMAN MEMORY THROUGH VOLITIONAL CONTROL OF HIPPOCAMPAL THETA OSCILLATIONS

POSTERS: K01.C. DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING

Vandana Prasad[1,2], Kramay Patel[2,3], Chaim Katz[2,4], Taufik Valiante[1,2,5]
[1]University of Toronto, Electrical And Computer Engineering, TORONTO, Canada, [2]Krembil Brain Institute, Toronto Western Hospital, TORONTO, Canada, [3]University of Toronto, Faculty Of Medicine, TORONTO, Canada, [4]University of Calgary, Faculty Of Medicine, Calgary, Canada, [5]University of Toronto, Division Of Neurosurgery, Toronto, Canada

Aims: Neurofeedback is a technique that allows individuals to control brain oscillations with incredible specificity and precision volitionally. Theta oscillations (3–8 Hz) are modulated during the encoding and retrieval of memories. We want to know if memory can be improved through neurofeedback up-regulation of theta oscillations. We will explore this question by increasing the power of hippocampal theta through neurofeedback before presenting a visual stimulus and determine if this improves the recollection of that stimulus.
Methods: Six individuals with drug-resistant epilepsy undergoing intracranial recordings were presented with a neurofeedback task designed to upregulate and downregulate theta rhythms. The study included recognition and associative memory components and presented visual stimuli following successful up-or-down-regulation of theta rhythms. The downregulation trials served as a control condition. After a brief distraction task, a combination of previously shown and new stimuli was presented and tested for recognition and associative memory performance.
Results: Preliminary results demonstrate the successful modulation of theta oscillations, as evidenced by observed theta power changes and reduced task completion times across consecutive trials. However, we did not observe a significant improvement in memory performance. Notably, these theta oscillation changes were localized to the electrode site used for neurofeedback training. Given the well-established fact that memory processes involve a distributed network of brain regions, this localized effect may explain the absence of consistent memory enhancement. Nevertheless, our findings offer initial evidence supporting the feasibility of volitionally enhancing hippocampal theta oscillations.
Conclusions: The present study provides evidence that individuals can volitionally control the amplitude of their hippocampal theta oscillation, modulated during human memory encoding and retrieval. These data thus represent critical first steps in understanding how neurofeedback could enhance memory formation and the possible development of novel neuroprosthetics.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1405 / #905

Poster Topic: *Theme K: Patient Care and Support / K01.d. Dementia and Cognitive Dyfunction: Support devices & monitoring*

FACTORS INFLUENCING THE SUCCESS OF SMARTWATCH BASED INTERVENTIONS IN PATIENTS WITH MCI OR DEMENTIA IN A CONTROLLED ENVIRONMENT

POSTERS: K01.D. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

Doreen Goerss[1,2], Stefanie Köhler[2], Eleonora Rong[1], Gerald Bieber[3], Stefan Teipel[1]
[1]Rostock University Medical Center, Department Of Psychosomatic Medicine, Rostock, Germany, [2]DZNE, Clinical Dementia Research, Rostock, Germany, [3]Fraunhofer, Igd, Rostock, Germany

Aims: Assistive technologies show promising features to support people with cognitive impairment in daily life. Direct interaction of people with cognitive impairment with smartwatches is little investigated. We examined which factors influence the success of smartwatch-delivered interventions.
Methods: We designed two tasks delivered by smartwatch: A) drinking water and B) circling bells on a worksheet. We created two modes of intervention-intensity affecting vibration, alarm sounds, text sizes and images. In case of failure, interventions were repeated up to three times. We observed n=40 patients' reactions to interventions remotely via cameras and rated success on a 5-step scale from 0 to 2. Patients were assigned (n=20/20) either to mode "regular" or mode "intensive". They answered questionnaires, underwent neuropsychological testing and were diagnosed with MCI (n=12) or dementia (n=28). We hypothesized that affinity for technology (ATI) and cognitive status (MMSE) would influence the success of the interventions. We also expected that intensive interventions would be more successful than regular interventions.
Results: The groups statistically did not differ with respect to mean age, MMSE or ATI. The intensive group was more successful than regular group; for each task and the global success score (mean 1.7 vs. 1.2, Welch t-test p=0.03). Sequential testing of linear regression models showed that "mode" significantly increases model fit: $H_{1\ age + sex + MMSE + ATI + mode}$ p=0.03 and adjusted R^2=21% vs. $H_{0\ age + sex + MMSE + ATI}$ p=0.31 and adjusted R^2=2,7%.
Conclusions: Tasks delivered from a smartwatch as intensive interventions are more likely to be solved by patients than regularly delivered ones. Intensity is more critical than the patient's baseline status with respect to cognition and technology-affinity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1406 / #1117

Poster Topic: *Theme K: Patient Care and Support / K01.d. Dementia and Cognitive Dyfunction: Support devices & monitoring*

MEASURING SOCIAL INTERACTION BETWEEN PATIENT AND CARER

POSTERS: K01.D. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

Derek Hill[1,2], Kate Mcleish[3], Jeremy Roche[3], Wan-Tai Au-Yeung[4], Jeff Kaye[4]
[1]University College London, Biomedical Engineering, London, United Kingdom, [2]Panoramic Digital Health SASU, R&d, ST PIERRE DE CHARTREUSE, France, [3]Panoramic Digital Health, R&d, SAINT PIERRE DE CHARTREUSE, France, [4]Oregon Health & Science University, Oregon Center For Aging And Technology (orcatech), Portland, United States of America

Aims: To measure social interaction in people with AD/PD using Digital Health Technologies.
Methods: This wearable platform comprises a *sensor bracelet* and *environment beacons* that can measure a patient's social interaction with a carer as well as sleep and activities. Environmental beacons are placed where the patient spends most of their time (eg: bedroom, living room, kitchen, bathroom). They contain environment sensors (temperautre, light level, noise level) and transmit these values over Bluetooth at 1.2Hz. The bracelet contains sensors (accelerometer, gyroscope, magnetometer, pressure sensor), listens to the beacon transmissions, and labels the bracelet sensor values with the signal strength of each beacon and the values of the environment sensors. The combined data is analyzed to calculate outputs including sleep time, daytime activity levels, and the location of the wearer through out the day. When no beacons are visible, the wearer is determined to be away from their home. Where a patient and carer both wear a bracelet, their relative location is derived to calculate measures of social interaction eg: how much time per day the patient is in the same room as their carer, in the same house but different room, either away from home or both away from home. Battery life between charging is 2 weeks..
Results: Example sensor output is shown in Fig 1 and summarised in Fig 2. Social interaction data can be associated with the raw data or activity level data for more fine grain analysis. Environment sensor values can control for impact of eg: room temperature on measurements.

Figure 1: Raw data view for participant A, combining Accelerometer data and RSSI from Bluetooth beacons

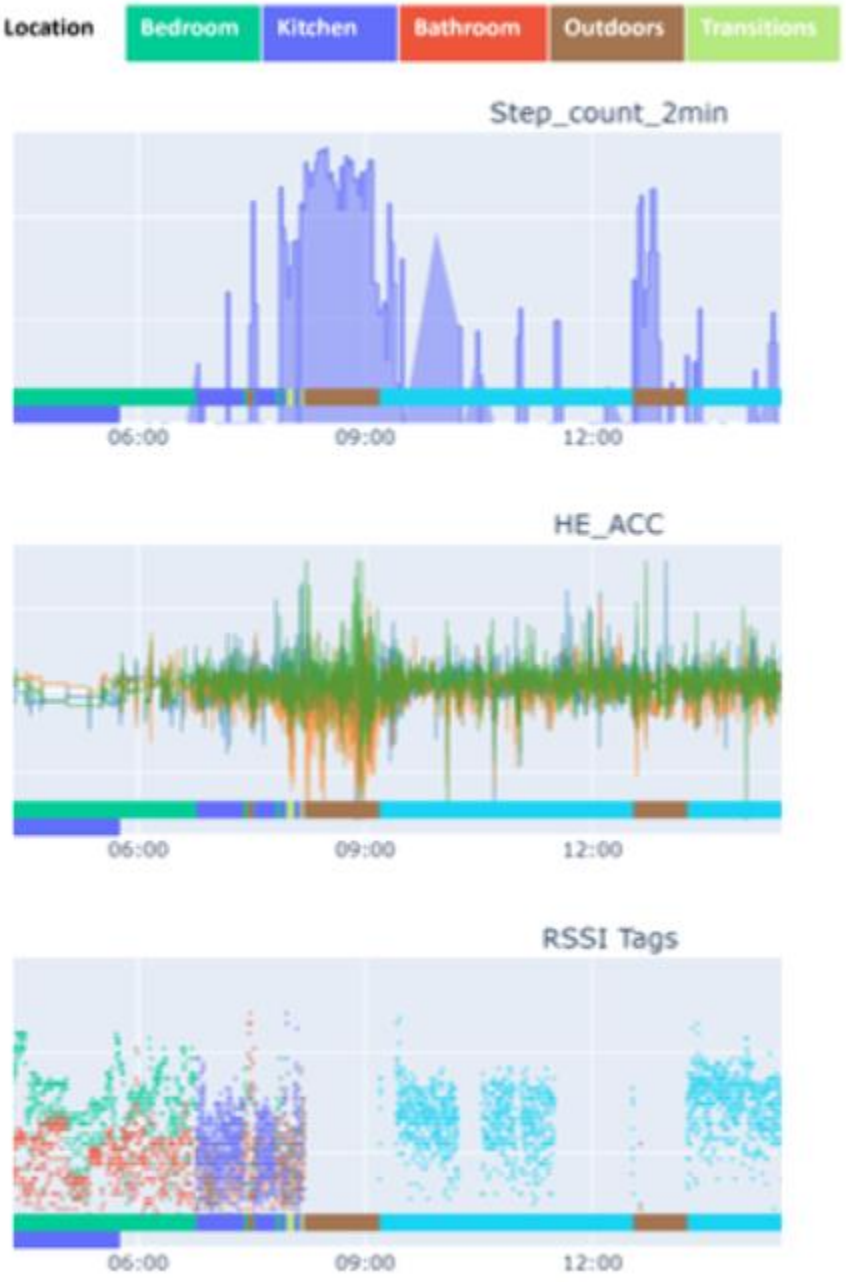
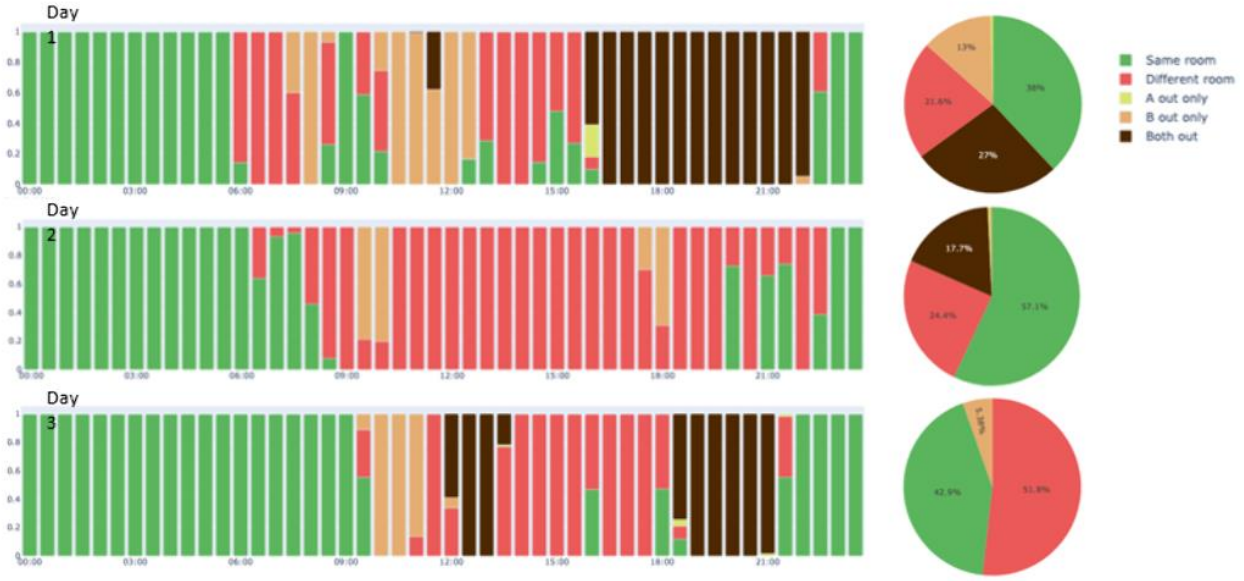


Figure 2: Time two participants, A and B, are together by hour (below) and daily summary (right)



Conclusions: We presented a wearable platform to measure social interaction as well as activites and behaviours to provide more detailed assessment of functioning of AD/PD patients in the home setting.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1407 / #902

Poster Topic: *Theme K: Patient Care and Support / K01.d. Dementia and Cognitive Dyfunction: Support devices & monitoring*

USABILITY OF PHONE-BASED COGNITIVE ASSESSMENTS FOR DEVELOPING A DIGITAL SPEECH-BASED BIOMARKER FOR EARLY DETECTION OF ALZHEIMER'S DISEASE

POSTERS: K01.D. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

Stefanie Koehler[1], Alexandra Koenig[2,3], Nicklas Linz[3], Slawek Altenstein[4], Wenzel Glanz[5], Michaela Butryn[5], Frank Jessen[6,7,8], Matthias Munk[9,10,11], Antje Osterrath[12,13], Björn Schott[14,15], Annika Spottke[8,16], Stefan Teipel[1,17]
[1]Deutsches Zentrum für Neurodegenerative Erkrankungen, Clinical Dementia Research, Rostock, Germany, [2]Université Côte d'Azur, Cobtek (cognition-behaviour-technology, Nice, France, [3]ki:elements GmbH, Speech Biomarkers, Saarbrücken, Germany, [4]Charité, Universitätsmedizin Berlin, Clinic For Psychiatry And Psychotherapy, Berlin, Germany, [5]Medical Faculty University Hospital Magdeburg, Neurology, Magdeburg, Germany, [6]University Hospital of Cologne, Department For Neurology And Psychiatry, Köln, Germany, [7]University of Cologne, Excellence Cluster On Cellular Stress Responses In Aging-associated Diseases (cecad), Cologne, Germany, [8]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Clinical Dementia Research, Bonn, Germany, [9]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Clinical Dementia Research, Tübingen, Germany, [10]Technical University Darmstadt, Systems Neurophysiology, Darmstadt, Germany, [11]University Hospital Tübingen, Psychiatry, Tübingen, Germany, [12]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Clinical Dementia Research, Dresden, Germany, [13]University Hospital Carl Gustav Carus, Clinic For Psychiatry And Psychotherapy, Dresden, Germany, [14]University Medical Center Göttingen, Clinic For Psychiatry And Psychotherapy, Göttingen, Germany, [15]Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Clinical Dementia Research, Göttingen, Germany, [16]University Hospital Bonn, Neurology, Bonn, Germany, [17]Rostock University Medical Center, Department Of Psychosomatic Medicine, Rostock, Germany

Aims: Automated speech recording via telephone using a chatbot technology and AI-driven speech analysis would enable resource-saving cognitive assessment for people with cognitive decline. To extract reliable digital speech biomarkers through a chatbot it needs to be adapted to the users' needs. Here, we implemented a user centered design approach to evaluate usability of a phone-based chatbot system for automated speech assessments for people with prodromal or preclinical Alzheimer's disease (AD).
Methods: Within the study PROSPECT-AD, participants of ongoing national cohort studies are automatically called for six times every three months by our chatbot "Mili". To date, 189 participants have been recruited out of 300 planned cases through September 2023. Each call consists of three cognitive tasks (Wordlist, Semantic Verbal Fluency, Story Telling). We applied a six-stage usability check for Mili. For deeper insights regarding the chatbot's usability, we conducted semi-structured interviews (n=22).
Results: To date, Mili has completed 356 assessments. The SUS revealed a good usability for Mili (n=140, Age: Ø=72.6, SD=6.6, SUS: 69.3/100, SD=22.2). Interviewees perceived the Wordlist without visual input as challenging. However, some wished for variety in the tasks. Additionally, two participants reported frustration as they did not have a positive event to report (Story Telling). Some interviewees preferred a more human like chatbot, while others perceived Mili as a human being. All interviewees wished for feedback regarding their performance.
Conclusions: Our results revealed a high usability and feasibility of the automated phone calls by Mili. Socially intelligent chatbots may be able to address emotional strain during cognitive assessments. Furthermore, based on our usability data, we would aim for an adequate feedback system for the participants regarding their cognitive performance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1408 / #2076

Poster Topic: *Theme K: Patient Care and Support / K01.d. Dementia and Cognitive Dyfunction: Support devices & monitoring*

A COMPUTER SIMULATION MODEL TO PREDICT COGNITIVE IMPAIRMENT

POSTERS: K01.D. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

Lewis Mehl-Madrona[1], Barbara Mainguy[2]
[1]Northern Light Acadia Hospital, Psychiatric Residency, Bangor, United States of America, [2]University of Maine, Intermedia, Orono, United States of America

Aims: Modifiable factors related to cognitive impairment and neurocognitive disorders (and their avoidance) are well recognized.
Methods: We designed a system's dynamics computer simulation model to predict the onset of cognitive impairment given data across the person's entire life. The model allows for studying multiple, interacting variables and an interactive patient and family motivational tool. The simulation model aims to portray the time course for a person to develop cognitive impairment and to progress to major neurocognitive disorder. It incorporated the role of exercise, genetic load, age, quality of diet, presence of diabetes and level of hemoglobin A1C, ongoing levels of cognitive stimulation, presence or absence of micronutrients, presence or absence of other co-morbidities, overall general health index, levels of smoking and other substance use, and family history. The model is based upon available data on individual risk factors with extrapolated interaction relationships. It was built with data on the life course of 14 individuals, adjusting parameters to make correct predictions for all people. Then we entered the data from another 18 people to determine how accurate the model would be with new individuals for whom it had not been developed. We defined success as a prediction of onset within 10% of the actual date and a prediction of the slope of the trend within 20%.
Results: We had 11 successes. We then modeled an additional 18 people, asking them what they would be willing to change to alter their predictions. We then re-ran the model using the changed variables to show what difference altering these factors could make. Thirteen indicated willingness.
Conclusions: Interaction with computer simulation models can provide tools of persuasion to overcome difficulties inherent in people changing their modifiable risk factors.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1409 / #2146

Poster Topic: *Theme K: Patient Care and Support / K01.d. Dementia and Cognitive Dyfunction: Support devices & monitoring*

EARLY DETECTION OF MILD COGNITIVE IMPAIRMENT USING AN EYE-TRACKING TECHNOLOGY

POSTERS: K01.D. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

Shin Teshirogi[1,2], Yuki Ito[1,3], Sho Yamamoto[1,2], Mizuki Katsuhisa[1,3], Yuya Ikegawa[1,3], Shuko Takeda[1,3]
[1]Osaka Psychiatric Research Cente, Osaka Psychiatric Medical Center, Hirakata, Japan, [2]Geriatric and General Medicine, Osaka University Graduate School Of Medicine, Suita City, Osaka Prefecture, Japan, [3]Department of Clinical Gene Therapy, Graduate School Of Medicine, Suita, Japan

Aims: The literature suggests that an early diagnosis and timely intervention can be effective for preventing dementia. Neuropsychological tests are commonly used to detect cognitive impairment; however, they are not sufficiently simple and rapid enough for use as routine screening tools in clinical settings. We previously reported a newly developed eye-tracking-based cognitive assessment (ETCA) tool (Oyama et al., *Scientific Reports* 2019) and demonstrated that ETCA scores are highly correlated with MMSE scores and show high diagnostic performance for dementia. In this study, we examined the ETCA's performance and utility in subjects with MCI and in cognitively normal individuals.
Methods: We assessed 94 participants using both the ETCA and traditional neuropsychological tests, including the MMSE, ACE-III, and RBMT, on the same day. The participants' mean age was 61.0 (SD 13.1), with a range of 40 to 91 (62 women and 32 men).
Results: The participants had relatively high scores on the neuropsychological tests, with mean values of 28.3 (SD 2.2) for the MMSE, 90.6 (SD 0.8) for the ACE-III, and 19.2 (SD 4.5) for the RBMT. Their ETCA scores were significantly correlated with the MMSE ($r = 0.443$), ACE-III ($r = 0.607$), and RBMT ($r = 0.595$) scores ($p < 0.0001$, Pearson). In subjects with an MMSE score of 24 or higher (the $27 \leq$ MMSE subgroup), the ETCA score showed statistically significant correlations with their ACE-III ($r = 0.556$) and RBMT ($r = 0.565$) scores, ($p < 0.0001$, Pearson).
Conclusions: The ETCA was able to detect a slight decline in the cognitive function in subjects with relatively preserved cognitive performance. The ECTA may provide a new platform for a sensitive detection of MCI or dementia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1410 / #252

Poster Topic: *Theme K: Patient Care and Support / K01.d. Dementia and Cognitive Dyfunction: Support devices & monitoring*

USING ELECTROENCEPHALOGRAPHY TO GRADE DEMENTIA SEVERITY

POSTERS: K01.D. DEMENTIA AND COGNITIVE DYFUNCTION: SUPPORT DEVICES & MONITORING

Chang-Yu Chen[1], Tzu-Chao Lin[2,3], Yuan-Han Yang[1,3,4,5]
[1]Kaohsiung Medical University, Post-baccalaureate Medicine, Kaohsiung City, Taiwan, [2]Kaohsiung Municipal Siaogang Hospital, Department Of Neurology, Kaohsiung City, Taiwan, [3]Kaohsiung Medical University, Neuroscience Research Center, Kaohsiung City, Taiwan, [4]Kaohsiung Municipal Ta-Tung Hospital, Department Of Neurology, Kaohsiung City, Taiwan, [5]Kaohsiung Municipal Ta-Tung Hospital, Memory & Aging Center, Kaohsiung City, Taiwan

Aims: Current treatments and researches have raised the importance of biological approaches to early stage of Alzheimer's dementia (AD) for better therapeutic outcome. Electroencephalography (EEG) is regarded as a functional evaluation for AD, but the relationships between EEG and dementia with various stages were not well defined. In this study, we will compute EEG to dementia severities to provide more clinical applications.
Methods: A longitudinal study to recruit clinically diagnosed AD patients by NINCDS-ADRDA criteria with EEG performed every 6 months and the annual neuropsychological assessments including clinical dementiarating (CDR), cognitive ability screening instrument (CASI), and neuropsychiatric inventory (NPI) has conducted. Severity of dementia was regarded as global CDR. EEG contained 19 electrodes to receive 8 different frequency brain waveforms has been used to extract significant features with XGBoost (eXtreme Gradient Boosting) for computing.
Results: In total, 404 AD patients with CDR0.5=102, very mild stage, CDR1=234, mild stage, CDR2=63, moderate stage, and CDR3=5, severe stage have been recruited into statistical analysis. EEG's 152 features of a patient were extracted to compute the associations among dementia severity through XGBoost. For identifying CDR=0.5, compared to other stages, this proposed method can make a successful prediction of accuracy and precision up to 81.48% and 72.73%, respectively.
Conclusions: We have successfully identified very mild dementia using EEG waveforms and CDR score in XGBoost model with the accuracy and precision of 81.48% and 72.73%. The extracted critical features in brain waves could be selected as key parameters to identify dementia patient at the early stage in the future clinical applications.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1411 / #1633

Poster Topic: *Theme K: Patient Care and Support / K01.e. Dementia and Cognitive Dyfunction: Quality of life*

NURSE SCREENING FOR VISION AND HEARING LOSS IN OLDER ADULTS WITH DEMENTIA LIVING LONG-TERM CARE

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

Fiona Höbler[1], Walter Wittich[2], Katherine Mcgilton[1,3]
[1]KITE Research Institute, Toronto Rehabilitation Institute – University Health Network, Research, Toronto, Canada, [2]Université de Montréal, École D'optométrie, Montréal, Canada, [3]University of Toronto, Lawrence S. Bloomberg Faculty Of Nursing, Toronto, Canada

Aims: Sensory impairments, including vision and hearing loss, become increasingly prevalent with older age, and are most prevalent among adults with dementia. In the long-term care (LTC) setting, combined vision, hearing, and cognitive impairment has been found in 30% of residents and is associated with expressive and receptive communication difficulties, and can negatively impact a resident's quality of care. We aimed at assessing the sensibility of sensory screening tools and strategies that could be used by nurses in LTC to detect vision and hearing loss in residents with dementia.
Methods: Environmental scans were first conducted with sensory specialists and LTC nurses to identify tools and strategies currently in use with older adults who have dementia. The results of these scans informed the selection of hearing and vision screening measures which were trialed by nurses and evaluated for their sensibility of use with residents in the LTC setting.
Results: Nurses expressed the need for timely and standardized screening for the early detection of sensory loss and the appropriate provision of interventions to maximize residents' quality of life. The most sensible screening tools, as evaluated by nurses, included otoscopic examination, vision and hearing history questionnaires, a test of pure-tone audiometry, as well as finger counting and hand motion measures.
Conclusions: These findings indicate that education on and implementation of sensory screening are feasible and acceptable to nurses caring for residents who have dementia. The timely identification and treatment of sensory loss in LTC residents living with dementia can support communication, help prevent social isolation, and thus enhance residents' quality of life.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1412 / #1218

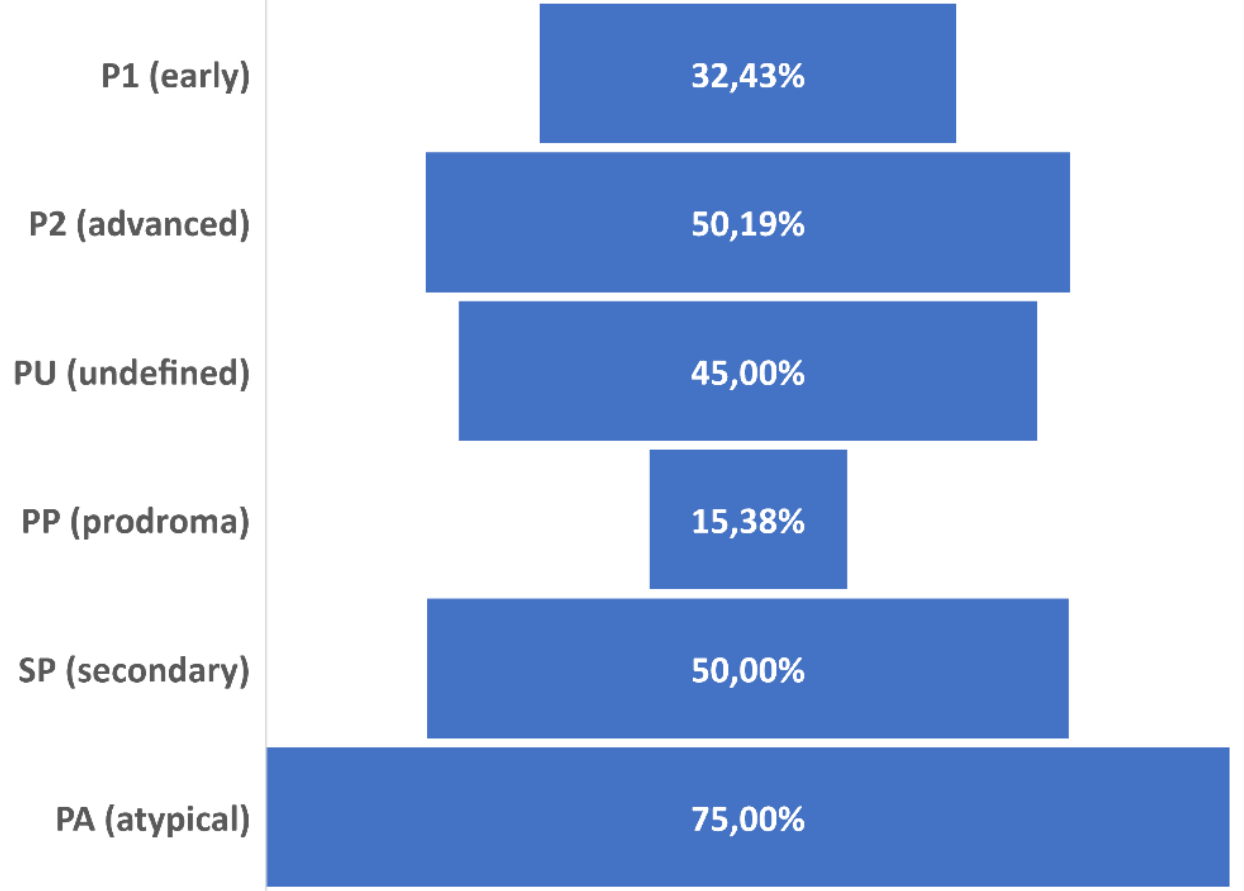
Poster Topic: *Theme K: Patient Care and Support / K01.e. Dementia and Cognitive Dyfunction: Quality of life*

VHI-10 AND COGNITIVE DYSFUNCTION - RELATIONSHIP AND APPROPRIATENESS OF USE IN PATIENTS WITH PARKINSON'S DISEASE

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

Diana Khasanova[1], Ildar Khasanov[2], Zuleykha Zalyalova[1]
[1]Republican Centre for Movement Disorders, Republican Centre For Movement Disorders, Kazan, Russian Federation, [2]LLC Brainphone, Llc Brainphone, Kazan, Russian Federation

Aims: The aim of the study was to assess the impact of cognitive impairment on the possibility of using Voice Handicap Index - 10 scale (VHI-10) as a tool for voice disorders evaluation in Parkinson's disease patients. The work was carried out within the framework of BRAINPHONE project for voice assessment with artificial intelligence (AI). Data was collected in the form of a continuous sample manner in the period from December 2022 to May 2023 in the Centre for Movement Disorders, Kazan, Tatarstan Republic.
Methods: Patients were selected in continuous sampling mannerd. All patients underwent cognitive testing using MOCA test and the VHI-10 scale. All patients were stratified into 5 groups: P1 - patients with 1-2 stages (Hoehn&Yahr), P2 - patients with 3-5 stages (Hoehn&Yahr), PA - patients with parkinsonism-plus syndroms, PU - patients with parkinsonism that cannot be classified on the first visit into one of the groups, PP - patients without obvious motor parkinsonian signs, but meet the criteria of prodromal Parkinson's disease according to MDS Prodromal PD Calculator. All patients were assessed by 2 experienced parkinsonologists.
Results: The study involved 433 subjects with Parkinson's disease, subjective speech impairment reported 46% of respondents (Figure
1).



197 subjects completed both the MOCA test and the VHI-10. Parameters stratified by group are presented in Table 1.

Group	Age (y)	PD duration (y)	MDS-UPDRS	MOCA	Sum_VHI-10	MOCA-VHI-10 correlation coeff.
P1	64.14	3.18	29.14	23.35	8.17	0.05
P2	69.73	6.45	46.26	20.27	12.71	-0.15
PA	67.50	3.9	42.11	15.00	12.67	-0.62
PU	60.64	3.73	31.11	21.64	14.27	0.46
PP	61.95	0.52	12.85	23.57	4.17	0.03
Total	66.49	5.3	40.38	21.31	10.49	-0.15

Conclusions: The relationship between cognitive status and speech impairment assessment is not statistically significant.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1413 / #1752

Poster Topic: *Theme K: Patient Care and Support / K01.e. Dementia and Cognitive Dyfunction: Quality of life*

ASSESSMENT OF INDEPENDENCE AMONG UNITED STATES VETERANS WITH ALZHEIMER'S DISEASE BY STAGE OF DISEASE

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

Byron J Aguilar[1], Joel Reisman[2,3], Peter Morin[4], Dan Berlowitz[5], Maureen O'Connor[1], Raymond Zhang[6], Amir Monfared[6,7], Quanwu Zhang[6], Weiming Xia[1,2,8]
[1]VA Bedford Healthcare System, Geriatric Research Education And Clinical Center, Bedford, United States of America, [2]University of Massachusetts, Lowell, Department Of Biological Sciences, Lowell, United States of America, [3]VA Bedford Healthcare System, Center For Healthcare Organization & Implementation, Bedford, United States of America, [4]Boston University Chobanian & Avedisian School of Medicine, Department Of Neurology, Boston, United States of America, [5]University of Massachusetts, Lowell, Department Of Public Health, Zuckerberg College Of Health Sciences, Lowell, United States of America, [6]Eisai, Inc., Alzheimer's Disease And Brain Health, Nutley, United States of America, [7]McGill University, Department Of Epidemiology, Biostatistics And Occupational Health, Montreal, Canada, [8]Boston University Chobanian & Avedisian School of Medicine, Department Of Pharmacology, Physiology & Biophysics, Boston, United States of America

Aims: Progression of Alzheimer's disease (AD) leads to a decline in the ability to perform activities of daily living (ADL) and increased dependence on caregiver support. The objective of this study is to assess changes in ADL among US Veterans with AD in the Veterans Affairs Healthcare System (VAHS).
Methods: Veterans with an AD clinical note in fiscal years 2010-2019 and a test result from Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) were included in the study. Severity of AD was classified into 5 levels. Three scales used to assess ADL in the VAHS and a general linear model was used to evaluate association of AD severity with ADL measures.
Results: The overall study population included 36,164 Veterans with MMSE/MoCA and ADL scores. 6,514 Veterans were assessed using the 6-pt Basic ADL (Bas-ADL) scale, 17,297 Veterans were assessed using the 8-pt Instrumental ADL (Ins-ADL) scale, and 31,198 Veterans were assessed using the 18-pt Independence ADL (Ind-ADL) scale. The mean(SD) Bas-ADL score for Veterans with an MMSE/MoCA score within the Normal, MCI, Mild AD, Moderate AD, and Severe AD range were 4.6(2.0), 4.4(2.1), 4.2(2.2), 3.5(2.4), and 3.6(2.4), respectively. Ins-ADL and Ind-ADL scores showed similar trends. Analysis showed that increasing severity was associated with ADL scores across all 3 ADL scales ($p<0.0001$).
Conclusions: The decline of independence assessed by three ADL scales utilized in the VAHS are associated with progression of AD severity

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1414 / #340

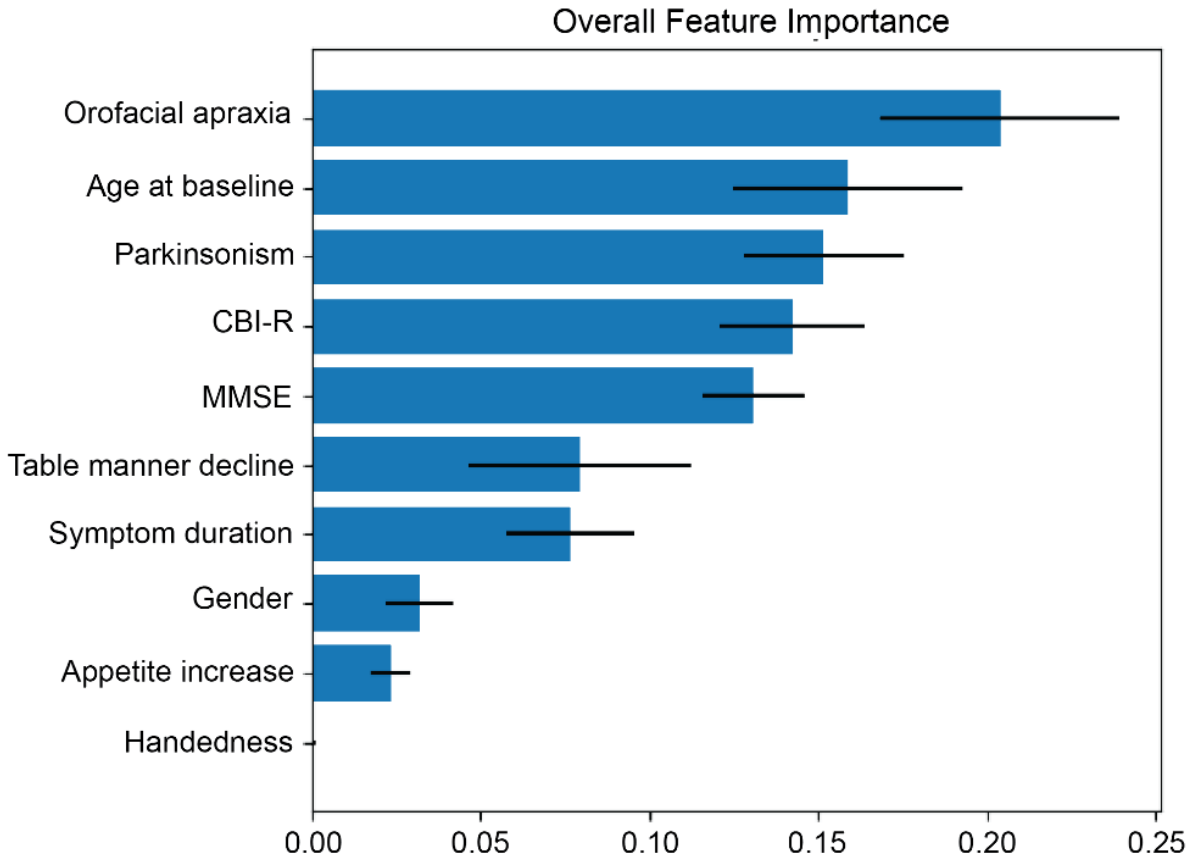
Poster Topic: *Theme K: Patient Care and Support / K01.e. Dementia and Cognitive Dyfunction: Quality of life*

RISK OF DYSPHAGIA IN PRIMARY PROGRESSIVE APHASIA: DEMOGRAPHIC, CLINICAL, BEHAVIOURAL AND NEUROANATOMICAL FEATURES

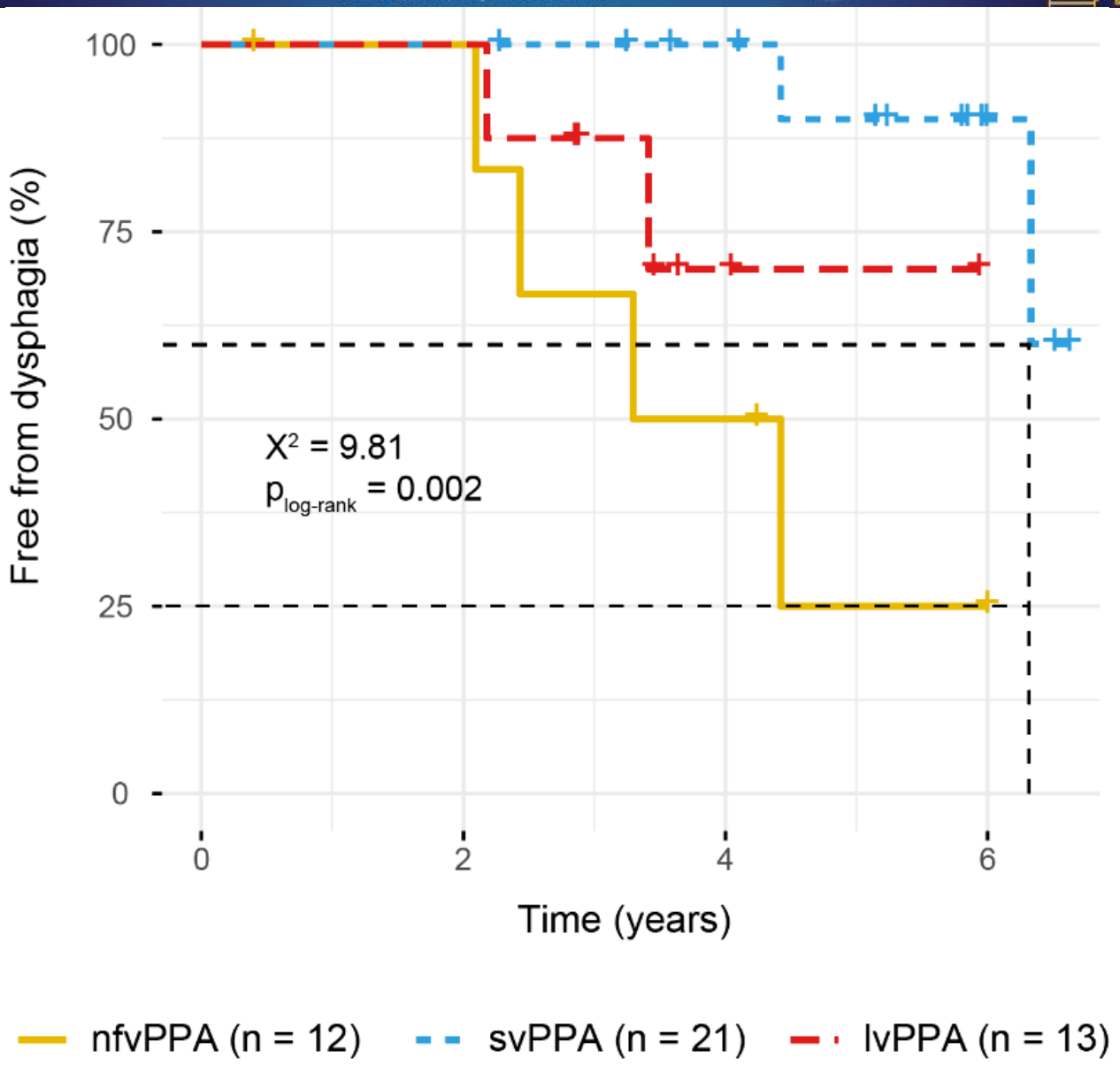
POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

Salvatore Mazzeo[1,2], Eoin Mulroy[1], Jessica Jiang[1], Jeremy Johnson[1], Chris Hardy[1], Michael Lassi[3], Jonathan Rohrer[1], Jason Warren[1], Anna Volkmer[4]
[1]University College London, Dementia Research Centre, Department Of Neurodegenerative Disease, Ucl Queen Square Institute Of Neurology, London, United Kingdom, [2]University of Florence, Department Of Neuroscience, Psychology, Drug Research And Child Health, Firenze, Italy, [3]Scuola Superiore Sant'Anna, The Biorobotics Institute And Department Of Excellence In Robotics And Ai, Pisa, Italy, [4]University College London, Department Of Psychology & Language Sciences, London, United Kingdom

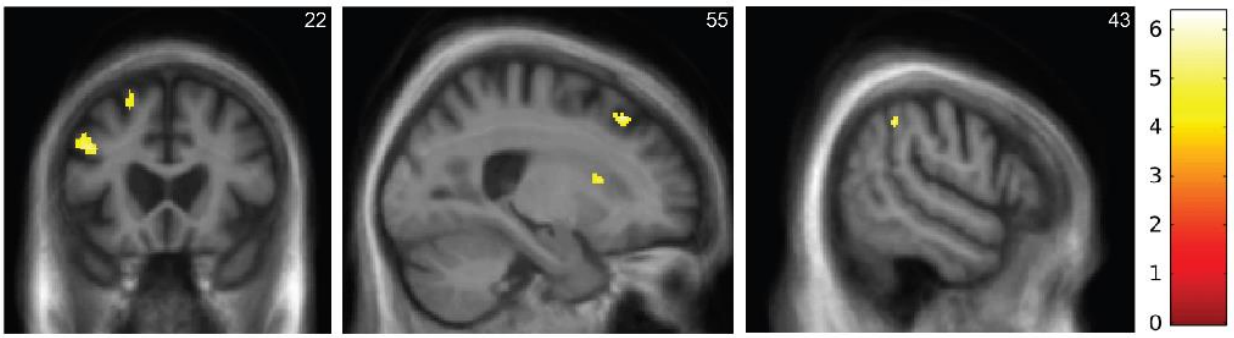
Aims: To investigate the clinical, neuropsychological, and neuroanatomical features associated with dysphagia in patients with primary progressive aphasia (PPA).
Methods: A cohort of 56 PPA patients were enrolled in this study, including 21 non-fluent/agrammatic variant PPA (nfvPPA), 22 semantic variant PPA (svPPA), and 13 logopenic variant PPA (lvPPA) cases. The presence of dysphagia at baseline or development of dysphagia during follow-up was recorded. Demographic, clinical, and behavioural data were used as candidate input features to train a random forest machine learning model. Brain MRI scans were processed using Voxel-Based Morphometry (VBM) to assess neuroanatomical associations.
Results: Dysphagia at baseline was more prevalent in nfvPPA (ten patients, 43%) compared to svPPA (one patient, 5%) and lvPPA (0%). The machine learning model revealed a hierarchy of features that accurately predicted dysphagia in the nfvPPA group, with the most important being orofacial apraxia, followed by age, presence of parkinsonism, Cambridge Behavioural Inventory Revised (CBI-R), minimental-state examination (MMSE) score, decline in table manners, and symptom duration (Figure 1).



During follow-up, dysphagia developed in eight (17%) of initially non-dysphagic PPA patients, with nfvPPA showing a significantly higher proportion. Eight patients were on modified diets or had behavioural strategies in place at follow-up. Cox's regression analysis revealed lower MMSE scores, the presence of orofacial apraxia, and higher CBI-R scores as predictors of dysphagia (Figure 2).



Neuroanatomically, dysphagia in nfvPPA was associated with regional grey matter atrophy in the left middle frontal gyrus, right superior frontal gyrus, right supramarginal gyrus, and right caudate (Figure 3).



Conclusions: This is the first study that identified demographic, clinical, behavioural, and neuroanatomical features associated with dysphagia in nfvPPA. These results provide valuable insights into identifying PPA patients at risk of dysphagia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1415 / #2002

Poster Topic: *Theme K: Patient Care and Support / K01.e. Dementia and Cognitive Dyfunction: Quality of life*

SEXUALITY IN ALZHEIMER'S DISEASE

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

Miguel Pão Trigo, Beatriz Calado Araújo, Bruno Da Luz, Joana Cavaco Rodrigues, Joaquim Sá Couto, Marco Mota Oliveira
Centro Hospitalar Universitário do Algarve, Departamento De Psiquiatria E Saúde Mental, Faro, Portugal

Aims: This abstract explores the intricate and often overlooked aspect of sexuality within the context of Alzheimer's disease. Our primary objectives were to investigate how Alzheimer's disease affects sexual behaviors, perceptions, and relationships among individuals with the condition and their caregivers. We aimed to shed light on the challenges and considerations in addressing the sexual needs and concerns of this vulnerable population.
Methods: We conducted a comprehensive literature review regarding sexuality in Alzheimer's disease. The research was carried out through the PubMed database.
Results: Our findings reveal that Alzheimer's disease can significantly impact an individual's sexuality, leading to changes in desire, inhibition, and the ability to engage in sexual activities. Caregivers often struggle with balancing their loved one's needs for intimacy while ensuring their safety and dignity. Misunderstandings, stigma, and a lack of appropriate guidance compound the challenges associated with addressing sexuality in Alzheimer's disease.
Conclusions: This review highlights the critical need for a comprehensive and compassionate approach to addressing sexuality in the context of Alzheimer's disease. The findings underscore the importance of healthcare professionals, caregivers, and support systems being well-informed and trained to navigate these sensitive issues with empathy and respect. Developing guidelines, resources, and support networks can help individuals with Alzheimer's disease and their caregivers navigate the complexities of sexuality while preserving their dignity and quality of life. Ultimately, recognizing and addressing the sexual aspects of Alzheimer's disease is integral to providing holistic care and improving the overall well-being of those affected by this condition.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1416 / #1124

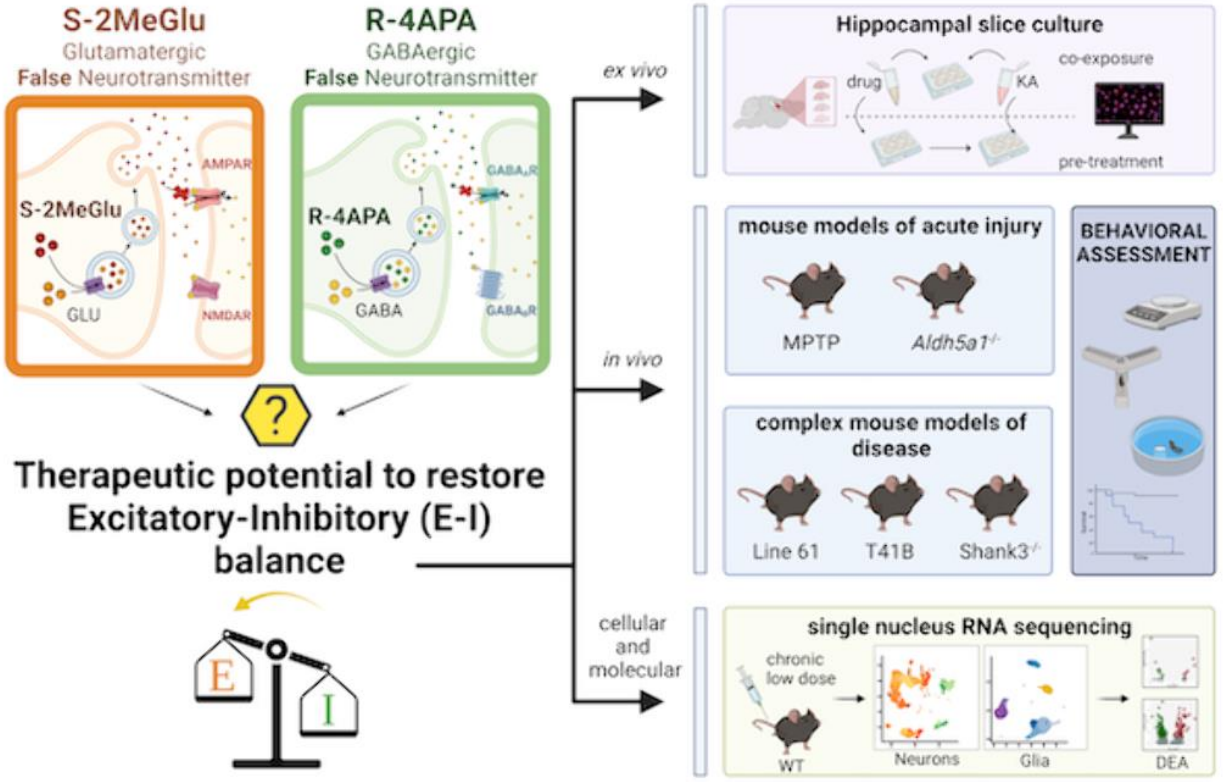
Poster Topic: *Theme K: Patient Care and Support / K01.e. Dementia and Cognitive Dyfunction: Quality of life*

REBALANCING THE BRAIN: THE THERAPEUTIC POTENTIAL OF FALSE NEUROTRANSMITTERS IN EXCITATORY-INHIBITORY IMBALANCE

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

Amalia Perna[1], Jing Zhao[1], Chandresh Gajera[1], Marcus Shonemann[1], Nay Saw[2], Mehrdad Shamloo[2], Thomas Montine[1]
[1]Stanford University, Pathology, Stanford, United States of America, [2]Stanford University, Behavioral And Functional Neuroscience Laboratory (bfnl), Palo Alto, United States of America

Aims: Excitatory-inhibitory (E-I) imbalance has been proposed to underlie many brain diseases including some forms of seizure, neurodegeneration, and behavioral disorders. Multiple drug development programs pursue novel agents that interact with specific glutamatergic or GABAergic receptors with the goal of E-I rebalancing. However, targeting specific receptors has potential limitations including dozens of potential targets with highly adaptable expression. We took an innovative approach and created the first false neurotransmitters, molecules handled like an endogenous neurotransmitter but upon synaptic release have no or very limited ability to engage receptors.
Methods: We tested the activity of the excitatory (S-2-methyglutamate or S-2MeGlu) and inhibitory (R-4-aminopentanoate or R-4APA) false neurotransmitters in a variety of *ex vivo* and *in vivo* mouse models of brain diseases hypothesized to derive in part from E-I imbalance. We extended our analysis to transcriptomic changes induced by chronic exposure to low-dose false neurotransmitters.



Results: Chronic exposure of mice to R-4APA broadly altered neuronal and glial transcriptomes in mouse cerebral cortex, including increased expression of immediate early genes in excitatory neurons that was the focused transcriptional impact of S- 2MeGlu. R-4APA improved motor performance in α-synuclein and Aβ overexpressing mice but also worsened some behaviors in Shank3$^{-/-}$ mice and raised safety concerns in the context of hyperexcitability and enhanced anxiety. S-2MeGlu was neuroprotective from kainic acid toxicity in hippocampal slice cultures, extended lifespan in a mouse model of severe epilepsy (Aldh5a1$^{-/-}$), and improved motor performance in two different models of Parkinson's disease as well as spatial working memory in Aβ overexpressing mice without raising toxicity concerns.
Conclusions: Our data encourage further investigation of S-2MeGlu as a potential therapeutic agent to protect neurons from hyperexcitation and to alleviate some motor and cognitive deficits in neurodegenerative diseases.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1417 / #1524

Poster Topic: *Theme K: Patient Care and Support / K01.e. Dementia and Cognitive Dyfunction: Quality of life*

SEXAGE: WHAT IS THE IMPACT OF STEREOTYPES REGARDING SEXUALITY OLDER PEOPLE ON SEXUAL HEALTH?

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

Cassandra Quin, Anne-Julie Vaillant-Ciszewicz, Laura Lantermino, Olivier Guérin
CHU DE NICE, Geriatrics, NICE, France

Aims: Scientific literature highlights the importance of sexuality for older people but also reveals the numerous barriers linked to its expression. In addition, the sexuality of older people faces several preconceived ideas that would have an impact on quality of life and sexual health. The consequences of these stereotypes on the sexual and psychological functioning of older people remain little studied to date. It should be noted that no study specifically explores the impact of sexual stereotypes on the sexuality of older people by considering place of life as a variable. **Main objectives:** Measure the impact of stereotypes towards sexuality on the sexual health of elderly people in nursing homes and at home. **Secondary objective:** Identify the specific needs of older people regarding sexuality in nursing homes and at home.
Methods: The exploratory study concerns people aged over 65 residing in nursing homes and at home. The data collect will begin in October 2023 after obtaining approval from a research ethics committee. A survey questionnaire developed by a psychologist trained in sexology and validated by a committee of experts will be distributed online via the Microsoft Forms platform.
Results: The study's hypotheses assume that the sexual needs of older people differ depending on where they live. In addition, it is expected to observe a greater impact of stereotypes on sexual health in nursing homes than at home.
Conclusions: It seems essential to integrate the sexological dimension into the care pathway and the life plan of institutionalized and at-home elderly people. The benefits of a satisfying sex life on quality of life are documented in the scientific literature. Thus, improving support for older people in terms of sexual health would improve their overall health.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1418 / #284

Poster Topic: *Theme K: Patient Care and Support / K01.e. Dementia and Cognitive Dyfunction: Quality of life*

DIABETES MANAGEMENT IN PEOPLE LIVING WITH DEMENTIA

POSTERS: K01.E. DEMENTIA AND COGNITIVE DYFUNCTION: QUALITY OF LIFE

Km Saif-Ur-Rahman
University of Galway, College Of Medicine, Nursing, And Health Sciences, Galway, Ireland

Aims: Dementia and diabetes are highly prevalent among the older society in Japan. People living with dementia (PLWD) often face hurdles in managing diabetes. This study explored the perspectives of healthcare providers in Japan regarding diabetes management in PLWD.
Methods: We conducted a qualitative study using in-depth interviews as a data collection method. A total of 15 physicians and nurses were interviewed. A qualitative content analysis of the codes was performed to generate the themes.
Results: The major themes focused on the management of medications/therapeutic regimen, difficulties of continuing health care, emotional aspects of PLWD for adherence to lifestyle modification, and varying direction and degree of family support for diabetes care.
Conclusions: PLWD in Japan face challenges in medication management, food restriction, and lifestyle modification. Policies to engage home visit care workers in medication management, consideration of the emotional aspect of PLWD, and utilisation of social support might help in the proper management of diabetes in PLWD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1419 / #116

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

HOME-BASED FAMILY CAREGIVER-DELIVERED MUSIC AND READING INTERVENTIONS FOR PEOPLE LIVING WITH DEMENTIA: AN INTERNATIONAL RANDOMISED CONTROLLED TRIAL (HOMESIDE TRIAL).

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Felicity Baker[1], Jeanette Tamplin[1], Anna Bukowska[2], Thomas Wosch[3], Karette Stensaeth[4], Ming Hsu[5], Helen Odell Miller[5]
[1]University of Melbourne, Music Therapy, Melbourne, Australia, [2]Institute of Applied Sciences, University of Physical Education, Music Therapy, Krakow, Poland, [3]Institute for Applied Social Sciences, Music Therapy Lab, Wurzberg, Germany, [4]Norwegian Academy of Music, Music Therapy, Oslo, Norway, [5]Anglia Ruskin University, Music Therapy, Cambridge, United Kingdom

Aims: To evaluate the impact of music interventions on dementia symptom management when provided by family caregivers trained in music use.
Methods: We implemented a superiority, single-masked RCT to evaluate if caregiver-delivered music was superior to usual care (UC) on reducing BPSD measured by the Neuropsychiatric Inventory-Questionnaire (NPI-Q). PwD (NPI-Q score >6) and their caregiver were randomly allocated to caregiver-delivered music, reading (active control), or UC. Caregivers received three online protocolised music or reading training sessions delivered and were recommended to provide minimum twice weekly over 90-days. The NPI-Q severity assessment of PwD was completed online by masked assessors at baseline, 90- (primary) and 180-days post-randomisation and analysed on an intention-to-treat basis using a likelihood-based longitudinal data analysis model. Secondary outcomes included: cognition (Mini-Mental State Examination), depression (Montgomery Asberg Depression Rating Scale),quality of life (Quality of Life-Alzheimer's Disease).
Results: Between 27th November 2019 and 7th July 2022, we randomised 432 eligible of 805 screened dyads (music n=143, reading n=144, UC n=145). There was no statistical or clinically important difference in the change from baseline BPSD between caregiver-delivered music (-0·15, 95% CI -1·41 to 1·10, p=0·81) or reading (-1·12, 95% CI -2·38 to 0·14, p=0·082) and UC alone at 90-days. Pre-specified subgroup analyses were performed for NPI-Q at 90- and 180-days post-randomisation. Compared with UC, PwD with moderate to severe cognitive impairment with a mixed diagnosis tended to be more responsive to music at 90-days. Short-term and rest-of-the day effects showed that longer durations of music use led to better outcomes. No related adverse events occurred.
Conclusions: Music interventions delivered by trained caregivers do not decrease enduring BPSD symptoms. Subgroup analyses suggest that people with some dementia types (vascular dementia) may be more responsive than others (Alzheimer's Disease).

P1420 / #2490

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

TRAUMATIC BRAIN INJURY AND NEURODEGENERATIVE CHANGES

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Cheryl Cottrol
Yale University school of Medicine Greenwich Hospital, Psychiatry, Old Greenwich, United States of America

Aims: This case report is an 18 month retrospective study of a 27 year old white female graduate student who experienced a traumatic brain inury (TBI) secondary to a motor vehcle accident in March 2022. Serial descriptions of her brain imaging and cognitive testing are described and are consistnt with long term cognitive impairment. Impllications of TBI as a potential cause of dementia are discussed
Methods: Record review of hospital, inpatient and outpatient charts Serial assessments of brain imaging studies including 1) initial MRI brain immediately after TBI; 2) MRI with Neuroquant sequencing 1 month after TBI; 3) SPECT imaging 3 months after TBI 4) Repeat MRI one year after TBI Standardized Neuropsychiatric testing using Evox Neuroscience to assess brain processing speed, memory, attention, concentration, impulsivity as well as questions to assess level of Depression, Anxiety and Post Traumatic Stress Disorder
Results: Initial MRI: small subarachnoid hemorrhage MRI with neuroquant analysis: abnormally low hippocampal volumes for age and bilateral thalami and basal ganglia atrophy and left parietal lobe atrophy SPECT scan showed mild hypo perfusion of the right parietal region MRI 1 year after TBI: foci of microhemorrhage in frontal lobes representing sequaelae of prior sheer axonal injury; 2 punctate foci of susceptibility related to signal loss within the subcortical white matter of the left paramedian precentral gyrus and the paramedian right frontal lobes Electrophysiological cognitive testing : difficulty with speed of processing, memory, attention as well as high scores for Depression, Anxiety and PTSD
Conclusions: 27 year old graduate student who sustained a traumatic brain injury 18 months ago, continues to have structural, cognitive and psychiatric changes consistent with cognitive decline. .Mechanisms contributing to this process are discussed.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1421 / #508

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

THE ASSOCIATION OF NUTRITIONAL STATUS AND REGIONAL BRAIN BLOOD PERFUSION WITH NEUROPSYCHIATRIC SYMPTOM AND ITS SUBTYPES IN ALZHEIMER'S DISEASE CONTINUUM: A PROSPECTIVE COHORT STUDY

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Jiwei Jiang, Wenyi Li, Jun Xu
Beijing Tiantan Hospital, Capital Medical University, Neurology, Beijing, China

Aims: To investigate the associations between baseline and long-term nutritional status and the regional cerebral perfusion with subsequent changes in neuropsychiatric symptoms (NPS) and its subtypes in patients with Alzheimer's disease (AD) continuum.
Methods: Totally, 435 participants {374 aMCI and AD (285 with NPS, 89 without NPS) and 61 HCs} were included from May 1, 2021 and April 30, 2023. Neuropsychiatric Inventory (NPI) and Mini-Nutritional Assessment (MNA) were used to evaluate the presence and severity of NPS and its 12 subtypes and nutritional status, respctively. Regional cerebral perfusion was evaluated by the corrected cerebral blood flow (cCBF) from the 7-delay pCASL. GLMMs were used to examine the association of baseline and longitudinal nutritional status and cCBF with the changes in the general or specific domain NPI scores after adjustment.
Results: During the (8.79±4.11) months follow-up, patients at risk or presence of malnutrition at baseline were significantly associated with subsequent increase in the NPI scores of general NPS (β=3.825, P=0.020), depression (β=0.841, P=0.004), apathy (β=0.702, P=0.048) and appetite/eating disturbances (β=0.639, P=0.002). Baseline increasing cCBF values of left putamen (β=0.135, P=0.001) and right ventral tegmental area (VTA) (β=0.069, P<0.001) were associated with subsequent deterioration of apathy, while baseline increasing cCBF values of left hypothalamus (β=0.062, P<0.001) and right VTA (β=0.028, P=0.016) were associated with deterioration of appetite/eating disturbances. The longitudinal decrease of MNA score was significantly associated with the increase NPI score of general NPS (β=-0.685, P=0.013), depression (β=-0.147, P=0.003), anxiety (β=-0.126, P=0.009), apathy (β=-0.149, P=0.012) and appetite/eating disturbances (β=-0.116, P=0.001).
Conclusions: Baseline and long-term poor nutritional status, and baseline hyperperfusion in dietary nutrition-related brain areas (putamen, VTA, and hypothalamus) can independently predict the deterioration of NPS and its sub-types in patients with AD continuum.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1422 / #2384

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

POST FALL NEUROPSYCHIATRIC SYMPTOMS AND COGNITION IN OLDER ADULTS AND PATIENTS WITH NEURODEGENERATIVE DISEASES (ND)

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Goldin Joghataie[1], Mohsen Hadian[2], Sabrina Hundal[3], Mario Masellis[4], Douglas Munoz[5], Richard Swartz[4], Ondri Investigators[1], Michael J Strong[6], David Tang-Wai[7,8], Corinne Fischer[9], Stephen Arnott[10], Andrew Frank[11], Agessandro Abrahao[4], Angela Roberts[12], Manuel Monteroodasso[4], Joseph Orange[13], Miracle Ozzoude[4], Connie Marras[8], Maria Tartaglia[2]
[1]University of Toronto Temerty Faculty of Medicine, Institute Of Medical Science, Toronto, Canada, [2]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [3]University of Toronto, Temerty Faculty Of Medicine, Toronto, Canada, [4]Sunnybrook Research Institute, Hurvitz Brain Sciences Program, Toronto, Canada, [5]Queen's University, Department Of Medecine, Kingston, Canada, [6]Western University, Schulich School Of Medicine, London, Canada, [7]University of Toronto, Department Of Medicine (neurology), Toronto, Canada, [8]University Health Network, Neurology, Toronto, Canada, [9]St. Michael's Hospital, Li Ka Shing Knowledge Institute, Toronto, Canada, [10]Baycrest Health Sciences, Baycrest Health Sciences Centre, Toronto, Canada, [11]University of Ottawa, Department Of Medicine, Ottawa, Canada, [12]Canadian Centre for Activity and Aging, Canadian Centre For Activity And Aging, London, Canada, [13]Canadian Centre for Activity and Aging, Iccan Lab, London, Canada

Aims: Falls are the most common mechanism of injury faced by millions of older adults and those with neurodegenerative diseases (NDs) each year and are often linked to accelerated decrease in quality of life. However, there are large gaps in literature and little research on fall related cognitive and neuropsychiatric symptoms. We hypothesized that experiencing falls will significantly increase the presence and severity of neuropsychiatric symptoms and lead to cognitive decline.
Methods: We used data from the Ontario Neurodegenerative Disease Research Initiative dataset (ONDRI) on 482 individuals in five ND types. Neuropsychiatric (NPI) measures were used to compare the frequency of 12 symptoms and their severity between patients with and without falls in the past 12 months and between different ND types. We also compared cognition between fallers and non-fallers longitudinally using six different cognitive assessments.
Results: For our p-value cut-off of <0.01, comparing those who experienced falls in the last year (n=169; mean-age=68.3±9; 36%Female), to those who had no falls (n=314; mean-age=68.7±7; 32%Female), there was significantly higher: total NPI severity (w=22497, p-value = 0.0061), frequency of anxiety (X2(df=1)=13.68; p-value=0.00026); anxiety severity (X2(df=3)=15.1; p-value=0.002); and partner anxiety-related distress (X2(df=3)=19.9; p-value=0.0005). Number of falls in past year had a highly significant (p <0.001) affect on six cognitive assessments both for the first visit and combining longitudianlly for two timepoints. The interaction between specific disease and presence of any fall significantly affected four different cognitive tests, including longitudinal combination of visits.
Conclusions: Anxiety frequency, severity and distress were significantly higher in patients with neurodegenerative disease who fell compared to those without falls. Fall number and the interaction between fall and specific disease impacted cognition, as seen through six different assessments and accounting for longitudinal changes.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1423 / #1458

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

ARE GLOBAL MEASURES OF GAIT AND COGNITION ASSOCIATED WITH SPATIAL NAVIGATION WHILE WALKING IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT (MCI)?

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Magnus Lindh-Rengifo[1], Sofie Fors[2], Sebastian Palmqvist[3,4], Erik Stomrud[3,4], Oskar Hansson[3,4], Maria Nilsson[1,3,4]
[1]Lund University, Department Of Health Sciences, Faculty Of Medicine, Lund, Sweden, [2]Skåne University Hospital, Lund, Rehabilitation Medicine, Lund, Sweden, [3]Lund University, Clinical Memory Research Unit, Malmö, Sweden, [4]Skåne University Hospital, Memory Clinic, Malmö, Sweden

Aims: The primary aim was to investigate how a global measure of gait as well as cognitive functioning are associated with spatial navigation while walking in patients with mild cognitive impairment (MCI). Moreover, executive/attentional cognitive functioning was also considered.
Methods: This cross-sectional study included 209 patients with MCI; their mean (SD) age was 72.4 (7.3) years and 86 (41%) were women. Spatial navigation was assessed by using the total time of completing the Floor Maze Test (FMT), i.e., the dependent variable in linear regression analyses. A global measure of gait (i.e., gait speed) was assessed by using an electronic walkway. Global cognitive functioning was assessed by using the Mini-Mental State Examination (MMSE, 0-30 points). Executive/attentional cognitive functioning was assessed by using a composite score from z-scores of three cognitive tests (i.e., Trail making Test A and B as well as the Symbol Digits Modalities Test). Multivariate analyses were adjusted for age and sex.
Results: Decreased gait speed was significantly associated (standardized β=-0.214, $p<0.003$) with an increased total time of the FMT, i.e., when controlling for age and sex. Global cognitive functioning was not associated ($p=0.098$) with FMT, whereas executive/attentional functioning showed a statistically significant association with FMT time (β=-0.291, $p<0.001$). When including both gait speed and executive/attentional functioning in the same model (controlled for age and sex), a higher gait speed (β=-0.154, $p<0.027$) and better executive/attentional cognitive functioning (β=-0.291, $p<0.001$) were independently associated with a decreased time to complete the FMT.
Conclusions: The findings suggest both gait speed and executive/attentional cognitive functioning might be pertinent factors to consider if assessing or addressing spatial navigation while walking in patients with MCI.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1424 / #672

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

PREVALENCE OF MULTIMORBIDITY AND SPECIFIC COMORBIDITIES IN PEOPLE WITH SEVERE BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Aline Mendes[1], Sverre Bergh[2], Bruno Cesana[3], Ron Handels[4], Alfonso Ciccone[5], Emmanuel Cognat[6], Andrea Fabbo[7], Sara Fascendini[8], Giovanni Frisoni[9], Lutz Froelich[10], Maria Cristina Jori[11], Patrizia Meccoci[12], Paola Merlo[13], Oliver Peters[14], Magdalini Tsolaki[15], Carlo Defanti[8]
[1]University Hospitals of Geneva, Division Of Geriatrics And Rehabilitation, Geneva, Switzerland, [2]Innlandet Hospital Trust, Research Centre For Age-related Functional Decline And Disease, Ottestad, Norway, [3]University of Milan, Department Of Clinical Sciences And Community Health, Unit Of Medical Statistics, Biometry And Bioinformatics "giulio A. Maccacaro" Faculty Of Medicine And Surgery, Milan, Italy, [4]Maastricht University Medical Centre, Faculty Of Health Medicine And Life Sciences, Department Of Psychiatry And Neuropsychology School For Mental Health And Neuroscience Alzheimer Centre Limburg, Maastricht, Netherlands, [5]ASST di Mantova, Department Of Neurology With Neurosurgical Activity "carlo Poma" Hospital, Mantova, Italy, [6]Lariboisière-Fernand Widal Hospital GHU AP-HP Nord, Cognitive Neurology Centre, Paris, France, [7]Local Health Authority of Modena (AUSL), Geriatric Service-cognitive Disorders And Dementia, Department Of Primary Care, Modena, Italy, [8]FERB, Alzheimer Centre, Gazzaniga, Italy, [9]University Hospitals of Geneva, Memory Centre, Division Of Geriatrics And Rehabilitation, Geneva, Switzerland, [10]Heidelberg University, Department Of Geriatric Psychiatry, Central Institute Of Mental Health,medical Faculty Mannheim, Mannheim, Germany, [11]Mediolanum Cardio Research, Mediolanum Cardio Research, Milan, Italy, [12]Karolinska Institutet Stockholm, Institute Of Gerontology And Geriatrics, Department Of Medicine And Surgery, University Of Perugia, Italy And, Division Of Clinical Geriatrics; Nvs Department, Stockholm, Sweden, [13]Humanitas Gavazzeni, Neurological Unit (pm), U.v.a. Centre, Bergamo, Italy, [14]Department of Psychiatry, Charité-universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany, [15]Aristotle University of Thessaloniki (AUTh), Greek Association Of Alzheimer's Disease And Related Disorders (gaadrd), Thessaloniki, Makedonia, Hellas. 1st Department Of Neurology, School Of Medicine, Macedonia, Greece

Aims: People with dementia present a high prevalence of comorbidities. We aimed to identify the prevalence of multimorbidity (I.e., ≥2 comorbidities) and specific comorbidities in the subgroup of people with severe behavioral and psychological symptoms of dementia (BPSD).
Methods: All data was analyzed at baseline and the three-year follow-up of people with severe BPSD (NPI ≥32) included in the European multicenter cohort ReCAGE (Respectful Caring for the Agitated Elderly).
Results: Of 508 people with dementia and BPSD, 54.9%% were female, with a mean age of 78 ± 7.93 years. The mean NPI score was 52.44 points, with the domains of apathy/indifference (85.4%), agitation/aggression (83.1%), depression/dysphoria (81.7%), and irritability/lability (80.9%) being the BPSD most frequently present. Multimorbidity was frequent in this population (90.6%), with hypertension (52.2%), dyslipidemia (17.5%), and diabetes (17.1%) being the most prevalent comorbidities documented. Comorbidities such as heart failure (2%), coronary artery disease (7.3%), osteoarthritis (4.8%), osteoporosis (4.8%), stroke (2.9%), carotid arteriosclerosis (2.8%), chronic kidney disease (2.4%), and chronic pulmonary obstructive disease (2.4%) had a lower prevalence than that observed in the general population. No comorbidity had a higher prevalence than expected for a population of the same age.
Conclusions: In people with severe BPSD, multimorbidity is very frequent. Conversely, the overall

prevalence of some comorbidities was lower than expected. Severe BPSD may undermine adequate diagnosis and management of comorbidities in people with dementia. Future studies should evaluate the reasons for this disparity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1425 / #788

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

BRAIN CONNECTIVITY AND METACOGNITION IN INDIVIDUALS WITH SUBJECTIVE COGNITIVE DECLINE (COSCODE PROJECT): BASELINE COHORT FEATURES

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Federica Ribaldi[1,2], Christian Chicherio[3], Chen Wang[1], Matthias Kliegel[4], Giovanni Frisoni[1]
[1]Geneva Memory Center, Department Of Rehabilitation And Geriatrics, Geneve, Switzerland, [2]University of Geneve, Laboratory Of Neuroimaging Of Aging (lanvie), Geneve, Switzerland, [3]Geneva University Hospitals, Geneva Memory Center, Department Of Rehabilitation And Geriatrics, Geneva, Switzerland, [4]University of Geneva, Laboratoire Du Vieillissement Cognitif, Geneva, Switzerland

Aims: Subjective Cognitive Decline (SCD) refers to the self-perceived decline in cognitive functions in the absence of objective evidence. The COSCODE project aims to identify SCD subjects who are at a high risk of cognitive decline. In this abstract, we present the baseline characteristics of the study participants.
Methods: A total of 441 participants were enrolled, comprising 105 volunteers, 109 individuals with SCD, 172 with Mild Cognitive Impairment (MCI), and 55 with dementia. Differences in demographics, clinical, and biomarker features were analyzed using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.
Results: SCD individuals were averagely older (65.7±9.3) than volunteers (60.9±8.1) but younger than MCI (70.8±8.3) and dementia (75.1±5.0,$p<0.001$). SCD (71%) and volunteers (77%) exhibited a high proportion of females. SCD and volunteers had a higher level of education compared to MCI and dementia ($p<0.001$). Additionally, SCD and MCI individuals reported higher levels of depression and anxiety than volunteers (<0.05). Notably, 21% of SCD individuals were carriers of the APOE ε4 allele. SCD participants showed a greater impairment in activities of daily living compared to volunteers ($p<0.05$) but less than MCI and dementia ($p<0.001$). SCD participants had higher cognitive complaints than volunteers, but lower than MCI and dementia ($p<0.005$). When assessing the difference between self and informant complaints, SCD individuals showed hyperawareness (self>informant) compared to MCI (self=informant) and dementia (self<informant,$p<0.05$). Moreover, SCD individuals reported higher levels of fatigue and stress compared to volunteers ($p<0.05$).
Conclusions: These findings shed light on the distinctive features of individuals with SCD, emphasizing their unique demographic, psychological, and clinical features. These insights contribute to a better understanding of SCD and its potential implications for dementia risk profiling and for the development of intervention strategies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1426 / #721

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

RESTING-STATE BRAIN ACTIVITY IN THE LEFT SUPRAMARGINAL GYRUS IN BETA BAND REFLECTS COGNITIVE DECLINE

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Yoshihito Shigihara[1], Hideyuki Hoshi[1], Momoko Kobayashi[2], Yoko Hirata[3], Kesuke Fukasawa[4], Sayuri Ichikawa[4]
[1]Hokuto Hospital, Precision Medicine Centre, Obihiro, Japan, [2]Kumagaya General Hospital, Precision Medicine Centre, Kumagaya, Japan, [3]Kumagaya General Hospital, Neurosurgery, Kumagaya, Japan, [4]Kumagaya General Hospital, Clinical Laboratory, Kumagaya, Japan

Aims: To identify the most responsible cortical regions for cognitive impairment in individuals who visited memory clinic.
Methods: We retrospectively obtained the resting-state magnetoencephalography data, neuropsychological assessment scores [Mini-mental state examination (MMSE) and frontal assessment battery (FAB)], and clinical diagnosis from 310 individuals. Resting-state cortical activities were estimated from magnetoencephalography data in terms of oscillatory intensities and they were compared with the neuropsychological assessment scores and between clinical groups.
Results: The oscillatory intensities (i.e., resting-state brain activity) in the widely distributed regions were associated with the MMSE and FAB scores from theta to high gamma bands. Negative correlations in the left frontal regions in alpha band and positive correlations in the left supramarginal gyrus in beta band were commonly found with the MMSE and FAB scores. The oscillatory intensities were significantly different between healthy individuals and patients with mild cognitive impartment, and between healthy individuals and patients with dementia, in multiple regions and frequency bands. Decreased oscillatory intensities in the left supramarginal gyrus in the beta and low gamma bands were commonly observed in the two comparisons. Taken together, decreased oscillatory intensities in beta band were common fingerprints along with progression of cognitive impairments.
Conclusions: Previous studies showed the low frequency oscillatory intensities in the caudal regions were corresponding with the pathology of Alzheimer's diseases. However, our finding demonstrated that high frequency (beta) oscillatory intensities in the caudal-dorsal region (i.e., supramarginal gyrus) were associated with cognitive impairments. This suggests the mismatching between the level of cognitive impairment and underling pathology. It implies that treating cognitive symptoms should be considered separately from treating pathology.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1427 / #532

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

FACIAL EMOTION RECOGNITION IN OLDER ADULTS WITH COGNITIVE COMPLAINTS

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Yongsoo Shim, Dongwon Yang
The Catholic University of Korea, Neurology, Seoul, Korea, Republic of

Aims: Facial emotion recognition deficits impact daily life, particularly in Alzheimer's patients. We aimed to assess these deficits in three groups: subjective cognitive decline (SCD), mild cognitive impairment (MCI), and mild Alzheimer's dementia (AD).
Methods: We used the Korean version of the Florida Facial Affect Battery (K-FAB) on 72 SCD, 76 MCI, and 76 mild AD subjects. The Mini-Mental State Examination (MMSE) was utilized to gauge overall cognitive status, while the Seoul Neuropsychological Screening Battery (SNSB) was employed to evaluate performance in five cognitive domains: attention, language, visuospatial abilities, memory, and frontal executive functions.
Results: showed that FAB subtest 1(facial identity discrimination) and subtest 2(facial affect discrimination) did not yield significant differences among the three groups. However, FAB subtest 3(facial affect naming), subtest 4(facial affect selection), and subtest 5(facial affect matching) exhibited notable differences across the three groups (p=0.001, 0.003, and 0.004, respectively), particularly in the recognition of angry and fearful emotions among the 5 target emotions (happy, sad, anger, fear, neutral). Specifically, the *post-hoc* comparison revealed a decline in the recognition of the 'angry' emotion in FAB subtest 5 as individuals progressed from SCD through MCI to mild AD. Additionally, the FAB tests exhibited correlations with age and education according to Pearson's correlation analysis. After controlling for age and education through partial correlation analysis, it was revealed that MMSE and frontal executive function were associated with FAB tests (in FAB subtest 5, r=0.507, p<0.001 and r=-0.288, p=0.026, respectively).
Conclusions: Emotion recognition deficits worsened from SCD to MCI to mild AD, especially for negative emotions. Complex tasks like matching, selection, and naming showed greater deficits, with a connection to cognitive impairment, especially frontal executive dysfunction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1428 / #1196

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

DISENTANGLING THE EFFECTS OF BEHAVIORAL SYMPTOMS ON SPECIFIC COGNITIVE FUNCTIONS IN PARKINSON'S DISEASE

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Scott Sperling
Cleveland Clinic, Center For Neurological Restoration, Department Of Neurology, Cleveland, United States of America

Aims: Disentangling the effects of behavioral symptoms on specific cognitive abilities in patients with Parkinson's disease (PD) is important to diagnostic accuracy, treatment, and clinical research.
Methods: We used linear regression to examine if the Beck Depression Inventory (BDI-II), Apathy Scale (AS), and/or Beck Anxiety Inventory (BAI) predicted discrete neuropsychological abilities in patients with PD, controlling for age, gender, and disease duration. Variables that were significantly associated with cognition on univariate analysis were entered into a multiple regression.
Results: Patients were on average 65.2(SD=8.93) years old with 8.6(SD=5.3) years disease duration. Their mean MoCA score was 21.2(SD=6.8). The mean BDI-II 9.9(SD=7.3), AS 11.4(SD=7.5), and BAI 11.6(SD=8.4) scores were subclinical. The BAI (p=.047), BDI-II (p<.001), and AS (p<.001) predicted HVLT-R delayed recall, but not HVLT-R or BVMT-R encoding or WMS-IV Logical Memory I or II scores. On univariate analyses, the BDI-II and AS predicted WAIS-IV Digits Forward, Trails A, Trails B-A, Stroop Interference, and JLO scores. Examined together, only AS contributed significantly to HVLT-R delayed recall $F(5,102) = 5.6$, p=.002, R^2=.22, (AS: p<.001); WAIS-IV Digits Forward $F(5,103) = 4.13$, p=.002, R^2=.17 (AS: p=.006); Trails A $F(5,105) = 8.9$, p<.001, R^2=.3 (AS: p<.001); Trails B-A $F(5,103) = 6.09$, p<.001 (AS: p=.032); Stroop Interference $F(5,93) = 3.61$, p=.005, R^2=.16 (AS: p=.025); and JLO $F(5,91) = 4.13$, p=.002, R^2=.19 (AS: p=.018) scores. AS also predicted Stroop Color Naming (p<.001), whereas BDI-II predicted Stroop Word Reading (p=.011), oral SDMT (p=.039), BVMT-R delayed recall (p<.001), and BNT-short (p=.032) scores.
Conclusions: Depression, anxiety, and apathy do not equivalently contribute to cognitive deficits across or within neuropsychological domains. Subclinical depressive symptoms have a broad effect on cognition, though comorbid symptoms of apathy are more significantly associated with cross-domain cognitive dysfunction.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1429 / #376

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

TECHNIQUES DERIVED FROM EMDR (EYE MOVEMENT DESENSITIZATION AND REPROCESSING) THERAPY FOR TREATING POST TRAUMATIC DISORDERS IN FRENCH NURSING HOME.

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Anne-Julie Vaillant-Ciszewicz, Olivier Guérin, Laura Lantermino, Fanny Lecerf, Aurélie Pinguet, Ines Occeli, Mélanie Jeannin, Cassandra Quin, André Quaderi
CHU DE NICE, Geriatrics, NICE, France

Aims: The scientific literature highlights the existence of various forms of Post-Traumatic Stress Disorder (PTSD, DSM5) in the elderly (Lapp et al, 2011; Maccarrone et al, 2021). However, there is little empirical data to date regarding the potential link between traumatic flashbacks, cognitive impairments, and psycho-behavioral disorders (Delrue, 2017).
Methods: The provided text describes a research method conducted by Master's students in Integrative Clinical Psychology and Aging at the University of Côte d'Azur (FRANCE). They were supervised by senior gerontopsychologists trained in EMDR therapy and implemented an adapted EMDR protocol for the elderly, mainly in Nursing home. Before implementing the protocol, the students conducted thorough patient histories, etiological investigations, and a differential diagnosis of PTSD (Post-Traumatic Stress Disorder, DSM5). The protocol spanned 3 to 8 weeks, involving multiple adapted EMDR therapy sessions for selected elderly individuals. The potential effects of this approach were evaluated using the neuropsychiatric inventory (NPI).
Results: A non-significant clinical effect of the adapted EMDR protocol is noted in the short term for all participants with behavior disorders (anxiety, agitation) on the NPI-ES, as well as clinical signs suggestive of Post-Traumatic Stress Disorder (PTSD, DSM-5). However, the results of the present study are not generalizable due to its heterogeneity and small sample size (sample of women in institutions, 74-96 years old, MMSE less than 10/30, presence of type II traumatic events).
Conclusions: EMDR therapy adapted for elderly could be a component of the non-pharmacological treatment for old post-traumatic stress disorders. These results should be considered with caution. Indeed, the study deserves to be reproduced in a standardized manner on a more representative sample of the population to draw conclusions. Adapted EMDR remains an interesting and innovative avenue in psychology of aging.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1430 / #401

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

DEVELOPMENT OF A RISK PREDICTION MODEL FOR MILD COGNITIVE IMPAIRMENT USING ELECTRONIC HEALTH RECORD DATA

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Gang Li[1], Viswanath Devanarayan[2], Rachel Halpern[3], Joanne Bell[1], Richard Batrla[4], Susan De Santi[1], Feride Frech[5], Jo Vandercappellen[1], Ara Khachaturian[6], Richard Crislip[7], Jeffrey Meyerhoff[8], Saul Perea[7], Soeren Mattke[9], Harald Hampel[1]
[1]Eisai, Inc., Global Medical Affairs, Nutley, United States of America, [2]Eisai, Inc., Clinical Data Science Biostatistics Neurology, Nutley, United States of America, [3]Optum, Life Sciences, Eden Prairie, United States of America, [4]Eisai, Inc., U.s. Medical Affairs Neurology, Nutley, United States of America, [5]Eisai, Inc., Us Heor & Rwe, Nutley, United States of America, [6]Prevent Alzheimer's Disease 2020, Inc. (PAD 20/20), Brain Watch Coalition, Rockville, United States of America, [7]OptumCare, Behavioral Health, Phoenix, United States of America, [8]Optum Behavioral Health, Clinical Policy And Quality, Portland, United States of America, [9]University of Southern California, The Center For Improving Chronic Illness Care, Los Angeles, United States of America

Aims: Timely identification of mild cognitive impairment (MCI) is key to early intervention and potential treatment with novel monoclonal antibodies. Primary care providers (PCPs) play a critical role in detecting early signs of MCI yet detection rates by PCPs as low as 6-15% have been reported. Here, we use electronic health record (EHR) data to build MCI risk prediction models, which could yield a rapid, adaptable, and low-cost tool for PCPs to detect potential MCI.
Methods: This retrospective case control study used EHR data to identify individuals ≥40 years old. The MCI cohort had ≥1 diagnosis record with an ICD-10-CM diagnosis code G31.84 (MCI cohort) with the first record as the index date. The non-MCI cohort had no diagnoses, medications, or mentions of MCI, dementia, or other cognitive disorders. Potential MCI risk factors were identified from the published literature, including sociodemographic characteristics, comorbidities, and medication use. Prediction models based on risk factors for discriminating between MCI and non-MCI will be constructed using machine-learning algorithms.
Results: A preliminary MCI cohort of 20,865 individuals has been identified with mean age 71.1 years, 59.1% female, 83.7% Caucasian, 10.7% African American, and 3.6% Hispanic. The final MCI and non-MCI cohorts will be compared to identify the significant MCI predictors and modeled for MCI risk prediction as described above.
Conclusions: Because our goal is an adaptable MCI risk prediction tool and inclusion of strong predictors is essential, results from the EHR data analysis will be complemented by an insurance claims data analysis to better discriminate between MCI and non-MCI individuals and, ultimately, to develop a triage tool for PCP use.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1431 / #1541

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

DETECTING MEANINGFUL CHANGES IN MINI-MENTAL STATE EXAMINATION SCORES IN LEWY BODY, PARKINSON'S, AND FRONTOTEMPORAL DEMENTIA

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Tamar Abzhandadze[1,2], Minh Tuan Hoang[2], Minjia Mo[2], Hong Xu[2], Maria Eriksdotter[2], Sara Ptacek[2]
[1]Sahlgrenska University Hospital, Department Of Occupational Therapy, Gothenburg, Sweden, [2]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, STOCKHOLM, Sweden

Aims: To interpret changes in Mini Mental State Examination (MMSE) scores, we must establish two psychometric properties: the Minimal Detectable Change (MDC) and the Minimal Clinically Important Difference (MCID). Remarkably, these values remain unexplored in individuals with Dementia with Lewy Bodies (LBD), Parkinson's Disease Dementia (PDD), and Frontotemporal Dementia (FTD). Hence, we have aimed to establish the MDC and the MCID of the MMSE in individuals with LBD, PDD, or FTD.
Methods: In this registry-based study, we will utilize Swedish dementia population data from the world's largest clinical register of dementia, SveDem. The study period will comprise baseline registrations from 2007 to 2020. We will include adult individuals with LBD, PDD, or FTD, with baseline and 12-month follow-up MMSE data. The MDC will be calculated as the upper limit of a 95% confidence interval of the standard error of the MMSE mean. The MCID will be determined using a distribution method where 0.2 standard deviations of the baseline MMSE score represent the MCID. Additionally, an anchor method will be utilized.
Results: The study sample consists of 5,579 individuals: 2,308 with LBD, 1,564 with PDD, and 1,707 with FTD. The analysis of MDC and MCID values is ongoing in the total sample, as well as stratified based on individual diagnoses.
Conclusions: Finding the MDC and MCID values of MMSE in rare dementia diagnoses will enable us to place all other cognitive decline measures into context. We can assess changes in cognitive function over time and determine the accuracy of the MMSE in identifying these changes. The results can also be used for planning and evaluating interventions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1432 / #1468

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

ASSESSING MORTALITY RISK AMONG INDIVIDUALS WITH DEMENTIA AFTER ADMISSION TO NURSING HOME, CONSIDERING UNDERLYING NURSINGCARE FACTORS: A COHORT FROM THE SWEDISH REGISTRY FOR COGNITIVE/DEMENTIA DISORDERS

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Madeleine Åkerman[1], Hong Xu[2], Marie Tyrrell[3], Dorota Religa[2], Maria Eriksdotter[2]
[1]Karolinska Institutet, Neurobiology, Care Sciences And Society, Stockholm, Sweden, [2]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, STOCKHOLM, Sweden, [3]Sophiahemmet University, Department Of Nursing Science, Stockholm, Sweden

Aims: Background: Prior studies have identified factors impacting the survival of individuals with dementia in nursing homes. However, research focusing on the comparison of mortality risk among specific nursing home populations in relation to nursing care factors and different dementia diagnoses is limited. **Objective:** To compare the associations between nursing care factors and dementia disorders and their impact on mortality in a nursing home dementia population.
Methods: A cohort of 6,192 individuals from the nursing home population in the Swedish Registry for Cognitive/Dementia Disorders (SveDem) who were followed up between 2010 and 2022 were included in the study. The study outcome was all-cause death. The association between gender, age, BMI, activity level (eating, walking, bowel/bladder function, bathing), risk assessments and preventive measurements (risk for falls, ulcers, malnutrition, poor oral health), medication, restraints, and person-centred care (life story, physical environment adjustments, interaction strategies, offered activities) were examined using cox-proportional hazard models with 95% confidence intervals (CI).
Results: Individuals were followed-up for a median of 3.1 years (IQR 1.8-4.8), a total of 3737 deaths occurred with 167.89 (CI 162.59-173.36) deaths/1,000 person-years. Age, reduced walking ability, bowel/bladder function, help with bathing, no drug review within 12 months, higher number of medications, use of restraints, lack of risk assessments and preventive measurements and person-centred care were associated with increased mortality risk. Individuals with Vascular dementia or Parkinson's disease dementia had higher mortality risk and those with Frontotemporal dementia lower mortality risk, compared to those with Alzheimer's disease.
Conclusions: Our study highlights important knowledge about how nursing care factors affect mortality in nursing homes for people with dementia, which can contribute to improved dementia care in nursing homes and thus increased quality of life.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1433 / #2287

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

DOWN SYNDROME - BASQUE ALZHEIMER INITIATIVE (DS-BAI): INTRODUCTION OF A NEW HEALTH PLAN AND DISCOVERY COHORT FOR MULTIMODAL BIOMARKERS

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Miren Altuna[1,2], Ainara Estanga[2], Jon Saldias[2], Marta Cañada[2], Adolfo Garrido[3], Maitane Echeverria[3], Maria Botella[2], Maite García-Sebastián[2]
[1]Osakidetza, Organización Sanitaria Integrada (OSI) Debabarrena, Spain, Neurology, Euskadi, Spain, [2]Cita-Alzheimer Foundation, Neurology, Donostia-San Sebastián, Spain, [3]Donostia University Hospital, Clinical Laboratory, Donostia-San Sebastián, Spain

Aims: Creation of a specific health and care plan, as well as a multimodal biomarkers research cohort, for adults with Down syndrome (DS) residing in the Basque Country.
Methods: Longitudinal Population-Based Observational Study. Recruitment of adults with Down syndrome (DS) and neurological-neuropsychological assessment adapted to the level of intellectual disability. Syndromic diagnosis in relation to cognitive and etiological status in symptomatic or asymptomatic Alzheimer's disease (AD). Option to complete the study through brain magnetic resonance imaging, blood analysis, and lumbar puncture. In parallel, a training program is provided for healthcare professionals, social and healthcare workers, and caregivers on the promotion of the health of this community
Results: During the first 9 months, 106 adults with Down syndrome (more than 10% of the target population) were recruited, with an average age of 46.3 years (25-65), and 46.2% were women. 35.3% were symptomatic for Alzheimer's disease (AD), and prior to their visit, less than 5.7% had been diagnosed. It has been shown that the risk of epilepsy increases in the symptomatic phase of AD (32% in dementia vs. 4% in asymptomatic individuals), and the prevalence of obstructive sleep apnea syndrome is over 70% in the population, with an underdiagnosis rate exceeding 80%. In turn, 53.5% of them benefited from treatment adjustment during the visit. Additionally, 62.3% had access to blood analysis, 49.1% to magnetic resonance imaging, and 34.1% to lumbar puncture for clinical and/or research purposes.
Conclusions: Symptomatic AD is underdiagnosed and undertreated in the adult population with DS. Specific health plans not only allow for the improvement of healthcare for adults with DS but also empower them to become central agents in clinical and translational research. The collective response is highly satisfactory.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1434 / #2155

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

THE 2-YEAR GREEK EXPERIENCE OF A TELEMEDICINE PROGRAM IN THE AEGEAN ISLANDS FOR ALZHEIMER'S DISEASE, PARKINSON'S DISEASE AND RELATED DISORDERS

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Efthalia Angelopoulou[1], Dionysia Kontaxopoulou[1], Stella Fragkiadaki[1], Evangelia Stanitsa[1], Dimosthenis Pavlou[2], John Papatriantafyllou[1], Christos Koros[1], Efstratia-Maria Georgopoulou[3], Anastasia Kaliontzoglou[3], Georgios Koukoulas[4], Christos Roilos[4], Mitja Luštrek[5], Pietro Hiram Guzzi[6], Vlado Dimovski[7], Guido Piccoli[8], Darja Šemrov[9], Panagiotis Bamidis[10], Gerasimos Siasos[11], Leonidas Stefanis[1], Sokratis Papageorgiou[1]
[1]Eginition University Hospital, Neurology Department, Athens, Greece, [2]University of West Attica, School Of Topography And Geoinformatics, Athens, Greece, [3]General Hospital of Rhodes, Neurology Department, Rhodes, Greece, [4]2nd Regional Health Administration of Piraeus and Aegean, 2nd Regional Health Administration Of Piraeus And Aegean, Athens, Greece, [5]Jožef Stefan Institute, Department Of Intelligent Systems, Ljubljana, Slovenia, [6]Municipality of Miglierina, Municipality Of Miglierina, Miglierina, Italy, [7]University of Ljubljana, School Of Economics And Business, Ljubljana, Slovenia, [8]ALOT, Alot, Brescia, Italy, [9]University of Ljubljana, Faculty Of Civic And Geodetic Engineering, Ljubljana, Slovenia, [10]Aristotle University of Thessaloniki, Lab Of Medical Physics And Digital Innovation, Thessaloniki, Greece, [11]Sotiria Thoracic Diseases General Hospital, Department Of Cardiology, Athens, Greece

Aims: Patients with Alzheimer's disease (AD), Parkinson's disease (PD) and related disorders in remote regions have limited access to specialized healthcare. Although telemedicine use was increased during the pandemic, the perceptions of patients', caregivers' and healthcare professionals (HPs) remain unclear, and evidence from Greece is scant. The aim of this study was to describe our 2-year experience from a newly designed tertiary telemedicine program for patients with AD, PD and related disorders in Greece.
Methods: Individuals with cognitive and movement disorders in the Health Centers of the Aegean islands were examined via videoconferencing in the "Outpatient Clinic for Memory, Dementia and PD through the National Telemedicine Network", during 03/2021-03/2023, by specialized neurologists, psychiatrists and neuropsychologists from Aiginition University Hospital. Surveys, including 10 questions [ranging from 0 (not at all) to 4 (extremely) on 5-point Likert scale] on satisfaction, and recommendations for improvement were anonymously filled by patients, caregivers and HPs being present during the remote examination.
Results: 119 (68 first, 51 follow-up) telemedicine visits were totally conducted. We received 64 questionnaires (25 patients, 18 caregivers, 21 HPs). Most participants were satisfied (3 or 4 on the survey scale) with all telemedicine aspects, including comfort (patients:84%, caregivers:94%, healthcare professionals:90%), access to specialized care (92%,100%,100%), number of transportations (92%,89%,95%), adequate follow-up (92%,83%,86%), future selection of telemedicine (100%,100%,95%), perceived reliable medical assessment (100%,94%,90%), effective information delivery (96%,100%,86%), health improvement (96%,94%,76%), cost (92%,94%,100%), and general satisfaction (100%,100%,95%). Commonest recommendations were the need for more frequent visits and raising the awareness of the service.
Conclusions: Telemedicine for AD, PD and related diseases in the Aegean islands is feasible, with high satisfaction rates among most participants, highlighting its significance for equal care especially in remote areas.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1435 / #1412

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

TESTAMENTARY CAPACITY ASSESSMENT TOOL (TCAT): AN UPDATE REPORT

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Panagiota Voskou[1], Athanasios Douzenis[2], Alexandra Economou[1,3], Sokratis Papageorgiou[1]
[1]University of Athens, 1st Neurology D., Athens, Greece, [2]University of Athens, 2nd Psychiatry D., Chaidari, Greece, [3]University of Athens, Psychology, Athens, Greece

Aims: The present study reviews all studies about TCAT and its use in clinical settings, as well as its validation in different cultures. TCAT is a recently developed, short instrument (15 minutes are required for its administration), with good psychometric properties, specialized for the assessment of testamentary capacity (TC) in dementia. It assesses memory, perception of financial parameters and judgment. It evaluates cognitive functions not measured by other traditional tools, such as social cognition and it does not require the use of collateral information regarding financial parameters.
Methods: Pubmed database as well as unpublished data have been used.
Results: For now, there are no other specialized TC assessment instruments with measured psychometric properties in the scientific literature. Unpublished data about amnestic mild cognitive impairment (aMCI) performance in TCAT shows no difference of aMCI in comparison to healthy adults at any part of the tool. Another unpublished data has studied the correlation between the three parts of TCAT and the expert opinion regarding TC in patients with dementia. It has concluded that the Part C of financial parameters demonstrates the highest relevance with the expert opinion. Validation and standardization of the TCAT in Greek population is under study. The preliminary results show that age, and not educational level or gender, may predict the performance in TCAT. Validation and normative data of the TCAT in an Italian population of 323 healthy adults is provided in a recent published study showing that it is useful as an adjuvant instrument for TC assessment in the elderly.
Conclusions: While TCAT is a useful tool, more studies are needed in different cultures, both in healthy adults and cognitively impaired adults, for its standardized use in forensic and clinical settings.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1436 / #2263

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

COGNITIVE AND BIOLOGICAL EFFECTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 36-WEEK CLINICAL TRIAL OF CITRUS PHYTOCHEMICALS IN SUBJECTIVE COGNITIVE DECLINE

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Elena Gatti[1], Moira Marizzoni[2], Giovanni Sgro[3], Natale Salvatore Bonfiglio[4], Andrea Geviti[4], Salvatore Genovese[5], Serena Fiorito[5], Lorenzo Marchetti[5], Giovanni B. Frisoni[6], Michela Pievani[1], Francesco Epifano[5], Samantha Galluzzi[1]
[1]IRCCS Centro San Giovanni di Dio Fatebenefratelli, Laboratory Alzheimer's Neuroimaging And Epidemiology, Brescia, BS, Italy, [2]IRCCS Centro San Giovanni di Dio Fatebenefratelli, Laboratory Alzheimer's Neuroimaging And Epidemiology, Laboratory Of Biological Psychiatry, Brescia, BS, Italy, [3]IRCCS Centro San Giovanni di Dio Fatebenefratelli, Molecular Markers Laboratory And Clinical Trial Service, Brescia, Italy, [4]IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, BS, Italy, Service Of Statistics, Brescia, Italy, [5]Università "G. d'Annunzio" di Chieti-Pescara, Laboratory Of Phytochemistry And Chemistry Of Natural Products, Department Of Pharmacy, Chieti, Italy, [6]University Hospitals and University of Geneva, University Hospitals And University, Genève, Switzerland

Aims: *Citrus*-derived phytochemicals influence several biological mechanisms associated with cognitive decline, including neuronal damage, oxidative stress and inflammation. Here, we present the preliminary results of a 36-week treatment with *citrus* peel extract in older adults with subjective cognitive decline (SCD) (ClinicalTrials.gov identifier: NCT04744922).
Methods: Eighty SCD were enrolled and randomly assigned to receive active treatment (400 mg *citrus* peel extract standardized in content of auraptene - 0.1 mg - and naringenin – 3 mg) or placebo in a 1:1 ratio. Cognitive outcomes included changes in global cognition (Repeatable Battery for the Assessment of Neuropsychological Status, RBANS), verbal memory (California Verbal Learning Test, CVLT), attention, executive and visuospatial functions, and subjective memory concerns (Multifactorial Memory Questionnaire, MMQ). Biological outcomes included biomarkers indicative of neuronal damage, oxidative stress, and inflammation. The statistical analysis was performed using the intention-to-treat approach by generalized linear mixed models. Associations of cognitive outcomes with biological measures was tested using Spearman correlation analysis.
Results: At baseline, cognitve and biological measures were similar between groups. A significant effect of time, but not time*treatment interaction, was found on the RBANS ($p<.001$), the CVLT ($p<.001$) and the MMQ (Satisfaction $p<.001$, Ability $p<.001$ and Strategies $p=.026$). In the treatment group, but not placebo, improved global cognition, verbal memory, and better memory satisfaction were significantly correlated with inflammatory mediators (i.e. MCP-1, IP10, MPI1-μ, IL-8, TNFR-2, $0.38 < |rho| < 0.52$, $p < 0.044$).
Conclusions: The finding that both treatment and placebo groups improved in global cognition, verbal memory and metamemory might indicate a placebo-effect. However, correlation analysis suggests that cognitive benefit may be underlined by a modulation of neuroinflammation in subjects treated with *citrus* phytochemicals.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1437 / #1150

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

COMMUNITY-BASED PHYSICIAN ATTITUDES TOWARD THE DIAGNOSIS AND TREATMENT OF EARLY ALZHEIMER'S DISEASE IN THE UNITED STATES

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Timothy Juday[1], Ashley Holub[2], Soeren Mattke[3], Keith Betts[4], Sophie Kitchen[2], Amyn Malik[2], Richard Batrla[5], Feride Frech[1], Ara Khachaturian[6]
[1]Eisai Inc., Us Medical Affairs, Nutley, United States of America, [2]Analysis Group, Rwe, Boston, United States of America, [3]University Of Southern California, Cesr, Los Angeles, United States of America, [4]Analysis Group, Healthcare Economics And Outcomes Research, Los Angeles, United States of America, [5]Eisai, Inc., U.s. Medical Affairs Neurology, Nutley, United States of America, [6]Prevent Alzheimer's Disease 2020, Inc. (PAD 20/20), Brain Watch Coalition, Rockville, United States of America

Aims: The two early symptomatic stages of Alzheimer's disease (AD) are mild cognitive impairment (MCI) and mild AD. With the advent of new medical therapies, it is important to understand the patient journey from the perspective of physicians in a community-based setting, where most patients are seen. This study examines physician attitudes toward diagnosis, referral, and treatment of early AD among community-based primary care physicians (PCPs) and neurologists in the US.
Methods: This physician survey collected data on the care of early AD drawing participants from a verified physician panel with broad representation from 41 US states. Community-based PCPs and neurologists in practice for 3 years or longer who have cared for at least 15 early AD patients in the past year were asked to complete a 20-minute survey about their experiences managing early AD patients, including selection of tests, decision to refer and treatments. Descriptive statistics for all study endpoints will be generated during the analysis phase.
Results: This study includes 301 physicians (176 PCPs and 125 neurologists). Target recruitment is 334 physicians. Mean years in practice was 19.7 for PCPs and 18.5 for neurologists. Mean early AD patients seen in prior year by PCPs was 192 and by neurologists 237. The vast majority of physicians (PCPs=86%, neurologists=94%) was from urban or suburban settings, though PCPs had more rural representation. Most physicians were male and white (78% and 54% of PCPs and 72% and 61% of neurologists, respectively). Physician recruitment is ongoing.
Conclusions: Results from this survey are intended to understand physician attitudes and challenges in caring for early AD patients in community-based settings and help inform the patient journey on more localized levels, particularly in underserved populations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1438 / #385

Poster Topic: *Theme K: Patient Care and Support / K01.f. Dementia and Cognitive Dyfunction: Behavioral & psychiatric symptoms*

IMPACT OF DELAYED DEMENTIA DIAGNOSISON HEALTHCARE UTILIZATION DURING INITIAL HOSPITALIZATION BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

POSTERS: K01.F. DEMENTIA AND COGNITIVE DYFUNCTION: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Szu-Nian Yang[1,2], Chen-Han Chueh[3], Chien-Liang Liu[4,5], Yi-Wen Tsai[3]
[1]Armed Forces Taoyuan General Hospital, Department Of Psychiatry, Taoyuan, Taiwan, [2]Jen-Teh Junior College of Medicine, Nursing and Management, Department Of Oral Hygiene, Miaoli, Taiwan, [3]National Yang Ming Chiao Tung University, Institute Of Health And Welfare Policy, Taipei, Taiwan, [4]Taipei City Hospital Heping-Fuyou Branch, Department Of Neurology, Taipei, Taiwan, [5]Taipei City Hospital, Dementia Center, Taipei, Taiwan

Aims: Psychiatric hospitalization due to behavioral and psychological symptoms of dementia (BPSD) signifies the presence of profound emotional, perceptual, and behavioral disturbances in individuals with dementia which are also common in other psychiatric disorders, and thus potentially resulting in underrecognition or misdiagnosis of dementia as it progresses. We aimed to investigate the correlation between the timing of dementia diagnosis and the utilization of healthcare services during the first episode of hospitalization for BPSD.
Methods: We retrospectively examined whether early diagnosis of dementia affected healthcare management at the first psychiatric hospitalization between 2005 and 2015 due to BPSD in 1,972 elderly patients using National Health Insurance claims data in Taiwan. Patients were classified into the early diagnosis group and delayed diagnosis group based on the time of the diagnosis of dementia before index admission. To counteract potential confounding, a doubly robust estimation approach was employed, encompassing both the inverse probability of treatment weighting (IPTW) and outcome regressions. The outcomes were chemical restraints, physical restraints, and healthcare utilization.
Results: Among the 1,972 patients, 89.6% had an early diagnosis, and 10.4% had a delayed dementia diagnosis. The delayed dementia diagnosis group was younger and had less comorbidity. After IPTW, the delayed diagnosis group received more chemical and physical restraints. The length of hospitalization in the delayed diagnosis group was 8 days longer than in the early diagnosis group. The delayed diagnosis group had significantly higher total expenses by NT$27,344 and total drug expenses by NT$1,912 than the early diagnosis group.
Conclusions: These findings underscored the imperative of dementia monitoring, particularly for younger elderly and those with less comorbidity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1439 / #886

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

CHANGES IN DEMENTIA TREATMENT PATTERNS ASSOCIATED WITH NATIONAL POLICY IN KOREA: MULTICENTER, RETROSPECTIVE CAPTAIN STUDY

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Junhong Lee[1], Jinran Kim[2], Yoona Lee[2]
[1]National Health Insurance Service Ilsan Hospital, Neurology, Goyang-si, Korea, Republic of, [2]Eisai Korea Inc., Marketing, Seoul, Korea, Republic of

Aims: South Korea has actively addressed combating dementia since 2008, expanding mandatory long-term care insurance (LTCI) for dementia patients in 2014. This study aimed to investigate changes in treatment patterns for Alzheimer's disease (AD) between July 2011 and June 2017 which spanned the 2014 revision.
Methods: This multicenter, retrospective, observational study of patients with newly diagnosed AD analyzed electronic medical records from 17 general hospitals across Korea. Based on their time of AD diagnosis, subjects were categorized into Cohort 1 (1 July 2011 to 30 June 2014) and Cohort 2 (1 July 2014 to 30 June 2017).
Results: Subjects (N=3,997) divided into Cohorts 1 (n=1,998) and 2 (n=1,999). Cohort 1 subjects were significantly older (P<0.0001) and had a lower number of comorbidities (P=0.002) compared with Cohort 2. Mean Mini-Mental State Examination (MMSE) scores in Cohorts 1 and 2 at the time of AD diagnosis or start of initial treatment were 16.87 and 17.09, respectively (P=0.2790). At 1 year, mean MMSE scores in Cohorts 1 and 2 increased to 17.89 and 17.43, respectively (P=0.1524). Donepezil was the most frequently administered medication overall (75.01%), with comparable rates between cohorts. Discontinuation and switch treatment rates were significantly lower (49.72% *vs.* 58.01%; P<0.0001), and mean duration of initial treatment significantly longer, in Cohort 2 *vs.* 1.
Conclusions: Comparison of cohorts before and after revision of the national LTCI system for dementia patients found no significant difference in mean MMSE scores (time of AD diagnosis or start of initial treatment). The reduction in the proportion of patients who discontinued or changed their initial treatment, and the significant increase in mean duration of treatment, are attributed to revision of the LTCI policy which enabled increased patient access to long-term care.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1440 / #1683

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

DEMENTIA AND SMOKING

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Anna Bezdenezhnykh
FSBEI HE Prof. V.F. Voino-Yasenetsky KrasSMU MOH Russia, Department Of Nervous Diseases With A Pe-course, Krasnoyarsk, Russian Federation

Aims: Recently nicotine consumption has been suggested to be protective against AD neuropathology via activation of nicotinic acetylcholine receptors (nAChR). The aim is to review interactions between smoking and cognitive decline.
Methods: Literature review of the relevant articles.
Results: Case-controlled and cohort studies with a tobacco industry affiliation demonstrated a significantly decreased risk for AD, while those with no tobacco industry affiliation showed a significantly increased risk for AD (Cataldo JK et al, 2010). Novadays it is clear that smoking increases the risk of cognitive impairments. Smokers have increased risk of dementia about 30%, risk of AD - 59-78% and risk of VD -35-78% comparing to non-smokers. 4.7 million (14%) cases of AD is connected with smoking. Compared to continual smokers, long-term quitters and never smokers had decreased risk of overall dementia (hazard ratio, HR 0.86 95% CI, confidence interval 0.75–0.99 and HR: 0.81; 95% CI: 0.71–0.91, respectively). Both long-term quitters (HR: 0.68; 95% CI: 0.48–0.96) and never smokers (HR: 0.71; 95% CI: 0.54–0.95) had decreased risk of vascular dementia compared to continual smokers (Choi, D., Choi, S. and Park, S.M., 2018). In a combined group of active and former-smokers, Tyas et al. found that smokers with 27–41 (OR = 2.55; 95% CI = 1.22–5.58), and 41–56 (OR = 2.92; 95% CI = 1.37–6.53) pack years, had significantly greater risk of AD compared to those with < 27 pack-years; however, those with > 56 pack years showed no statistically significant increased risk for AD (OR = 1.37; 95% CI = 0.53–3.44), which was attributed to a strong survivor bias.
Conclusions: Smoking is essential risk factor of dementia. Harm reduction principles can be applied to those patients who can not quit smoking immediately.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1441 / #1450

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

360° TURN TEST (SINGLE AND DUAL TASK) - PATIENTS WITH MILD COGNITIVE IMPAIRMENT VS. COGNITIVELY HEALTHY INDIVIDUALS.

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Magnus Lindh-Rengifo[1], Sebastian Palmqvist[2,3], Erik Stomrud[2,3], Oskar Hansson[2,3], Maria Nilsson[1,2,3]
[1]Lund University, Department Of Health Sciences, Faculty Of Medicine, Lund, Sweden, [2]Lund University, Clinical Memory Research Unit, Malmö, Sweden, [3]Skåne University Hospital, Memory Clinic, Malmö, Sweden

Aims: To better understand potential motor differences, this study aimed to investigate turn duration (a 360° turn in standing, i.e., as a single task and while dual tasking) in patients with mild cognitive impairment (MCI) and cognitively healthy older persons.
Methods: This cross-sectional study included 420 individuals. Patients with MCI (n=140) had a mean age (SD) of 74.2 years (4.9), 37% were women. Cognitively healthy (n=280) had a mean age (SD) of 77.7 years (5.2), 62.5% were women. The assessment of turning 360° in standing included two turns (i.e., both directions), which were timed by using a digital stopwatch (seconds). Turning was initially assessed as a single task and thereafter while dual tasking (continuous subtraction of 3, starting from 99). The Mann-Whitney U test was used for group comparisons. Turn duration (single and dual tasking, respectively) was also used as the dependent variable in linear regression analyses where sample was used as an independent variable (controlled for age and sex).
Results: Patients with MCI had an increased turn duration as compared to cognitively healthy older persons, both when assessed as a single task ($p<0.001$) and while dual tasking ($p<0.001$). In linear regression analyses (controlled for age and sex), having MCI was associated with an increased time to perform a 360-turn both as a single task (B 1.20, 95% CI 0.83-1.57, $p<0.001$) and while dual tasking (3.05, 2.10-3.99, $p<0.001$).
Conclusions: From a clinical perspective, the Turn 360° test might be a relevant and easy test to implement. Although our findings suggest that patients with MCI perform a 360° turn slower than those who are cognitively healthy, the clinical relevance of this assessment needs to be confirmed in future longitudinal studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1442 / #2717

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

REVERSIBLE SPLENIAL LESION SYNDROME IN METABOLIC ENCEPHALOPATHY CAUSED BY HYPERNATREMIA

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Won Tae Yoon
Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Neurology, SEOUL, Korea, Republic of

Aims: A wide variety of clinical conditions may involve the splenium of the corpus callosum on magnetic resonance imaging. But, reversible focal lesions in splenium of the corpus callosum (SCC) or reversible splenial lesion syndrome are extremely rare and little known about their pathophysiology. Our aim is to report unusual case of a woman who manifested reversible isolated splenial lesion in metabolic encephalopathy caused by hypernatremia and rapid improvement with correction of electrolyte imbalance.
Methods: Single case report and description of clinical characteristics.
Results: A 39-year-old female visited Emergency room with poor oral intake and fever. When coming to Emergency room, she had 39.1℃ fever and had stuporous mental status. After an extensive workout to exclude acute neurological disorders including ischemic, demyelinating disease and CNS infection, a clinical diagnosis of metabolic encephalopathy caused by hypernatremia. Initial magnetic resonance imaging (MRI) of the brain showed an isolated lesion in the SCC characterized by high signal intensity on FLAIR sequence and diffusion weighted imaging (DWI) showed restricted diffusion. There was no enhancement following Gadolinium administration. We administered ICU management and correcting hypernatremia, and then splenial high signal lesion of corpus callosum resolved markedly within several days. We can conclude final diagnosis as reversible splenial lesion syndrome in metabolic syndrome caused by hypernatremia.
Conclusions: For now, we report for the first time a rare manifestation of metabolic encephalopathy caused by hypernatremia presenting reversible splenial lesion syndrome. Along with this case, if there are acute isolated SCC lesion in MRI, it should be considered underlying emergent metabolic encephalopathy including hypernatremia.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1444 / #1157

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

IMPACT OF TREATMENT DURATION AND ROUTE OF ADMINISTRATION OF DISEASE-MODIFYING ALZHEIMER'S TREATMENTS ON MEDICAL COSTS AND CAREGIVER BURDEN (20 WORDS MAX)

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Soeren Mattke, Tabasa Ozawa, Grigory Franguridi
University Of Southern California, Cesr, Los Angeles, United States of America

Aims: Several disease-modifying treatments for early-stage Alzheimer's disease (AD) are approved or in late-stage development. Their properties differ by route of administration, treatment frequency/duration and monitoring requirements. We analyze how these properties affect the treatments' value in terms of medical and social-care costs and caregiver burden.
Methods: We compare five treatments: three for intravenous infusion, including two for chronic use with infusions every two or four-weeks until progression to moderate dementia (mean 7.25 years), one for 52-week treatment with monthly infusions, one for chronic bi-weekly subcutaneous injection and one for oral daily administration. We assume all reduce progression by ~30% at the MCI stage, and a 25% ARIA risk in the first year with injectables agents, with monitoring requirements per US label. We used gross-value estimates of treatments from the published literature, administration costs and monitoring from Medicare rates, and caregiver burden from a survey of 28 clinical sites, inquiring about time use for visits and travel and proportion of patients accompanied.
Results: Table 1. Gross value and Value Reductions Per Treatment Modality

		st of burden of treatment administration and monitoring				
		Absolute and relative impact by modality				
	Gross lifetime value	iv biweekly	iv four-weekly	iv 52 weeks	subcutaneous four-weekly	oral
Cost offsets	$24,165	-$47,825(198%)	-$25,593(106%)	-$6,307(26%)	-$5,284(22%)	-$2,258(9%)
Caregiver benefit	$4,298	-$7,467(174%)	-$3,879(90%)	-$1,141(27%)	-$746(17%)	-$581(14%)

Conclusions: Burden of chronic intravenous treatments would exceed gross medical and social care cost savings and value of caregiver benefit. Subcutaneous and oral agents have lower and lowest burden, respectively. Subcutaneous and oral AD treatments that reduce clinic visits have greater potential to preserve the value of treatment benefit.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1445 / #1832

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

DELIRIUM INCIDENCE IN ALZHEIMER'S DISEASE AND DEMENTIA WITH LEWY BODIES BEFORE AND AFTER DEMENTIA DIAGNOSIS

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Kristin Eidsheim Sønnesyn[1], Kristoffer Haugarvoll[2], Dag Aarsland[3,4], Ragnhild Skogseth[1,5]
[1]Haraldsplass Deaconess Hospital, Neuro-sysmed, Department Of Internal Medicine, Bergen, Norway, [2]Haukeland University Hospital, Neuro-sysmed, Department Of Neurology, Bergen, Norway, [3]Institute of Psychology, Psychiatry & Neuroscience (IoPPN), King's College London, Department Of Old Age Psychiatry, London, United Kingdom, [4]Stavanger University Hospital, Centre For Age-related Medicine (sesam), Stavanger, Norway, [5]University of Bergen, Department Of Clinical Science, Bergen, Norway

Aims: Delirium is reported to be more common in Dementia with Lewy bodies (DLB) than in Alzheimer's disease (AD). Delirium is proposed to be one presentation of prodromal DLB, in addition to neuropsychiatric and mild-cognitive impairment onset. However, the frequency is unknown and symptoms of DLB resemble those of delirium. The aim was to analyze differences in incidence of delirium in DLB and AD patients before and after dementia diagnoses in a dementia cohort in Norway.
Methods: The Dementia Study of Western Norway included 247 persons with mild dementia (Mini Mental State Examination (MMSE) ≥ 20, Clinical Dementia Rating Scale (CDR) ≤1), who were followed annually until death. 181 subjects with DLB (n=75) and AD (n= 106) were included in this analysis. Delirium was retrospectively diagnosed through chart review assessing all available information in 732 acute or planned hospital admissions into psychiatric and somatic wards from 5 years before dementia diagnosis until death.
Results: Delirium was recorded in 221 (30,2 %) hospital admissions. 49 (65,3 %) DLB patients and 71 (67,0 %) AD patients had at least one delirium episode. There was a significant difference in the number of DLB patients with at least one delirium episode before diagnosis compared to the AD group (p.023), and the incidence rates of delirium after diagnosis were higher in DLB than AD, 20 versus 15 per 100 person-years respectively (p.033).
Conclusions: Delirium seems to be more common in DLB patients than in AD patients both before and after diagnosis. This holds true when delirium diagnoses are made by chart review by dementia specialists, thus reducing the risk of misinterpreting DLB symptoms as delirium. More studies are needed to establish the frequency and trajectory of delirium onset DLB.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1446 / #2540

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

EVALUATION AND TREATMENT OF DIZZINESS / IMBALANCE IN PATIENTS WITH VASCULAR DEMENTIA

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Ioseb Burduladze
Research Institute of Clinical Medicine (TODUA Clinic), Neurology, Tbilisi, Georgia

Aims: The prevalence of balance problems in people aged more than 70 years reaches 40-45%, and due to aging of world population, the number of patients is rapidly increasing, mainly in patients with Vascular Dementia (VD). The terms Imbalance cover a variety of symptoms regarding disorders of spatial orientation, such as the illusion vertigo or unsteadiness, which can affect objectively the ability to achieve a posture, stable gaze, and normal gait. The aim of this study was to recognize main signs of this problem and determine rapid support recommendations.
Methods: 30 patient wish VD, with acute dizziness, admitted to Neurological department, were investigated. The main symptoms was acute vertigo with fall (n=21) and acute vertigo with unsteadiness (n=9). After exclusion of cerebral stroke (CS) and other acute vascular pathologies, investigation of balance system was provided by vestibular Romberg test, Fukuda step test, vestibular ocular reflex (VOR) and Dix–Hallpike maneuver (DHM). In some cases (n=5), after the fast stabilization, video head impulse testing (VHIT) was done.
Results: In all patients, CS was not revealed. In 18 cases, reason of dizziness was bilateral vestibulopathy, in 5 cases, - benign paroxysmal positional vertigo, in 3 cases, - vestibular neuritis and in 4 cases, somatosensory loss. In all cases, VOR and DHM were effective for balance recovery as well as first medical support. After the acute period (24hr) vestibular rehabilitation (VR) exercises were more effective than DHM.
Conclusions: Dizziness/Imbalance in patients with VD (except of Stroke) can be treated with physical and pharmacological therapy to help improve symptoms and reduce risk for falls.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1447 / #1314

Poster Topic: *Theme K: Patient Care and Support / K02.b. Movement Disorders: Motor coordination & exercise*

EFFICACY OF ROBOTIC GAIT TRAINING IN PARKINSONIAN PATIENTS USING THE END-EFFECTOR ROBOTICS

POSTERS: K02.B. MOVEMENT DISORDERS: MOTOR COORDINATION & EXERCISE

Seong-Yeol Kim[1,2], Da-Sol Kim[1,2], Gi-Wook Kim[1,2], Yu Hui Won[1,2], Sung-Hee Park[1,2], Jeong-Hwan Seo[1,2], Myoung-Hwan Ko[1,2]
[1]Jeonbuk National University Hospital, Department Of Physical Medicine And Rehabilitation, Jeonju, Korea, Republic of, [2]Jeonbuk National University Hospital, Research Institute Of Clinical Medicine - Biomedical Research Institute, Jeonju, Korea, Republic of

Aims: This research aims to determine the effectiveness of RAGT, specifically using the “Morning Walk®” end-effector gait robotic system, in enhancing both motor and non-motor manifestations in Parkinsonism patients.
Methods: We conducted a prospective randomized controlled trial at a single center. A total of 20 Parkinsonism patients were enlisted and divided randomly into RAGT (n=9) group and conventional physical therapy (CPT, n=11). The RAGT group utilized the "Morning Walk®" robotic system, while the CPT group underwent standard therapeutic exercises and manual therapy in 18 sessions over six weeks. Primary evaluations were based on the 2-minute walk test (2MWT) and the 10-meter walk test (10MWT). Secondary outcomes were assessed using tools like the Berg Balance Scale(BBS), Timed Up and Go (TUG) Test, MDS-UPDRS part I,II, and III, and the Non-Motor Symptoms Assessment Scale(NMSS), with assessments taken before and after the treatment sessions.
Results: The results showed a significant improvement in 2MWT in both the RAGT (E2-E1: 14.00±12.80 meter, p=0.007) and the CPT (E2-E1: 8.25±7.69 meter, p=0.019) while 10 MWT showed significant improvement only in the RAGT (E2-E1 -3.20±4.33 second, p=0.005). However, there were no significant differences in primary outcomes between the two groups. BBS (p=0.004) and TUG (p=0.042) showed significant improvement while MDS part II (p=0.010) and III (p=0.036) showed significant decrease only the RAGT. Both group showed significant decrease in MDS part I (p=0.035 in RAGT and p=0.044 in CPT). In non-motor symptom measurements, RAGT showed significant decrease in NMSS in total scale, anxiety, urinary, and gastrointestinal subscale (p=0.028, 0.043, 0.042, 0.039) whereas the CPT did not. There were no other significant differences between groups.
Conclusions: RAGT, especially when utilizing the 'Morning Walk®' system, presents a promising avenue for addressing both motor and non-motor symptoms in Parkinsonism.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1448 / #1471

Poster Topic: *Theme K: Patient Care and Support / K02.b. Movement Disorders: Motor coordination & exercise*

EFFECT OF UPPER EXTREMITY TRAINING VIA VIDEOCONFERENCE ON COGNITIVE FUNCTION IN PATIENTS WITH PARKINSON'S DISEASE: AN OBSERVATIONAL STUDY

POSTERS: K02.B. MOVEMENT DISORDERS: MOTOR COORDINATION & EXERCISE

Sefa Eldemir[1], Kader Eldemir[2], Fettah Saygili[3], Rezzak Yilmaz[4], Muhittin Cenk Akbostancı[4], Arzu Guclu-Gunduz[5]
[1]Sivas Cumhuriyet University, Department Of Physiotherapy And Rehabilitation, Sivas, Turkey, [2]Ordu University, Department Of Physiotherapy And Rehabilitation, Ordu, Turkey, [3]Aydın Adnan Menderes University, Department Of Physiotherapy And Rehabilitation, Aydın, Turkey, [4]Ankara University, Department Of Neurology And Ankara University Brain Research Center, Ankara, Turkey, [5]Gazi University, Department Of Physiotherapy And Rehabilitation, Ankara, Turkey

Aims: Upper extremity skills and cognitive function in addition to balance and mobility are impaired in patients with Parkinson's disease (PwPD), which leads to difficulties in activities of daily living. Most intervention is focused on lower extremity treatment rather than upper extremity and cognitive functions. However, training that aims to improve upper extremity skills has the potential to both make it easier for patients to cope with activity limitations in daily life and improve their cognitive functions. The aim of this study is to investigate the effectiveness of task-oriented training applied to the upper extremity via videoconference on cognitive functions in PwPD.
Methods: Fourteen PwPD (aged between 45 and 70 years, Hoehn & Yahr stage I-III) were included in the study. All individuals received a treatment that included task-oriented training of the upper extremity via videoconference three days a week for six weeks. Task-oriented training of the upper extremity is a 1-hour exercise program consisting of 15 workstations. Cognitive status was evaluated with a Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA).
Results: After rehabilitation, a statistically significant improvement was observed in terms of global cognitive status (MoCA, p=0.003 and MMSE, p=0.010).
Conclusions: This is the first study showing that task-oriented training of the upper extremity via videoconference improved cognitive functions. The training of the upper extremity via videoconference may be recommended as an effective option, especially for PwPD with barriers to reaching the clinic.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1449 / #1746

Poster Topic: *Theme K: Patient Care and Support / K02.b. Movement Disorders: Motor coordination & exercise*

INVESTIGATING THE RELATIONSHIP BETWEEN UPPER EXTREMITY FUNCTION AND BALANCE AND FUNCTIONAL MOBILITY IN PATIENTS WITH PARKINSON'S DISEASE

POSTERS: K02.B. MOVEMENT DISORDERS: MOTOR COORDINATION & EXERCISE

Kader Eldemir[1], Sefa Eldemir[2], Fettah Saygili[3], Rezzak Yilmaz[4], Muhittin Cenk Akbostancı[4], Arzu Guclu-Gunduz[5]
[1]Ordu University, Department Of Physiotherapy And Rehabilitation, Ordu, Turkey, [2]Sivas Cumhuriyet University, Department Of Physiotherapy And Rehabilitation, Sivas, Turkey, [3]Aydın Adnan Menderes University, Department Of Physiotherapy And Rehabilitation, Aydın, Turkey, [4]Ankara University, Department Of Neurology And Ankara University Brain Research Center, Ankara, Turkey, [5]Gazi University, Department Of Physiotherapy And Rehabilitation, Ankara, Turkey

Aims: Functional disability in the upper extremity, loss of balance, and mobility limitation are common problems in patients with Parkinson's Disease (PwPD), and these problems significantly affect the quality of life of patients. This study's objective was to examine the relationship between upper extremity functions and balance and mobility for PwPD.
Methods: Twenty-two PwPD (aged 45–70 years, Hoehn & Yahr stage I-III) were recruited in this study. The Nine-Hole Peg Test (9-HPT) was used to evaluate upper extremity function. Balance and functional mobility were evaluated with the Berg Balance Scale (BBS), Functional Reach Test (FRT), and Timed Up and Go Test (TUG).
Results: The result of correlation analyses showed that both sides' of upper extremity functions were related to BBS, FRT, and TUG scores ($r = -0.640$ to 0.675, $p<0.05$).
Conclusions: These results indicate that PwPD with better functional skills in the upper extremities perform better in activities related to balance and functional mobility. In addition, these results point out that the upper extremity has an important role in developing strategies and creating protective reactions to maintain the position of the center of gravity on the support surface to maintain balance while standing or walking. Therefore, the physiotherapy program should include exercise stations aimed at improving functional skills in the upper extremity.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1450 / #2813

Poster Topic: *Theme K: Patient Care and Support / K01.g. Dementia and Cognitive Dyfunction: Other*

OPINIONS OF MCI/DEMENTIA PATIENTS AND THEIR FAMILY CAREGIVERS ABOUT UNDERGOING A DETAILED EVALUATION

POSTERS: K01.G. DEMENTIA AND COGNITIVE DYFUNCTION: OTHER

Aiko Osawa[1], Shinichiro Maeshima[2], Takako Yoshimura[3]
[1]National Center for Geriatrics and Gerontology, Department Of Rehabilitation Medicine, Obu, Japan, [2]National Center for Geriatrics and Gerontology, Education And Innovation Center, Obu, Japan, [3]Kyoto University of Advanced Science, Department Of Speech Pathology, Kyoto, Japan

Aims: In selecting treatment for dementia, a detailed neuropsychological background and ability to perform activities of daily living should be assessed to determine the individual patient's medical condition and daily living problems. However, necessary assessments are often not conducted due to the assumption by healthcare providers that "it is pitiful to conduct detailed assessments on people with dementia. Therefore, this study investigated the opinions of people with mild cognitive impairment (MCI) and dementia receiving non-pharmacological treatment and their family caregivers about undergoing detailed evaluations.
Methods: A questionnaire survey was conducted among people with31 MCI/dementia patients and 50 family caregivers undergoing Holistic physio-cognitive rehabilitation at the National Center for Geriatrics and Gerontology.
Results: 94% of the persons with MCI/dementia indicated that being evaluated was a good thing, 86% wanted to be evaluated, and 66% wanted a longer but more detailed evaluation. 29% were saddened to find out what they can't do and 89% were happy to find out what they can do. 96% of the family caregivers also answered that the evaluations were a good thing. 84% said that the evaluation was helpful, and 86% said that the evaluation was necessary to reduce the burden of caregiving, and more than 90% wanted to be present during the evaluation.
Conclusions: It was clear that both parties with MCI/dementia and family caregivers expect the correct evaluation of their medical conditions and appropriate treatment and care suggestions based on the evaluation, even if it takes time. It was considered that detailed evaluation and feedback of the results should be conducted based on such requests from the parties with dementia, and treatment should be selected based on these requests.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1451 / #2421

Poster Topic: *Theme K: Patient Care and Support / K02.b. Movement Disorders: Motor coordination & exercise*

INVESTIGATION OF THE RELATIONSHIP BETWEEN FUNCTIONAL MOBILITY AND EXECUTIVE FUNCTIONS IN PATIENTS WITH EARLY AND INTERMEDIATED PARKINSON'S DISEASE

POSTERS: K02.B. MOVEMENT DISORDERS: MOTOR COORDINATION & EXERCISE

Aybuke Cansu Kalkan[1,2], Turhan Kahraman[3], Deniz Yerlikaya[4], Berril Donmez Colakoglu[5], Gorsev Yener[6,7], Ahmet Ozkurt[8], Arzu Genc[9]
[1]Dokuz Eylul University, Institute Of Health Sciences, Izmir, Turkey, [2]Izmir Katip Celebi University, Faculty of Health Sciences, Department Of Physiotherapy And Rehabilitation, Izmir, Turkey, [3]Izmir Katip Celebi University Faculty of Health Sciences, Department Of Physiotherapy And Rehabilitation, Izmir, Turkey, [4]Dokuz Eylul University, Institute of Health Sciences, Department Of Neurosciences, Izmir, Turkey, [5]Dokuz Eylul University, Faculty of Medicine, Department Of Neurology, Izmir, Turkey, [6]Izmir University of Economics, Faculty of Medicine, Department Of Neurology, Izmir, Turkey, [7]Dokuz Eylul University, Izmir Biomedicine And Genome Center, Izmir, Turkey, [8]Dokuz Eylul University, Department Of Electronical And Electronics Engineering, Izmir, Turkey, [9]Dokuz Eylul University, Faculty Of Physical Therapy And Rehabilitation, Izmir, Turkey

Aims: The aim of this study was to investigate the relationship between functional mobility and executive functions in patients with early and intermediated Parkinson's disease (PD).
Methods: Seventeen patients (7 females, 10 males) with PD were included in the study. The Modified Hoehn and Yahr Scale (MHYS) was used to evaluate disease severity, and the Unified Parkinson's Disease Rating Scale (UPDRS) was used to evaluate disability in PD. Functional mobility was assessed by the Timed and Up Go Test (TUG) under 3 conditions: TUG-single task; TUG-cognitive dual task (TUG-cog), TUG-manual dual task (TUG-man). The Montreal Cognitive Assessment (MoCA), the Trail Making Test (TMT), and the Stroop Test Çapa Version (STROOP) were used to evaluate executive functions.
Results: The median age of the participants was 60.0 years. The median total UPDRS score was 49.0. The relationship between functional mobility and executive functions was presented in Table 1. **Table 1.** The relationship between functional mobility and executive functions

	TUG-single task
	rho/p
MoCA	-0.518/0.033*
TMT-A	0.799/<0.001*
TMT-B	0.576/0.016*
STROOP-Experiment 1	0.645/0.005*
STROOP-Experiment 2	0.600/0.011*
STROOP-Experiment 3	0.620/0.008*

TUG: Timed and Up Go Test, TUG-cog: TUG-cognitive dual task, TUG-man: TUG-manual dual task, MoCA: Montreal Cognitive Assessment, TMT: Trail Making Test, STROOP: Stroop Test Çapa Version, rho:Spearman's correlation coefficient, *p<0.05.
Conclusions: There are strong relationships between TUG under single and dual task conditions and executive functions in patients with early and intermediated PD. As the

executive functions of patients are impaired, functional mobility may be negatively affected.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1452 / #1831

Poster Topic: *Theme K: Patient Care and Support / K02.c. Movement Disorders: Support devices & monitoring*

INTERRATER RELIABILITY OF HAND MOTOR FUNCTION: ASSESSMENT IN PARKINSON'S DISEASE: IMPACT OF CLINICIAN TRAINING

POSTERS: K02.C. MOVEMENT DISORDERS: SUPPORT DEVICES & MONITORING

Lorna Kenny[1], Zahra Azizi[1], Kevin Moore[1], John Barton[2], Salvatore Tedesco[2], Marco Sica[2], Colum Crowe[2], Suzanne Timmons[1]
[1]University College Cork, Centre For Gerontology And Rehabilitation, School Of Medicine, Cork, Ireland, [2]University College Cork, Tyndall Institute, Cork, Ireland

Aims: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by motor and non-motor symptoms. Clinicians may vary in rating the severity of motor features. This study aims to determine the interrater reliability (IRR) of hand motor function assessment among expert clinicians and explore potential for improvement.
Methods: People with PD performed six standardized hand movements from the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS), while two cameras simultaneously recorded from the front and side. The severity of tremor and bradykinesia was rated independently by eight clinicians, using a visual analogue scale (VAS). We compared intraclass correlation coefficient (ICC) before and after a training/group calibration session, where four participant videos with high variance were reviewed, and the MDS-UPDRS rating instructions were discussed.
Results: In the first round, bradykinesia received higher mean severity scores than tremors in both hands. Poor agreement was observed for various hand movements, with best agreement found in resting tremors (right hand: ICC 0.66; 95% CI 0.50-0.82; left hand: ICC 0.66; CI 0.50-0.81). Postural tremor in the left hand had the least agreement (ICC 0.14; 95% CI 0.04-0.33), as did wrist pronation and supination in the right hand (ICC 0.34; 95% CI 0.19-0.56). In post-training assessments, agreements improved, especially in the right hand. Best agreement was observed for hand open close in the left hand (ICC 0.82, 95% CI 0.64-0.94) and resting tremor in the right hand (ICC 0.92, 95% CI 0.83-0.98). Least agreement was seen for kinetic tremor in the left hand (ICC 0.25, 95% CI 0.06-0.60) and HOC in the right hand (ICC 0.48, 95% CI 0.22-0.78).
Conclusions: Experienced clinicians vary in their rating of (video-recorded) PD motor features but this can be improved somewhat with training.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1453 / #1337

Poster Topic: *Theme K: Patient Care and Support / K02.c. Movement Disorders: Support devices & monitoring*

AUXILIARY DEVICES SITUATION IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS IN THE REPUBLIC OF KAZAKHSTAN

POSTERS: K02.C. MOVEMENT DISORDERS: SUPPORT DEVICES & MONITORING

Larissa Kuanova
University Medical Center, Program Of Neurology, Astana, Kazakhstan

Aims: Assistive devices include medical devices designed to compensate the loss of function and improve daily life. The lack of analysis of the situation with auxiliary devices in Kazakhstan for patients with ALS and other motor neuron diseases significantly affects their duration and quality of life. The purpose of this study is to determine the need for assistive devices for patients with ALS living in Kazakhstan.
Methods: We conducted a questionnaire survey concerning the process of providing assistive devices among 65 patients with ALS registered in the social network "Life is beautiful". The social network unites patients living in the Republic of Kazakhstan with this diagnosis, receive advice on a wide range of issues, and morally support each other. The interview moderators were resident doctors of the first and second years of study. Diagnostic aspects and phenotypes of the disease were studied according to the extracts from medical records.
Results: According to the clinical spectrum of phenotypes, classical bulbar onset was noted in (17%), pseudobulbar paralysis (16%), progressive bulbar paralysis (20%), classical cervical onset (31,6%), "hanging arms", "hanging legs" syndromes (15, 4%). Depending on the phenotype, there is a need for the use of non-invasive pulmonary ventilation, a cough suppressant, orthoses, mobile devices, moving devices, communication devices.
Conclusions: The goal of preventive adaptation of assistive devices is to be one step ahead of the need for assistive devices, planning adaptations to functional limitations before they become pronounced. The results show that difficulties in obtaining and financing assistive devices are an unsolved problem among patients with ALS in the Republic of Kazakhstan. There is a need for an interdisciplinary approach to the provision of assistive devices and public financing.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1454 / #2335

Poster Topic: *Theme K: Patient Care and Support / K02.b. Movement Disorders: Motor coordination & exercise*

EFFECTS OF LSVT-BIG THERAPY ON MOTOR FUNCTION AMONG PEOPLE LIVING WITH PARKINSON DISEASE: A 6-MONTHS FOLLOW-UP STUDY

POSTERS: K02.B. MOVEMENT DISORDERS: MOTOR COORDINATION & EXERCISE

Fariba Yadolahi[1], Najmeh Hosseini[2]
[1]KUMS, Rehabilitation, Kermanshah, Iran, [2]SBMU, Rehabilitation, Tehran, Iran

Aims: Parkinson's disease (PD) is a neurodegenerative disease with motor and non-motor symptoms affecting the lower limbs. Abnormal motor function is one of the reasons leading to restriction in independence and morbidity among them. LSVT-BIG therapy is an efficient model of exercise therapy that can be beneficial in improving mobility in people living with Parkinson's disease. Current literature focuses on conventional exercise training in this population. The purpose of this study was to investigate the effects and persistence of LSVT-BIG treatment versus conventional therapy on people living with Parkinson's disease.
Methods: Twenty-four participants with URPDS levels 2-3 randomized into LSVRT class (n=12) and conventional class (n=12). Both groups underwent 4 sessions of therapy in a week for two months. The blind examination was done using the 10 Meter Walk Test, Time Up and Go, Time Up and Down Stairs (TUDS), and 6 Minute Walk Test (6MWT). Test means were compared before intervention, at the end of treatment and after 6 months using repeated measures ANOVA with a Tukey correction, p value < .05.
Results: All participants completed the treatment sessions without adverse effects. After four weeks of treatment, the LSVT-BIG group showed statistically significant improvement in TUG ($p<0.05$) and TUDS ($p=0.001$), and 10MWT ($p<0.05$). The conventional group only showed statistically significant improvement in 6MWT ($p<0.05$). Significant improvements were noted after 6 months when comparing initial evaluation ($p<0.05$).
Conclusions: This study suggest that LSVT-BIG therapy is an effective intervention with long-term retention to improve motor function in individuals with Parkinson's disease. These findings need to be confirmed by appropriately-powered trials.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1455 / #1674

Poster Topic: *Theme K: Patient Care and Support / K02.d. Movement Disorders: Quality of life*

DEVELOPMENT OF A MOTOR FLUCTUATIONS PATIENT JOURNEY MAP FOR PEOPLE LIVING WITH PARKINSON'S DISEASE

POSTERS: K02.D. MOVEMENT DISORDERS: QUALITY OF LIFE

Nelson Lopes[1], Alberto Albanese[2], Ryan Case[1], Anat Amit[1], Shmuel Ben-Hamo[1]
[1]NeuroDerm.com, Clinical Development, Rehovot, Israel, [2]IRCCS Humanitas Research Hospital, Neurology, Milan, Italy

Aims: Develop a Motor Fluctuations Patient Journey Map (MFPJM) for people with Parkinson's disease (PwP) to describe the holistic experience from pre-diagnosis through long-term treatment, with a focus on motor fluctuations.
Methods: The MFPJM is in development based on in depth surveys with PwP (n=33), their care partners (n=40), and healthcare professionals with experience of treating Parkinson's disease (n=61) in the UK, Germany, France, and USA.
Results: Qualitative analysis supported five stages of the journey: onset & awareness, referral & diagnosis, early treatment, living with motor complications, and palliative care. PwP described experiencing subtle (often non-motor) symptoms long before they suspected PD. Across the 4 countries, PwP typically started their first treatment (often levodopa monotherapy) immediately following diagnosis. PwP described consistent symptom control for the first few years of treatment. After this 'honeymoon' phase, oral medications typically become less effective, and PwP/care-partners recalled noticing a more frequent re-emergence of motor and non-motor symptoms. However, 75% of PwP said they were not previously aware of the possibility of motor fluctuations until they developed them. While HCPs aim to minimize OFF time, treatment is centered around the patient's personal tolerance/comfort level with symptoms, side effects, and pill burden. PwP and care partners described the 'trial-and-error' process of frequently adjusting and optimizing the treatment plan as particularly frustrating. Eventually, as treatment options are no longer effective, PwP become dependent on their care partner or other support services for daily life and seek more advanced treatments.
Conclusions: The MFPJM is in development as a visual aid to enable service providers to identify unmet needs, potential gaps, and barriers in service provision, as well as identifying new opportunities for innovation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1456 / #245

Poster Topic: *Theme K: Patient Care and Support / K02.d. Movement Disorders: Quality of life*

ROLE OF PALLIATIVE CARE IN ADVANCED PARKINSON'S DISEASE - A PATIENT-CENTERED APPROACH

POSTERS: K02.D. MOVEMENT DISORDERS: QUALITY OF LIFE

Alexandra Armitage
Baylor Scott and White Health, Supportive Palliative Care, Temple, United States of America

Aims: Palliative care has a pivotal role in the management of advanced Parkinson's disease. Non-motor symptom management, caregiver support, the value of individualized medical decisions, and the holistic approach of an interdisciplinary team are explored.
Methods: A case study approach supported by the best evidence-based practice; this talk aims to highlight the multifaceted aspects of Palliative Care in advanced Parkinson's disease embracing the holistic philosophy of interdisciplinary collaboration.
Results: Advanced Parkinson's disease management extends beyond motor symptoms, with complex non-motor manifestations that often carry the greatest burden to both patient and caregiver. Managing these symptoms by a palliative care team can complement regular neurological care due to longer palliative appointment lengths, focus on symptoms management and holistic approach to care. Patients with Parkinson's disease exhibit diverse medical decisions influenced by their personal values, preferences, and goals. Therefore, engaging in explicit goals of care discussions, including advanced directives, becomes imperative to ensure that patient autonomy and wishes are upheld, even in the face of disease progression. Palliative care stands as an embodiment of holistic patient-centered care. Its interdisciplinary approach amalgamates medical expertise, nursing care, psychological support, and allied health interventions. This holistic philosophy caters to the physical, emotional, and spiritual needs of patients, ultimately enhancing their overall well-being and dignity.
Conclusions: By advocating for the integration of palliative care into the comprehensive management of advanced Parkinson's disease we propose a patient-centered approach. Bringing Palliative Care to the table empowers the neurological team to optimize the quality of life for patients living with advanced Parkinson's disease and their caregivers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1457 / #624

Poster Topic: *Theme K: Patient Care and Support / K02.d. Movement Disorders: Quality of life*

ASSOCIATION OF APATHY WITH CLINICAL MOTOR AND NON-MOTOR SYMPTOMS IN DE-NOVO PATIENTS WITH PARKINSON'S DISEASE

POSTERS: K02.D. MOVEMENT DISORDERS: QUALITY OF LIFE

Sun Ju Chung, Sungyang Jo, Jihyun Lee, Sangjin Lee
Asan Medical Center, Neurology, Seoul, Korea, Republic of

Aims: Apathy is a common non-motor symptom of Parkinson's disease (PD) that may associate with motor and other non-motor symptoms in PD patients. The clinical implication of apathy in early PD is still lacking. Therefore, we aimed to investigate the association of apathy with the motor and non-motor clinical features in patients with de-novo PD.
Methods: This study retrospectively investigated de-novo PD patients at Asan Medical Center from March 2021 to December 2022. We analyzed baseline demographics, severity of motor symptom assessed by Unified Parkinson's Disease Rating Scales (UPDRS) part III, apathy assessed by Apathy Evaluation Scale (AES), and quality of life assessed by The Parkinson's Disease Questionnaire (PDQ-39). Additionally, we investigated non-motor symptoms other than apathy using Non-Motor Symptoms Scale (NMSS), which includes 8 subscores (cardiovascular, sleep and fatigue, mood, problem, hallucination, attention and memory, gastrointestinal symptoms, urinary symptoms, and miscellaneous).
Results: Study subjects included 68 patients with de-novo PD, including 38 female (55.9%), with mean age of 64.7 ± 9.9 years. The mean severity of motor symptoms, assessed by UPDRS part III, was 22.4 ± 11.1 and mean AES was 44.8 ± 7.9. In the univariable linear regression analysis, the severity of motor symptoms was significantly associated with apathy (beta=0.469, $P < 0.001$). The severity of apathy was significantly associated with non-motor symptoms, assessed using NMSS, BDI, HADS, and PDQ-39. In the multivariable linear regression analysis, the severity of sleep symptoms was significantly associated with AES score (beta=2.999, $P = 0.008$).
Conclusions: Our study suggests that the severity of apathy is associated motor and non-motor symptoms in de-novo PD patients. Further researches are required to clarify the pathomechanisms of the correlation among apathy, sleep problem, and quality of life in de-novo PD patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1458 / #1130

Poster Topic: *Theme K: Patient Care and Support / K02.d. Movement Disorders: Quality of life*

PROGRESSION OF PARKINSON'S DISEASE IN ASIAN AND NATIVE HAWAIIAN AND PACIFIC ISLANDER PATIENTS

POSTERS: K02.D. MOVEMENT DISORDERS: QUALITY OF LIFE

Kirra Borrello[1,2], Shay Nakahira[1,2], Paul Fontana[1,3], Darrel Guittu[1], Chanel Hunter[1], Anson Lee[1,2], Julia Jahansooz[1,2], Edward Weldon Iv[1,2], Meliza Roman[4], Hyeong Jun Ahn[4], Jason Viereck[1,2], Enrique Carrazana[1,2], Kore Liow[1,2,4]
[1]Hawaii Pacific Neuroscience, Parkinson's And Movement Dis. Center & Center For Neuroscience Diversity, Honolulu, United States of America, [2]University of Hawaii, John A. Burns School Of Medicine, Honolulu, United States of America, [3]University of Michigan, Department Of Biopsychology, Ann Arbor, United States of America, [4]John A. Burns School of Medicine, University of Hawaii, Department Of Quantitative Health Science, Honolulu, United States of America

Aims: Parkinson's disease (PD) is a neurodegenerative disorder caused by dopaminergic cell death and is the second most common neurodegenerative disorder after Alzheimer's. However, a detailed exploration of PD in Asian, as well as Native Hawaiian and Pacific Islander populations (NHPI) has not been well documented. This study aimed to investigate the comorbidities and progression of PD severity among these understudied populations.
Methods: This retrospective study analyzed data from an outpatient neurological care facility between 2017-2022. ICD-10 codes were used to identify PD patients and data was collected through manual chart abstraction. Variables included demographics, date of diagnosis, and original and current Parkinson's medications and dosing. Severity of PD was measured by medication dosage amount and frequency using the Levodopa Equivalent Daily Dosage (LEDD). Descriptive statistics were calculated as appropriate. Additionally, Spearman's rank correlation test was used to identify the relationship between LEDD scores and PD duration.
Results: Overall, 262 patients (48.1% White, 36.6% Asian, 11.5% NHPI, 3.8% Other) were included for analysis. Aside from rates of dementia ($p=0.006$) and alcohol use ($p=0.017$), comorbidities did not vary significantly by race. Mean LEDD score also did not differ significantly by population, but Spearman's rank correlation identified a positive correlation between time from PD diagnosis and LEDD score among Asians ($p<0.001$) and NHPIs ($p<0.001$). Conversely, LEDD scores did not increase significantly among White patients even over a longer disease duration.
Conclusions: PD severity was found to be positively associated with PD duration in both Asians and NHPI. Further understanding of these race-specific differences is essential in managing patient expectations about the progression of their disease and planning interventions.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1459 / #2938

Poster Topic: *Theme K: Patient Care and Support / K02.d. Movement Disorders: Quality of life*

QUALITY OF LIFE IN PATIENTS WITH HUNTINGTON'S DISEASE: THE ROLE OF PATIENTS' AND CAREGIVERS ILLNESS PERCEPTIONS

POSTERS: K02.D. MOVEMENT DISORDERS: QUALITY OF LIFE

Ines Martin
Hospital Clinic de Barcelona, Psychiatry And Clinical Psychology, Barcelona, Spain

Aims: Huntington disease (HD) is a chronic, debilitating genetic disease that affects physical, emotional, cognitive, and social health. The progressive nature of the motor, cognitive, psychiatric, behavioral and functional symptoms of Huntington's disease can cause a deterioration in the perception of the quality of life of patients and their caregivers. Moreover, research suggests that chronically ill patients and their caregivers perceive illness differently, and that these differences have a negative impact on patients' quality of life (QoL). The aim of this study is describe the health-related quality of life in patients with Huntington's disease and caregivers, and assess whether illness perceptions of patients with Huntington's disease (HD) differ from those of their caregivers and affect their quality of life.
Methods: Descriptive cross-sectional study with comparison group of 22 patients with genetic testing for diagnosis and first-degree caregivers. We used the WHOQOL-BREF scale to assess quality of life. It evaluates four areas: physical health, psychological health, social relationships and environment.
Results: Statistically significant differences were found in the perception of quality of life and satisfaction with health status in the group of patients with Huntington's disease compared to the group of caregivers. The most affected areas of quality of life in patients were social relationships and the environment. Also, chronically ill patients and their caregivers perceived illness differently, and that these differences have a negative impact on patients' quality of life.
Conclusions: Due to the complexity of the signs and symptoms of Huntington's disease, the study of quality of life provides a comprehensive and valid evaluation of satisfaction with the state of health and well-being of patients and their caregivers.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1460 / #580

Poster Topic: *Theme K: Patient Care and Support / K02.c. Movement Disorders: Support devices & monitoring*

A SMARTPHONE MONITORING TOOL FOR PARKINSON'S DISEASE AND DEMENTIA: NEU HEALTH PLATFORM

POSTERS: K02.C. MOVEMENT DISORDERS: SUPPORT DEVICES & MONITORING

Kinan Muhammed[1], Francis Chmiel[1], Siddharth Arora[2], Masud Husain[3,4], Michele Hu[3]
[1]Neuhealth Digital Limited, Neu Health, London, United Kingdom, [2]University of Oxford, Somerville College, Oxford, United Kingdom, [3]University of Oxford, Nuffield Department Of Clinical Neurosciences, Oxford, United Kingdom, [4]University of Oxford, Experimental Psychology, Oxford, United Kingdom

Aims: To develop an objective, multi-modal digital platform (Neu Health) aimed at improving the management of patients with Parkinson's disease (PD) and dementia by remotely and objectively capturing digital markers of motor, non-motor and cognitive decline using a smartphone app.
Methods: A software-based platform was built to utilise smartphone sensors that can remotely quantify symptoms associated with PD and dementia. Digital assessments included voice; balance; gait; finger tapping; reaction time; rest tremor; and postural tremor. Cognitive tests measured working memory, processing speed and executive function. 689 healthy controls and 1076 patients with either idiopathic PD or Alzheimer's disease completed the assessments. Clinical scores were also performed including Unified Parkinson's disease rating scale (UPDRS) and Addenbrookes cognitive assessment (ACE-III). Using smartphone derived features, heuristic analysis and random forest machine learning algorithms were developed to estimate clinical scores and predict risk of clinical outcomes.
Results: Individual features derived from smartphone motor tests significantly correlated with corresponding clinical questions from the UPDRS (r ranging from 0.11 to 0.51, $p<0.05$) and were sensitive to daily symptom fluctuations in PD. Digital cognitive tests also correlated with ACE-III ($r>0.52$, $p<0.05$). Smartphone features alone could estimate clinical scores, and future clinical outcomes including the risk of falls, freezing, cognitive decline and functional needs, were predictable 18 months in advance (AUC above 0.7 for all).
Conclusions: It is possible to estimate clinical scores and clinical risk outcomes using remote digital smartphone assessments. The development of a reliable digital platform that combines digital assessment and predictive capabilities could significantly improve the management of patients with neurodegenerative conditions. Future research is needed to evaluate the clinical and service impact of the platform.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1461 / #158

Poster Topic: *Theme K: Patient Care and Support / K02.d. Movement Disorders: Quality of life*

TRAJECTORIES OF OUTCOMES IN NEUROLOGICAL CONDITIONS (TONIC): MOTOR NEURONE DISEASE & PARKINSON'S DISEASE

POSTERS: K02.D. MOVEMENT DISORDERS: QUALITY OF LIFE

Sulev Koks[1], Abigail Pfaff[1], Denise Howting[2], Lewis Singleton[2], Jack Price[2], Carolyn Young[3]
[1]Murdoch University, Centre Of Molecular Medicine And Innovative Therapeutics, Perth, Australia, [2]Perron Institute for Neurological and Translational Science, Perron Institute, Nedlands, Australia, [3]The University of Liverpool, Department Of Neurology, Liverpool, United Kingdom

Aims: Based on the Trajectories of Outcomes in Neurological Conditions (TONIC) from the Walton Centre, Liverpool, [https://www.finders-study.org/tonic] on MS and methodology MND, we are exploring trajectories of patient experience in Parkinson's disease in addition to MND. Both MND and PD are complex diseases where genetic predisposition and environmental factors interact. Our aim is to characterise the less well-understood non-motor symptoms of MND and PD, their influence on quality of life (QoL), seek new potential causative or modulating genetic variants and investigate any possible influence upon non-motor symptoms and translate findings into more comprehensive clinical care.
Methods: A longitudinal design with 6 to12 monthly administration of questionnaires of validated patient-reported outcome measures (PROMs) to people with MND and PD. These encompass domains such as physical functioning, dyspnoea, fatigue, sleep, pain, anxiety, apathy, depression, disability, quality of life, coping, hope, social withdrawal, self-efficacy, self-esteem, stigma, worry, clinical and community communication, and health-related costs.
Genomic analysis involving custom SNP panel, GWAS, WGS, and structural variants, STRs, transposable elements, and RNA sequencing may play a role in disease mechanism, age of onset, progression or phenotype. Recruitment of partners/domestic cohabiters as genetic controls.
Modelling PROMs and genetics to determine the genetic factors that influence the patients' well-being, QoL, and their perception of the disease.
Results: Recruitment is ongoing at present. We have recruited 28 MND participants with 16 controls, and 89 PD participants with 63 controls.
Conclusions: TONIC is a suitable protocol for the complex analysis of the Quality of Life of PD patients, The Combination of patients' reported Quality of Life outcomes with the genomic analysis would give us a unique opportunity to identify the genetic markers for the progression of PD.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1462 / #759

Poster Topic: *Theme K: Patient Care and Support / K02.d. Movement Disorders: Quality of life*

NON-MOTOR SYMPTOMS IN PRODROMAL PARKINSON'S DISEASE ARE LINKED TO REDUCED QUALITY OF LIFE

POSTERS: K02.D. MOVEMENT DISORDERS: QUALITY OF LIFE

Sinah Röttgen[1,2], Marie-Sophie Lindner[2], Aline Seger[1], Johanna Kickartz[2], Kim-Lara Weiß[2], Christopher Doppler[1], Gereon Fink[1], Anja Ophey[3], Michael Sommerauer[2]
[1]Research Center Jülich, Institute For Neuroscience And Medicine, Cognitive Neuroscience, Jülich, Germany, [2]University Hospital Cologne, Neurology, Cologne, Germany, [3]University of Cologne, Medical Psychology | Neuropsychology & Gender Studies, Medical Faculty And University Hospital Cologne, Cologne, Germany

Aims: Background: Isolated REM sleep behavior disorder (iRBD) is the most specific prodromal marker of Parkinson's disease (PD), often accompanied by various non-motor symptoms. In PD, non-motor symptoms are strongly associated with reduced health-related quality of life (hrQoL). **Objectives:** To identify factors linked to poorer hrQoL in patients with iRBD and to compare their hrQoL to healthy control participants (HC) and patients with PD.
Methods: Methods: Sixty-two patients with iRBD (*age:* 66.44±6.14 years), 29 patients with PD (*age:* 67.21±7.23 years), and 19 HC (*age:* 67.57±8.16 years) were included. We administered the 36-Item Short Form Health Survey (SF-36) to assess hrQoL. Additionally, participants underwent a comprehensive clinical evaluation of non-motor symptoms.
Results: Results: The SF-36 total score was significantly lower in patients with iRBD (83.33±16.96) compared to HC (92.29±5.49, U = 390.00, Z = -2.218, p = .027, r = 0.246). Poorer hrQoL in patients with iRBD was linked to self-reported neuropsychiatric symptoms, sleep-wake disturbances, and a higher burden of autonomic symptoms (all r = -.25 to -.76, all p < .05). Multiple regression analysis revealed fatigue and depressive symptoms as significant independent determinants of poorer hrQoL in patients with iRBD (F (5.56) = 51.59, p < .001, adjusted R^2 = 0.81).
Conclusions: Conclusions: This study highlights the importance of non-motor symptoms for hrQoL in prodromal PD, irrespective of motor symptoms. Fatigue and depressive symptoms arise as the most relevant therapeutic targets in the prodromal stage of PD to optimize the patient's quality of life.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1463 / #1619

Poster Topic: *Theme K: Patient Care and Support / K02.e. Movement Disorders: Behavioral & psychiatric symptoms*

MOVEMENT ANALYSIS SYSTEM FOR EARLY RECOGNITION OF CIGNITIVE DECLINE

POSTERS: K02.E. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Gergely Hanczar[1], Bence Borbely[2], Agnes Chripko[2], Andras Horvath[3], Anita Kamondi[3]
[1]Cursor Insight, Head Of Research & Development, London, United Kingdom, [2]Cursor Insight, Research, London, United Kingdom, [3]National Institute of Mental Health, Neurology and Neurosurgery, Neurocognitive Research Center, Budapest, Hungary

Aims: Current early stage diagnostic methods for cognitive decline are not suitable for regular wide scale screening. The Hungarian National Institute of Mental Health, Neurology and Neurosurgery (NIMNN) has partnered with Cursor Insight Ltd. (CI), a deep tech company specialized in movement analysis solutions in order to develop an easy to use screening system based on fine motor movement analysis to make early recognition of cognitive decline accessible to the wider population.
Methods: Digital solution - Dynamic movement components are assessed for predictive power regarding different variants and stages of cognitive decline by implementing the digitized versions of the following tests on a tablet + digital pen setup: handwritten signature; writing down heard numbers; Trail Making Test (A); Benson Figure Copy; Archimedes spiral. Subject groups - 50 clinically tracked patients at various stages of cognitive decline and 50 age matched controls. Expressive features are extracted from fine motor movement dynamics based on anonymized clinical track records.
Results: Results from a pilot study [1] showed that dynamic features of fine motor movements can be used for proper early screening. The current work brought significant improvements to the pilot setup both in terms of usability and data quality and was utilized to discover new predictive fine motor dynamics features for cognitive decline. [1] https://doi.org/10.1016/j.imu.2022.101120
Conclusions: In a collaboration between clinical (NIMNN) and industrial (CI) partners, an easy to use screening system is proposed based on movement analysis that holds the promise of making early recognition of cognitive decline possible and accessible to the wider population.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1464 / #908

Poster Topic: *Theme K: Patient Care and Support / K02.e. Movement Disorders: Behavioral & psychiatric symptoms*

AGE AND GENDER-RELATED DIFFERENCES OF NON-MOTOR SYMPTOMS IN PATIENTS WITH PD IN BULGARIA

POSTERS: K02.E. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Desislava Marinova[1,2], Yoanna Todorova[1,2], Maya Danovska-Mladenova[1,2]
[1]Medical University, Neurology, Pleven, Bulgaria, [2]University Multiprofile Hospital for Active Treatment (UMHAT) "Dr. Georgi Stranski", Neurology, Pleven, Bulgaria

Aims: To evaluate the incidence and age- and gender-related differences of non-motor symptoms (NMS) of patients with PD treated at UMHAT-Pleven.
Methods: A total of 73 patients with Parkinson's disease (44 men and 29 women) were included in this study. The average age was 66.41 (+/- 7.60). The variety of NMS were compiled into 15 main groups and a special questionnaire to encompass all of them was developed. Depression was assessed on the Hamilton scale and cognitive impairment on MMSE and ISAACS scale.
Results: All patients had at least one NMS, with the majority of them showing a combination of multiple NMS. For both groups, the most common NMS were: pain - 79.45%, followed by symptoms of the urinary and gastrointestinal systems - 73.98% each. Statistically significant gender-related differences were shown in the groups of sexual disorders ($\chi 2$= 6.57, Df=1, p= 0.0104) and skin symptoms ($\chi 2$= 6,70 Df=1, p=0.0096), which were more commonly encountered in men. Significant age-related difference was established among respiratory symptoms, as they were more prevalent in older PD patients (age over 71,44years.) (F=5.36, p=00235). Age-related correlation was documented with sensory symptoms as well, which were found primarily among men older than 70 years with incidence 70,31% (F=5,46, p=0.223).
Conclusions: All of our patients reported having NMS of PD, with their severity increasing with age and disease progression. The search for and establishment of dominant NMS is important for the implementation of additional treatment that will surely improve the quality of life of all patients, regardless of age and gender.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1465 / #1876

Poster Topic: *Theme K: Patient Care and Support / K02.e. Movement Disorders: Behavioral & psychiatric symptoms*

DIFFERENCES OF COGNITIVE PERFORMANCE TRAJECTORIES BETWEEN PARKINSON PATIENTS WITH AND WITHOUT IMPULSE CONTROL DISORDERS

POSTERS: K02.E. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Adina Lorena Patru[1,2,3], Lucas Ronat[1], Simona Brambati[2,3], Alexandru Hanganu[1,4]
[1]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Neuroimaging Of Emotions Laboratory, Montreal, Canada, [2]University of Montreal, Department Of Psychology, Montreal, Canada, [3]Centre de recherche de l'Institut de Gériatrie de Montréal, Lingua Lab, Montreal, Canada, [4]University of Montreal, Psychology, Montréal, Canada

Aims: Neuropsychiatric symptoms play a central role in Parkinson's disease (PD) since they are related to a lower quality of life as much as motors symptoms. One of the neuropsychiatric symptoms often seen in PD is impulse control disorder (ICD) with a prevalence of 23%. However, the association of ICD and cognitive performance has been little studied from a longitudinal perspective. The main objective is to characterize cognitive trajectories in PD participants with ICD (PD-ICD) vs. PD participants without ICD (PD-no-ICD).
Methods: Parkinson's Progression Markers Initiative data of 1105 participants with idiopathic PD was analyzed over 4 years of follow-up on average. ICD assessment was based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease short version (QUIP-S) and neuropsychological assessment included Judgment of line orientation, Hopkins Verbal-Learning test, Letter-number sequencing test, lexical fluency, Modified Boston Naming test, Semantic fluency task, Symbol Digit Modalities test, Trail Making test and MoCa. Linear mixed-effects regressions were used to test the longitudinal effect of ICD (interaction between QUIP-S score and time) on each cognitive task. Age, sex, and years of education were considered as covariates.
Results: A higher QUIP-S score for PD participants was associated with a greater decline in the Symbol digit modalities test and the Trail making test part B over time. Also, a higher QUIP-S score for PD participants was associated with worst performance on Hopkins Verbal Learning Test-Revised immediate recall trial 2.
Conclusions: This study suggests that, in PD, the higher the ICDs symptoms, the higher the decline in processing speed, mental flexibility and attention over time. Future studies should also investigate brain morphology changes related to PD-ICD comorbidity and take in consideration PD treatment implications.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1466 / #2907

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

RISK DISCLOSURE IN PATIENTS WITH ISOLATED REM SLEEP BEHAVIOR DISORDER

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Sinah Röttgen[1,2], Ramona Hartung[2], Annette Rogge[3], Eva Schaeffer[4], Michael Sommerauer[1,2]
[1]Research Center Jülich, Institute For Neuroscience And Medicine, Cognitive Neuroscience, Jülich, Germany, [2]University Hospital Cologne, Neurology, Cologne, Germany, [3]Paracelsus Nordseeklinik, Neurology, Helgoland, Germany, [4]Christian-Albrechts University, Neurology, Kiel, Germany

Aims: Isolated REM sleep behavior disorder (iRBD) is an early α-synucleinopathy associated with a high risk for phenoconversion to Parkinson's Disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA). Recently, a debate arose regarding the risk disclosure of these patients regarding the increased risk for phenoconversion to one of the α-synucleinopathies. Studies consulting movement disorders specialists are inconclusive as to whether and, if so, how risk disclosure should be performed in patients with iRBD. Patients with PD were mostly skeptical regarding early disclosure of risk due to the lack of disease-modifying treatment. However, patients with iRBD report that they would have liked to have received prognostic information. Our study aims to answer the question if *active* recruitment of patients with iRBD from the general population is ethically justifiable.
Methods: We designed a questionnaire to assess preferences on risk disclosure that has been dispatched to our growing Cologne iRBD cohort. Patients have been recruited via newspaper advertisements that were followed by thorough telephone screening and, if applicable, polysomnography. After polysomnography-confirmed iRBD diagnosis, patients were invited to our clinical consultation hour at the university hospital of Cologne where we perform yearly follow-ups.
Results: At present, no results are available yet. We anticipate revealing insights into our patients' experiences regarding risk disclosure, as well as preferences for managing risk education in the clinical setting.
Conclusions: This study is the first to retrospectively describe the views of affected individuals who have already been diagnosed with iRBD and were educated in this setting about their increased risk for phenoconversion. The results will provide valuable insights for the recruitment of further iRBD cohorts, which are essential to conduct therapeutic intervention studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1467 / #2180

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

NEUROLOGICAL EXAMINATION OF PATIENTS WITH PARKINSON'S DISEASE THROUGH TELEMEDICINE: A SYSTEMATIC REVIEW

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Efthalia Angelopoulou[1], Evangelia Stanitsa[1], Stella Fragkiadaki[1], Dionysia Kontaxopoulou[1], Evangelia Smaragdaki[1], Kalliopi Vourou[1], John Papatriantafyllou[1], Dimosthenis Pavlou[2], Christos Koros[1], Leonidas Stefanis[1], Sokratis Papageorgiou[1]
[1]Eginition University Hospital, Neurology Department, Athens, Greece, [2]University of West Attica, School Of Topography And Geoinformatics, Athens, Greece

Aims: Individuals with Parkinson's disease (PD) living in remote and underserved areas have limited access to specialized healthcare, due to mobility issues, financial reasons, and long waiting lists. Despite the increasing use of telemedicine, the reliability of the video-based examination remains unclear. The aim of this systematic review is to examine which parts of remote neurological assessment are reliable in PD.
Methods: We performed a systematic search on MEDLINE database using as keywords: "Parkinson's disease", "neurological examination", "virtual", "telemedicine", "teleneurology", "videoconference", and "remote" in various combinations. Clinical studies (observational studies, clinical trials) published until 08/2023 were included.
Results: Among 439 relevant articles, 26 were included. Most parts of the video-based neurological examination in PD are feasible, even in the absence of a third party, including stance and gait –if an assistant device is not required-, bradykinesia, tremor, dystonia, some ocular mobility parts, coordination, and gross muscle power and sensation assessment. Technical issues (video quality, internet connection, camera placement) might affect bradykinesia and tremor evaluation, especially in mild cases, possibly due to their rhythmic nature. Rigidity, postural instability and deep tendon reflexes cannot be remotely performed unless a trained healthcare professional is present. A modified version of incomplete UPDRS-III and an equation lacking rigidity and pull testing items can reliably predict total UPDRS-III. MoCA, UPDRS-II,-IV, Timed "Up and Go", PDQ-39, and NMSQ can be reliably administered remotely, while the remote MDS-UPDRS-III requires further investigation.
Conclusions: Most parts of neurological examination can be reliably performed virtually in PD, except for rigidity and postural instability, while technical issues might affect the assessment of mild bradykinesia and tremor. The combined use of wearable devices may at least partially compensate for these challenges in the future.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1468 / #244

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

WHAT WE KNOW ABOUT FOOD AND PARKINSON'S DISEASE: AN EVIDENCE-BASED EXPLORATION INTO NUTRITIONAL IMPACTS

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Alexandra Armitage
Baylor Scott and White Health, Supportive Palliative Care, Temple, United States of America

Aims: The relationship between nutrition and Parkinson's Disease (PD) is complex yet significant, affecting patient outcomes and quality of life. This presentation offers an over-arching analysis of how various foods and dietary regimes influence PD symptoms and progression.
Methods: A review of existing medical literature was conducted. Findings were organized and synthesized into common themes according to specific food groups and dietary patterns.
Results: Certain foods offer notable benefits for PD patients. We explore beneficial foods which have been shown to have neuroprotective qualities and lower PD morbidity and mortality rates. Fruits and vegetables, especially those rich in flavonoids, can mitigate oxidative stress and neurodegeneration. A fiber-rich diet improves gut health and medication effectiveness, while coffee can lessen PD risk and improve motor skills. There is some evidence that moderate red wine consumption may reduce PD risk due to its polyphenols, while excessive alcohol is neurotoxic. Certain foods should be eaten with caution. Protein-rich foods can interfere with levodopa absorption, so timing protein intake around medication is crucial. Diary has been linked to both an increased risk of developing PD as well as poorer PD outcomes. Examining popular diets, the Mediterranean diet, low in dairy and animal proteins but rich in fresh produce, seems beneficial for PD patients. Both vegan and ketogenic diets have been shown to improve function in PD patients.
Conclusions: Nutritional choices play a pivotal role in PD management and should be considered an adjunct treatment. The presentation aims to arm healthcare providers and patients with actionable, evidence-based recommendations for managing PD through diet. By investing in a deeper understanding of the relationship between nutrition and PD, we open doors to improve symptom management and enhance the quality of life for affected individuals.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1469 / #368

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

PARKINSONISM AS A MANIFESTATION OF STIFF-PERSON SYNDROME

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Mohammad Golzarian, Mehri Salari
shahid beheshti university, Medicine School Of Shahid Beheshti University, tehran, Iran

Aims: We investigate the relationship between anti-amphiphysin antibody with parkinsonism and cortical ribbon sign by reporting 2 cases. Our case series expand the phenotypic spectrum of antiamphyphisin related disorders. We report 2 antiamphiphysin positive cases with parkinsonism. One of them manifested with cortical ribbon's sign beside parkinsonism which has not been reported yet.
Methods: We conducted a systematic review of papers in English indexed in PubMed with no time restriction reporting cases of positive antiamphyphisin. We used the following search terms, either as plain text or as MeSH terms: ("amphyphisin) AND ("parkinsonism" OR "parkinsonian disorder*) , "Autoimmune Diseases of the Nervous System" AND "amphiphysin" , ("stiff-man syndrome" OR "stiff-person syndrome") AND ("anti amphiphisin antibody") , "ribbon sign" AND "antiamphyphisin" , "cortical ribboning" AND "antiamphiphysin" , "cortical diffusion restriction" AND "amphiphysin" , "movement disorder*" AND "antiamphiphysin" , "movement disorder*" AND "neuronal antibod*" , ("parkinsonian disorder" OR "parkinsonism") AND ("neuronal antibod") and "antiamphyphisin". All results of the literature search were reviewed and relevant information was extracted and summarized. References of the included articles were also screened for eligible studies. Finally with duplication a total of 74 records were identified and assessed for eligibility, with 32 articles included in the review, some of these studies reviewed several cases retrospectively 1 additional article was identified via screening of references of articles, with 33 studies finally included in the review.
Results: We ruled out all of differential diagnosis of parkinsonism and cortical ribbon sign and realized that there might be a novel relationship between anti-amphyphisin antibody with parkinsonism and cortical ribbon sign.
Conclusions: Prkinsonism and cortical ribbon sign should be considered as new manifestations in the phenotypic spectrum of antiamphyphisin antibody-related disorders.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1470 / #2081

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

RELATIONSHIP OF COGNITIVE DECLINE WITH GLUCOCEREBROSIDASE ENZYME ACTIVITY AND AMYLOID-BETA DEPOSITION IN DLB AND PD

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Maria Camila Gonzalez Velez[1], Linn Oftedal[2], Johannes Lange[2], Diego Tovar-Rios[3], Ole-Bjørn Tysnes[4], Claire Paquet[5], Marta Marquié[6], Merce Boada Rovira[7], Daniel Alcolea[8], Konrad Rejdak[9], Jakub Hort[10], Cristian Falup-Pecurariu[11], Dag Aarsland[3], Guido Alves[2], Jodi Maple-Grødem[2]
[1]Stavanger University Hospital, Sesam/ Nkb, Stavanger, Norway, [2]Stavanger University Hospital, Stavanger, Norway., The Centre For Movement Disorders,, Stavanger, Norway, [3]Stavanger University Hospital, Centre For Age-related Medicine (sesam), Stavanger, Norway, [4]Haukeland University Hospital, Bergen, Norway, Department Of Neurology, Bergen, Norway, [5]Inserm U1144, Therapeutical Optimization In Neuropsychopharmacology, Paris, France, [6]Ace Alzheimer Center Barcelona, Department Of Artificial Intelligence And Big Data Applied To Neurology, Barcelona, Spain, [7]Ace Alzheimer Center Barcelona, Ace Alzheimer Center Barcelona, Barcelona, Spain, [8]Hospital of Sant Pau, Neurology, Barcelona, Spain, [9]Medical University of Lublin, Department Of Neurology, Lublin, Poland, [10]Second Faculty of Medicine, Charles University, Department Of Neurology, Prague, Czech Republic, [11]County Clinic Hospital, Faculty of Medicine, Transilvania University, Department Of Neurology, Brasov, Romania

Aims: We aimed to investigate the relationship between baseline cerebrospinal fluid (CSF) glucocerebrosidase (GCase) activity and amyloid-beta 1-42 (Aβ42) with longitudinal cognitive decline in two large Dementia with Lewy bodies (DLB) and Parkinson's disease (PD) cohorts.
Methods: DLB (n=122) and PD (n=117) patients were included from the European-DLB Consortium (E-DLB) and the Norwegian ParkWest Study, respectively. CSF GCase activity was assessed using a validated assay and CSF Aβ42 levels were categorized as normal or abnormal based on local reference standards. Information on *GBA1* mutations and the *APOEε4* allele was collected. Patients were divided into tertiles according to baseline GCase activity. Cognitive decline was evaluated using a transformed Mini-Mental State Examination score in a linear mixed-effects model, with adjustments for potential confounders including age, sex, education, and *GBA1* and *APOEε4* status.
Results: Table 1 outlines the cohorts' baseline characteristics. Abnormal CSF Aβ42 levels at baseline predicted greater cognitive decline in DLB (95% CI -1.03; -1.16, p=0.03) but not in PD, a trend persisting after adjusting for demographics and genetic factors. However, this was not significant in PD patients. Conversely, reduced GCase activity at baseline predicted faster cognitive decline in PD patients (95% CI -0.06; -0.01, p=0.02), independent of demographic and genetic factors, but not in DLB patients.
Conclusions: Our study confirms that abnormal Aβ42 levels are associated with accelerated cognitive decline in DLB while decreased CSF GCase activity is associated with accelerated cognitive decline in newly diagnosed PD. These findings provide valuable insights into the clinical presentation and aberrant pathways involving Aβ and GCase in DLB and PD. Future studies with larger cohorts will be needed to compare the effect size of the two biomarkers in the diagnostic groups.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1471 / #2413

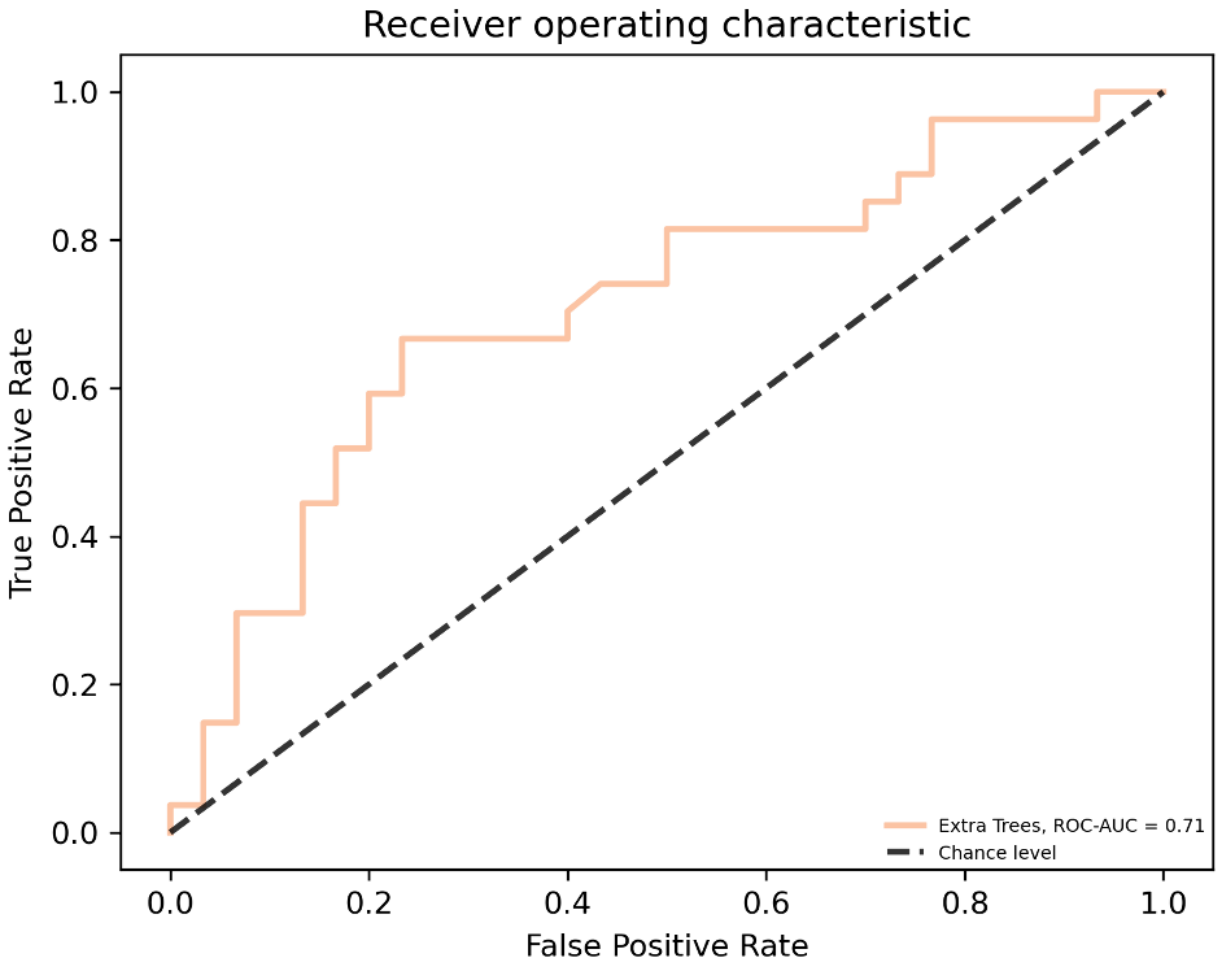
Poster Topic: *Theme K: Patient Care and Support / K02.e. Movement Disorders: Behavioral & psychiatric symptoms*

USING ACOUSTIC SPEECH BIOMARKERS TO DETECT ISOLATED REM SLEEP BEHAVIOR DISORDER

POSTERS: K02.E. MOVEMENT DISORDERS: BEHAVIORAL & PSYCHIATRIC SYMPTOMS

Johannes Tröger[1], Elisa Mallick[1], Sinah Röttgen[2,3], Ebru Baykara[1], Nicklas Linz[1], Tabea Thies[3], Michael Barbe[3], Michael Sommerauer[3]
[1]ki:elements, Research, Saarbrücken, Germany, [2]Research Center Jülich, Institute For Neuroscience And Medicine, Cognitive Neuroscience, Jülich, Germany, [3]University Hospital Cologne, Neurology, Cologne, Germany

Aims: Isolated REM sleep behavior disorder (iRBD) is an early alpha-synucleinopathy and can precede overt motor Parkinson's Disease (PD) for decades. Speech changes have proven to be a robust and sensitive indicator of motor-function and coordination impairment in PD. Recently automatic speech analysis has shown to be an early biomarker of incipient motor dysfunction in individuals with iRBD (Hlavnička et al., 2017). The goal of this research is to evaluate the feasibility of using speech biomarkers to automatically detect iRBD as compared to healthy controls (HC).
Methods: This feasibility research is based on German pilot data with 27 iRBD (4F, mean age = 61,43 ± 8,59) and 30 HC (10F, mean age = 64,67 ± 5,71) with recordings from maximum phonation of the vowel /a/ and fast syllable repetitions of the sequence /pataka/. From the recordings, acoustic features were extracted using the Dysarthria Analyser Software (DYSAN) (Hlavnicka, 2019). We normalized acoustic features for age and gender effects and subsequently trained extra trees machine learning classifiers using leave one out cross-validation and feature selection.
Results: The extra trees model was able to differentiate between iRBD and HC with an AUC of .71 (sensitivity and specificity both around .67). The receiver operating characteristics of all models evaluated can be seen in the figure
below.



Conclusions: The results show that acoustic speech biomarkers could be potentially utilized to screen for iRBD. Future research has to show whether this result persists in a study with a larger population and different languages. Results might impact future applications both in clinical trials as well as healthcare.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1472 / #1957

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

USER EXPERIENCE (UX) SUPPORT: SUCCESSFUL REMOTE ENGAGEMENT STRATEGY FOR INDIVIDUALS AT RISK FOR PARKINSON'S DISEASE IN PPMI

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Lynell Lemon[1], Ken Marek[2], Kim Fabrizio[2], Craig Stanley[2], Bridget Mcmahon[1], Maggie Kuhl[3], Roseanne Dobkin[3]
[1]Institute for Neurodegenerative Disorders, Site Management Core, New Haven, United States of America, [2]Institute for Neurodegenerative Disorders, N/a, New Haven, United States of America, [3]The Michael J. Fox Foundation, Clinical Research, New York City, United States of America

Aims: Describe practices for progressive User Experience (UX) in a remote risk screening study. Discuss strategic use of technology to engage participants through a multi-step digital process. Illustrate the Parkinson's Progression Markers Initiative (PPMI) Smell Test (ST) Direct screening web-based portal design to sustain progressive UX and facilitate study compliance.
Methods: ST Direct engages individuals from the general population aged 60 and older without a PD diagnosis living in the US, Canada, and England. Participants are led to a web portal via QR code or URL and screened for eligibility; contact information is collected and consent is completed online. A smell test is mailed to participants to complete and submit test responses via web-based portal. At launch of study, moderate rates of attrition were observed related to technology and ease of use. The study team then created a vanity URL, added Help Desk phone line access, restructured web-portal features including device platform compatibility, simplified portal page format, and an option to return later. Enhanced communication practices included an adapted smell test instruction sheet and additional reminder emails to address incomplete tasks in the process.
Results: This multi-layer approach provides a reliable mechanism for engagement and progressive UX illustrated in conversion rates from eligible participants to registration at 36% (61,600), registration to consent 62% (38,070), consent to clinical questionnaire 69% (26,168), and smell test sent to submission of smell test data 62% (16,303).
Conclusions: Strategic use of technology and supportive UX throughout the study process may enable investigators to successfully engage and support interested participants, help maximize limited resources, and lead to more cost-effective and efficient clinical trial management of study participants as modes of UX and connection evolve among target populations.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1473 / #1476

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

WORSENING OF EXTRAPYRAMIDAL SYMPTOMS AFTER LIVER TANSPLANTATION IN A PATIENT WITH WILSON'S DISEASE

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Iva Sarac[1], Helena Sarac[2], Fran Borovečki[2], Neven Henigsberg[1,3], Ida Ivek[4], Zdravko Krešić[5]
[1]University of Zagreb, Medical School, HR-Šalata 3, Zagreb, Croatia, Medical School, Zagreb, Croatia, [2]KBC Zagreb, Neurology, Zagreb, Croatia, [3]University of Zagreb, Schoool of Medicine, Psychiatry, Zagreb, Croatia, [4]KBC Zagreb, Internal Medicine, Zagreb, Croatia, [5]General Health Center East, General Practice, Zagreb, Croatia

Aims: Wilson's disease (WD) san genetic disorder which causes symptoms related to excess copper accumulation in various tissues, especially liver and brain. Patients may presented with symtpoms of acute liver failure, while other patients exhibited serious neurological symptoms. Liver transplantation (LT) is recommended only to WD patients with acute liver failure and severe severe neurological symptoms, particularly in patients resistant to pharmacological decoppering therapy. Neurological symptoms improved at a rate of 71.2% after the operation. Worse outcome was described in WD patients with neurological presentations, while reversal of symptoms in patients with persistent neurological involvement is less likely.
Methods: we present the case of 42-yrs old young male affected with WD with hepatic and neurological involvement, who underwent orthopic liver transplantation (OLT) in 2014 for acute liver failure. Clinical, neuroradiological, neuropsychological examination were performed before and after OLT
Results: During the early postoperative period, a worsening of extrapyramidal symptoms (EPS) and balance disturbances were observed. Further worsening of EPS was observed on subsequent control examinations. Control MRI scans (2015-2023) showed diffuse atrophy with pronounced atrophy of basal ganglia around copper deposits and cerebral peduncles.
Conclusions: Acute and then gradual worsening of brain MRI changes in the days after LT in a WD patient, in correlation with the clinical worsening of his EPS, was the most likely consequence of the massive release of copper into the circulation during the operation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1474 / #1294

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

MEDICATION DEVIATIONS, CONTRAINDICATED MEDICATIONS, AND CLINICAL OUTCOMES IN HOSPITALIZED PATIENTS WITH PARKINSON'S DISEASE

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Scott Sperling[1], Jeryl Ritzi Yu[1], Claire Sonneborn[1], Olivia Hogue[1], Debolina Ghosh[2], James Liao[1], Shannon Shaffer[1], Hubert Fernandez[1], Anne Brooks[3], Benjamin Walter[1]
[1]Cleveland Clinic, Center For Neurological Restoration, Department Of Neurology, Cleveland, United States of America, [2]Case Western Reserve, School Of Medicine, Cleveland, United States of America, [3]Parkinson's Foundation, Strategic Initiatives, Miami, United States of America

Aims: Up to 28% of people with Parkinson's disease (PD) are hospitalized each year. We examined the frequency of administered antidopaminergic medications and PD medication deviations between home and inpatient medication regimens, and their associated clinical outcomes, in patients with PD.
Methods: We examined the records of 492 patients with PD who had 725 hospital admissions during a 12-month period. We compared patients' home and inpatient medication administration records to establish the frequency of deviations in levodopa equivalent daily doses (LEDD), omissions of time-critical PD medications, substitutions of levodopa compounds, and administration of antidopaminergic medications. We used logistic regression to assess the relationships between these variables and clinical outcomes.
Results: LEDD deviations occurred in 68% of hospital admissions and 43% of hospital days. Levodopa formulation substitutions occurred in 19% of patients and 22% of patients missed at least one levodopa dose. An LEDD underdose was associated with 78% higher odds of 30-day readmission/death (OR 1.78, 95%CI 1.08-2.93, p=0.025) and every additional day with an underdose was associated with 14% higher odds of 90-day mortality (OR 1.14, 95% CI 1.05-1.24, p=.002). Antidopaminergic medications were administered during 10% of admissions and associated with 85% higher odds of 30-day readmission/death (OR 1.85, 95% CI 1.02-3.45, p=0.041) and over two-fold odds of 90-day mortality (OR 2.2, 95% CI 1.2-4.3, p=0.018). Length of stay (LOS) was associated with LEDD overdose (median 6.5 vs 4.1 days; p<0.001) and the administration of antidopaminergic medications (median 7.6 vs 3.8 days; p<0.0001).
Conclusions: Deviations between patients' home and inpatient medication regimens, and the administration of antidopaminergic medications, were common in hospitalized patients with PD and associated with greater risk of poor outcomes. Specialized PD education and intervention programs for inpatient providers are needed.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1475 / #781

Poster Topic: *Theme K: Patient Care and Support / K02.f. Movement Disorders: Other*

NEURAL CORRELATES OF BALANCE IN PARKINSON'S DISEASE: A SYSTEMATIC REVIEW

POSTERS: K02.F. MOVEMENT DISORDERS: OTHER

Patrick Tait[1], Lisa Graham[1], Rodrigo Vitorio[1], Emily Timm[2], Joanne O'Keefe[2], Tamlyn Watermeyer[3], Samuel Stuart[1], Rosie Morris[1,4,5]
[1]Northumbria University, Sports, Excersise And Rehabilliation, Newcastle upon Tyne, United Kingdom, [2]RUSH medical college, Department Of Anatomy & Cell Biology, Chicago, United States of America, [3]Northumbria University, Psychology, Newcastle upon Tyne, United Kingdom, [4]Northumbria Healthcare NHS Foundation Trust, Northumbria Nhs Foundation Trust, North Shields, United Kingdom, [5]Northumbria University, Sports, Exercise And Rehabilitation, Newcastle upon Tyne, United Kingdom

Aims: An increasing number of studies employ cortical brain-imaging techniques, such as functional near-infrared spectroscopy (fNIRS) and mobile electroencephalography (EEG). Similarly, behavioural studies have evaluated cognitive performance in relation to balance, in people with Parkinson's disease (PwPD). This review aims to provide a comprehensive overview of all studies that have assessed cognitive associations of balance in PwPD, and/or assessed cortical function, using fNIRS and/or EEG, in relation to standing tasks.
Methods: Scopus, PubMed, and ProQuest were searched between January 1980 and December 2022. Two authors (PT & LG) reviewed the search results independently, using pre-established selection criteria detailing the measurement technique, cohort, and balance task/device. I
Results: Behavioural studies generally demonstrate a positive association between cognitive function and performance on balance tasks. Only seven brain-imaging studies met the inclusion criteria, revealing distinct cortical activity in PwPD compared with healthy age-matched controls during standing tasks. PwPD exhibited higher levels of HbO^2 in the prefrontal cortex and greater inter-regional and inter-hemispheric connectivity. Additionally, PwPD with balance issues showed differences in cortical activation patterns, including lower mid-frontal and mid-cerebellar theta-band power, compared to PwPD without balance impairments. This suggests a compensatory mechanism that attempts to redress and ameliorate the postural control issues caused by subcortical dysfunction.
Conclusions: The limited number of studies and lack of standardisation regarding protocols, measurement devices, and data analysis make it challenging to draw concrete conclusions. A nuanced approach that considers all relevant variables regarding protocol and data analysis is recommended. Moreover, the integration of behavioural (cognitive) measures, in addition to objective balance measures, may be a valuable addition to mobile imaging studies.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1476 / #1155

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01a. Neuropathology of Covid-19*

NEUROINFLAMMATION AND -PATHOLOGY IN SARS-COV-2 INFECTED MACAQUES: GLIAL CELLS, NEURODEGENERATION AND PROTEIN AGGREGATION

POSTERS: L01A. NEUROPATHOLOGY OF COVID-19

Juliana Nieuwland[1], Erik Nutma[1], Mirjam Pikaart[1], Ella Zuiderwijk-Sick[1], Elga De Vries[2], Marieke Stammes[1], Jinte Middeldorp[1]
[1]Biomedical Primate Research Centre, Neurobiology & Aging, Rijswijk, Netherlands, [2]Amsterdam UMC, location VU, Medical Cell Biology And Immunology, Amsterdam, Netherlands

Aims: Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) results in respiratory symptoms, yet neurological symptoms are common as well, both in acute phase as well as months later in patients with post-COVID syndrome. With longitudinal PET scans using [^{18}F]DPA714, a tracer for 18 kDa translocator protein, we were able to visualize the onset and progression of inflammation in the brain following a SARS-CoV-2 infection in rhesus macaques. These results together with post-mortem immunostainings showed that more than 7 weeks after infection neuroinflammation is still ongoing in the brains of these animals. Similar results have now been observed in patients with post-COVID syndrome. To investigate how these long-term effects progress and cause further damage in the brain, macaques are infected with various SARS-CoV-2 variants for different time periods.
Methods: Nasal and throat swabs are obtained to detect viral presence and replication, and blood and cerebrospinal fluid for proteomic analyses. Brain tissue is collected for postmortem analyses.
Results: Preliminary data suggests functional and morphological glial cell changes in certain brain regions of SARS-CoV-2 infected monkeys, as well as changes in T cell numbers. In the substantia nigra a decline in the number of dopaminergic neurons is also demonstrated together with alpha synuclein pathology. Moreover, alpha- and phosphorylated synuclein aggregates are seen in the meninges and choroid plexus of infected animals.
Conclusions: Protein aggregation following viral infections has been observed in previous studies, however this research is the first to demonstrate protein aggregation together with neuron decline in the substantia nigra following a SARS-CoV-2 infection. This study provides information on the progression of the neuroinflammatory process and neuropathology and can help to understand mechanisms behind neurological symptoms during COVID-19 and post-COVID syndrome.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1477 / #795

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01c. Neurological manifestations of Covid-19*

OBSERVATIONAL PILOT STUDY ON THE IMPACT OF TRANCRANIAL PULSED STIMULATION (TPS) ON PATIENTS WITH POST-COVID-19 NEUROLOGICAL INVOLVEMENT (LONG COVID).

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

Cristina Guijarro-Castro[1], Miguel Ángel Fernández Blázquez[2], Rubén Sebastián-González[1], Lucía Fernández-Arana[1], Javier Martín[3], Karin Freitag[4]
[1]Clínica DKF, Neuroscience Department, Madrid, Spain, [2]Universidad Autónoma de Madrid, Department Of Biological And Health Psychology, Madrid, Spain, [3]Clínica DKF, R&d Department, Madrid, Spain, [4]Clínica DKF, Rheumatology Department, Madrid, Spain

Aims: Trancranial pulsed stimulation (TPS) has been shown to improve cognitive performance in patients with mild cognitive impairment, and there are already studies with transcranial stimulation that have improved Neuro Long-Covid. With our study, we expect to confirm the usefulness of TPS on the "Neuro-Long Covid", since there is no specific treatment for this entity.
Methods: Observational, blinded, pilot study to verify the safety, usefulness for cognitive impairment in Neuro-LongCovid. This study recruit a total of **20 subjects** aged between 18 and 75 years, diagnosed with Neuro-LongCovid19. All subjects are randomized into either the intervention group or the sham TPS group in a 1:1 ratio. All patients will undergo MRI. The inclusion criteria are the persistence of self-reported cognitive impairment at least after 12 weeks of suffering from Covid19, manifestation of symptoms of Covid19, positive Sars-Cov2 PCR and full recovery from Covid-19 at the time of evaluation. Cognitive impairment are screened using the Montreal Cognitive Assessment (MoCA) test and a self-perception scale of cognitive complaints (EMQ). A neuropsychological evaluation are conducted for all patients, before and after treatment, investigating attention and executive functions (The Trail Making Test, The Symbol-Digit Modalities Test, the Stroop test). Also, we will asses attention (D2 test), episodic memory (Free and Selectively Facilitated Recall Test) and depressive symptomatology (BDI). We also perform evaluations using the Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS), and questionnaires PHQ9 (Patient Health Questionnaire-9) and EuroQoL-5D.
Results: Preliminary results will be presented at the congress
Conclusions: We propose an observational pilot study on the TPS impact as treatment on patients with post-Covid-19 neurological involvement (Long covid). This treatment is safe and without side effects.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1478 / #739

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01c. Neurological manifestations of Covid-19*

EFFECTS OF VIRAL RNA MIMETIC LOXORIBIN ON NEURONAL-GLIA CO-CULTURES

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

Silvija Jankeviciute, Katryna Pampuscenko, Vilmante Borutaite
Lithuanian University of Health Sciences, Neuroscience Institute, Kaunas, Lithuania

Aims: Neurotropic viruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can invade and harm the central nervous system (CNS). Studies show that neurological symptoms linked to SARS-CoV-2 are associated with immune-mediated mechanisms and inflammatory responses affecting the brain, potentially leading to neurotoxicity, and may contribute to neurodegenerative diseases. However, the exact mechanism of viruses induce neurotoxicity remains unclear. To get more insight into mechanisms of viral RNA-induced neurotoxicity, we treated primary rat neuronal-glial co-cultures with RNA-mimetic loxoribine (Lox), a selective Toll-like receptor 7 (TLR7) agonist. TLR7 is vital in recognizing single-stranded RNA viruses triggering immune responses crucial for host defense against viral infections.
Methods: In this study, co-cultures were incubated with 1-100 µg/ml Lox for 24-72 h. The viability, number of neuronal and microglia cells, and phagocytic activity were assessed by fluorescence microscopy.
Results: Our results show that Lox causes concentration-dependent loss of viable neurons without increasing neuronal apoptosis or necrosis. Selective elimination of microglia by treatment of cultures with L-leucine-methyl-ester (LME), prevented Lox-induced neuronal loss suggesting that Lox-induced neuronal loss is microglia-mediated. We found that Lox stimulates microglial proliferation and induces morphological changes such as increased average cell body area in co-cultures. Lox does not affect NO production but stimulates TNF-α production in cell co-cultures after 72h treatment. In microglial monocultures, Lox stimulates phagocytic activity of cells as measured by engulfment of fluorescently labelled latex beads by microglial cells.
Conclusions: In conclusion, our data suggest that viral RNA-mimetic Lox causes microglial activation leading to neuronal loss from mixed neuronal-glial cell cultures. This work was supported by the Research Council of Lithuania, Researcher Groups projects No S-MIP-23-98 (APNEVIR).

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1479 / #1052

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01c. Neurological manifestations of Covid-19*

GENOTOXIC STRESS DRIVES NEUROLOGICAL AND COGNITIVE SEQUELAE OF VIRAL INFECTION IN A NOVEL MOUSE MODEL OF LONG COVID

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

Xinli Tian, Jiyu Li, Hongbo Zhang, Kelsea Keys, Jian Wang, Andrew Yurochko, Xiao-Hong Lu
LSU Health, Pharmacology, Toxicology, And Neuroscience, Shreveport, United States of America

Aims: There are growing concerns arise regarding whether SARS-CoV-2 infection or other emerging viral infections, especially those affecting the population on a pandemic scale, could instigate and propagate neurological and cognitive sequelae (PASC) with the possibility of progress to cognitive decline and neurodegenerative conditions. SARS-CoV-2 and other viral infections have been associated with genotoxic stress and cell senescence. COVID-19 induces molecular markers of brain aging, strongly correlated with cellular responses to DNA damage.These findings align with our earlier research, which found that persistent genotoxic stress is a prominent feature in Parkinson's disease (PD) and Huntington's disease (HD).
Methods: To facilitate the longitudinal study PASCs in vivo, we created a human ACE2 transgenic mouse model with full-length human ACE2 regulatory regions that faithfully recapitulated the structure, tissue distribution, and gene regulation of the human gene. A strategy was developed to model the immunopathology of SARS-CoV-2 infection with signature cytokine storm, ARDS, and characteristic gene expression profiling to facilitate the longitudinal analysis in an ABSL-2 facility.
Results: The mice manifested PASCs and many brain aging-like features, including brain genotoxic stress, cell senescence, autophagy dysfunction, proteotoxicity, long-lasting neuroinflammation, anosmia, and cognitive deficits. Importantly, we have both in vitro and in vivo, indicating that inhibiting genotoxic stress response can effectively lessen acute and PASC-like symptoms.
Conclusions: These results support the hypothesis that viral inflammation inflicted genotoxic stress accelerates brain aging to drive neurological and cognitive post-acute sequelae of SARS-CoV-2 Infection. Our study aims to advance a unique human ACE2 mouse model of PASC for investigating concurrent aging and neurodegenerative processes and will prove advantageous for the development of novel therapeutic strategies targeting aging pathways for preventing and treating PASC.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1480 / #1861

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01c. Neurological manifestations of Covid-19*

POST-COVID19 COGNITIVE DYSFUNCTION: CLINICAL FEATURES AND DETERMINING FACTORS IN A CASE SERIES

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

Antonio Palasi, Jesus Pizarro, Belen Gutierrez, Diana Liebana, Alejandro Ballvé, Olga Maisterra, Manuel Quintana, Paulo Gutiérrez-Rodríguez, Francesc Pujadas, Pilar Delgado
Hospital Universitari Vall d'Hebron, Unitat De Demències, Neurology Department, Barcelona, Spain

Aims: Long COVID (LC) encompasses a wide range of symptoms, with cognitive impairment (CI), fatigue and mood disorders being among the most commonly reported. Our objetives were first to describe the characteristics of the cognitive profile and the symptomatic spectrum associated with the CI in a series of LC patients. Also, an association between subjectively perceived cognitive impairment and objective neuropsychological examination scores was investigated.
Methods: Patients referred to our Dementia Unit between 2020-2022 affected by LC and CI after the COVID-19 infection were selected. Validated questionnaires were used to measure subjective cognitive complaints(MFE-30), fatigue (MFIS), and anxiety/depression symptoms (HADS). All CL symptoms were systematically collected and the patient was evaluated with a neuropsychological examination
Results: 39 patients were recruited for the study, with a predominance of women (66%), an average age of 56.7±10 and MMSE scores of 28.5 (26.3-29). In all patients the infection occurred before receiving the first dose of COVID-19 vaccine. The most common symptomatology associated with CI were fatigue (85.7%), respiratory symptoms (68%), pain (64.3%), and mood disorders (57%). The neuropsychological scores were on average within normal values. However, for attentional, executive (phonetic fluency and cognitive flexibility) and short-and long-term memory were at the low limit. Patients with dizziness were significantly associated with higher subjective CI and mood disorders scores, while those with brain fog with more severe fatigue. There was no association between subjective CI and neuropsychological scores.
Conclusions: CI in LC patients is commonly associated with a wide variety of symptoms. The neuropsychological profile, although within normal limits, could suggest greater impairment of attention, executive and memory functions. In our series, there was no association between the subjective perception of DC and the scores of the neuropsychological tests

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1481 / #601

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01c. Neurological manifestations of Covid-19*

TRANSCUTANEOUS VAGUS NERVE STIMULATION AS A TREATMENT FOR LONG COVID IN FEMALE PATIENTS: A PILOT STUDY

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

Amy Zheng, Benjamin Zhang, Niko Fullmer, Caroline Schnakers, Emily Rosario
Casa Colina Hospital and Centers for Healthcare, Casa Colina Research Institute, Pomona, United States of America

Aims: Long COVID, a post-viral illness affecting 10-30% of COVID-19 patients, presents a wide range of symptoms that persist for months, impacting multiple organs. This condition disproportionately affects female patients and those with pre-existing anxiety/depression, which are also more prevalent in females. The vagus nerve, an essential component of the parasympathetic nervous system, has been implicated in a variety of physiological and neuropsychological functions. In this pilot study, we aimed to explore the potential therapeutic effects of non-invasive transcutaneous vagus nerve stimulation (tVNS) on some of the most common long COVID symptoms.
Methods: 24 female long-haulers underwent 10 daily tVNS sessions remotely, lasting one hour each day. The primary outcome measure was cognition (NIH toolbox), with anxiety, depression, sleep, and fatigue as secondary outcome measures. Assessments occurred at three timepoints: pre-intervention, post-intervention, and 1-month follow-up.
Results: The study found significant pre- to post-intervention improvements with moderate to large effect sizes across all the domains, except for fatigue. Notably, when comparing one-month follow-up data with pre-intervention data, we observed significant improvements across all five domains, including fatigue.
Conclusions: Despite the encouraging results of this pilot study, further research is needed to confirm these findings, investigate the long-term effects of tVNS, and explore the underlying mechanisms responsible for the observed improvements. Moreover, future studies should consider larger samples and the use of control groups to validate the effectiveness of tVNS.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1482 / #2132

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01c. Neurological manifestations of Covid-19*

POST COVID NEUROLOGICAL SEQUELAE

POSTERS: L01C. NEUROLOGICAL MANIFESTATIONS OF COVID-19

Maria Roberta Vazzana[1], Antonia Nucera[2], Michela Papa[3]
[1]grande ospedale metropolitano, Urgency Medicine (mcae), reggio di calabria, Italy, [2]f. spaziani hospital, Urgency Medicine, frosinone, Italy, [3]moscati asl ce, General Medicine, aversa, Italy

Aims: Introduction:The World Health Organization declared the coronavirus a global health emergency because of its rapidly transmissible nature,increasing mortality rate.Long-term sequelae of SARS-Cov-2 infection have become increasingly recognized and need and huge effort to prevent and care.
Methods: We set up a 3 months follow-up of 160 patients,82 women and 78 men,admitted in the Emergency-Medicine-Covid from october 2020 to march 2021.The mean age was 60. Asthenia,fever,cough,myalgia,headache,anosmia,ageusia are the most common primary symptoms.
Results: All the patients performed blood-test,neuroimaging,respiratory and neurological assessment.We noticed a decrease in the laboratory findings inflammatory response.The Chest Ct showed that 70 patients had significant pulmonary fibrosis.80 patients had a neuropsychological conseguences associated with depression,sleep impairment,anxiety,loss of memory and concentration,ageusia,anosmia,headache and asthenia.Patients with pre-existent disease experiencied a worsening,especially those with cognitive decline.
Conclusions: Conclusion:Currently,as we are still experiencing the pandemic and its effects,it is too early to describe the full clinical picture of post-covid syndrome.We need for more long-term clinical follow-up data to prevent long-term sequelae and post-covid Neurological Syndromes.We need ongoing neurological cognitive and affective monitoring of all cases of Covid-19 to formulate relevant prevention and intervention strategies.Finally,the economic impact of this disorder,together with patient care,must be worked out in advance.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1483 / #2134

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01e. CNS invasion of SARS-CoV2*

NEUROLOGICAL INVOLVENT IN COVID-19 INFECTION,DATA FROM A SMALL COMMUNITY HOSPITAL

POSTERS: L01E. CNS INVASION OF SARS-COV2

Maria Roberta Vazzana[1], Antonia Nucera[2], Michela Papa[3]
[1]grande ospedale metropolitano, Urgency Medicine (mcae), reggio di calabria, Italy, [2]f. spaziani hospital, Urgency Medicine, frosinone, Italy, [3]moscati asl ce, General Medicine, aversa, Italy

Aims: Introduction:A comprehensive review of the neurological disorders reported during the current COVID-19 pandemic demonstrates that infection affects the central nervous system,the peripheral nervous system and the muscle.
Methods: In this retrospective,observational study,we enrolled 748 patients,with laboratory confirmed diagnosis of severe acute respiratory syndrome from coronavirus infection.Data were collected from march to may 2020 and from october to april 2021and were estracted from electronic medical records.Neurological symptoms included central nervous system headache, dizziness,impaired consciousness,acute cerebrovascular disease,and epilepsy, peripheral nervous system symptoms ,hypogeusia,hyposmia,hypopsia,and neuralgia,and skeletal muscle injury.Data of all neurological symptoms were checked by a multidisciplinary team .
Results: Of 814 patients admitted to the Urgency Medicine ward 284 were severe and 530 were nonsevere patients.Severe patients were older,and showed less typical symptoms.633patients had neurologic manifestations hypoageusia,hyposmia,neuralgia,headache,29 patients had stroke,2 Myastenic syndrome,2 Guillaime Barre,1 encefhalitis.
Conclusions: Conclusion:The SARS-CoV-2 pandemic has implications for all areas of medicine.SARS-CoV-2 infection is associated with an increased incidence of neurological manifestations .Involvement of the nervous system carries a poor prognosis.The pathobiology of these neuroinvasive viruses is still incompletely known, and it is therefore important to explore the impact of CoV infections on the nervous system.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1484 / #2854

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01d. Comorbidity of Neurodegeneration with Covid-19*

TITLE: "LONG COVID EXACERBATES VASCULAR DEMENTIA VIA ENDOTHELIAL INFLAMMATION"

POSTERS: L01D. COMORBIDITY OF NEURODEGENERATION WITH COVID-19

Grant Talkington[1], Gregory Bix[1], Saifudeen Ismael[2]
[1]Tulane University School of Medicine, New Orleans, LA 70112, United States., Clinical Neuroscience Research Center, Department Of Neurosurgery,, New Orleans, United States of America, [2]1. Clinical Neuroscience Research Center, Department of Neurosurgery, Tulane University School of Medicine, New Orleans, LA 70112, United States., Neuro Surgery, New Orleans, United States of America

Aims: Vascular dementia (VaD), the second most common cause of dementia, is characterized by cognitive decline due to reduced cerebral blood flow and blood brain barrier disruption. Current evidence demonstrates that not only are VaD patients at higher risk of severe COVID-19 illness and mortality, but also that pre-existing cognitive dysfunction/dementia is associated with increased COVID-19 incidence. Conversely, SARS-CoV-2 infection alone worsens dementia-related mild cognitive impairment (MCI) and increases risk of cognitive decline, supported by similar fMRI findings demonstrating hypoperfusion. Therefore, we hypothesize that both vascular dementia and long COVID bear a common vascular mechanism.
Methods: To investigate, we conducted a chronic-phase COVID-19 study utilizing an innovative non-transgenic mouse model with Mouse Adapted 10 (MA-10) strain of SARS-CoV-2 following surgical treatment with bilateral carotid artery stenosis (BCAS) to model VaD. We inoculated 12-week-old C57 mice intranasally with 1x10^4 PFU of MA-10 and followed them to 15 days post-infection. Bulk RNA sequencing on brain tissues and analysis with Ingenuity Pathway Analysis (IPA) was performed.
Results: Bulk RNA sequencing on brain tissues and analysis with Ingenuity Pathway Analysis (IPA) revealed substantial net alterations to several signaling pathways, potentially providing critical insights into the mechanisms underpinning acute and chronic COVID-19 morbidities. Our findings confirm a significant mechanistic interaction between VaD and long COVID, suggesting that existing therapies targeting VaD may also be effective in long COVID.
Conclusions: In conclusion, our study provides compelling evidence that vascular dementia and long COVID share a common pathophysiological basis, likely rooted in vascular dysfunction via endothelial inflammation.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1485 / #717

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01e. CNS invasion of SARS-CoV2*

IDENTIFICATION OF SARS-COV2 SUSCEPTIBLE AREAS IN HUMAN BRAIN: STUDY OF VIRAL ENTRY PROTEINS

POSTERS: L01E. CNS INVASION OF SARS-COV2

Tulika Gupta
Post Graduate Institute of Medical Education and Research, Anatomy, Chandigarh, India

Aims: The Coronavirus Disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which mainly targets respiratory cells. Emerging clinical evidence suggests that neurological involvement is also an important aspect of the disease and the SARS-CoV2 can directly infect neurons and glia. SARS-CoV-2 entry into a target cell requires co-expression of ACE2 (angiotensin-converting enzyme-2) and TMPRSS2 (trans membrane serine protease-2). Relevant literature on human neurological tissue is sparse and mostly focused on the olfactory areas. Therefore, the present study was carried out to map the entire brain for co-expression of afore-mentioned viral entry proteins, along with determining the age-related changes in their expression pattern.
Methods: Methods: Brain tissues samples were collected from cerebral cortex, hippocampus, basal ganglia, thalamus, hypothalamus, brain stem and cerebellum; and were divided into two groups - up to 40 years (n=10) and above 40 years (n=10). Real time PCR and Immunohistochemistry analysis was performed to check the gene and protein expressions, respectively. Finally, immunofluorescence (IF) analysis for co-expression of proteins was done using confocal microscopy.
Results: Evaluation of ACE2 and TMPRSS2 gene expression using real-time PCR indicated their presence in all the regions of the brain studied. Similarly, the Immunohistochemistry using monoclonal antibodies against ACE2 and TMPRSS2, demonstrated their presence in all regions. Cellular location of both could be studied in detail. Further, co-expression of both the proteins was observed in different regions of the brain. Age related changes were most marked in the cerebellum.
Conclusions: The expression of both these viral entry receptors suggests that normal human brain is susceptibility to SARS-CoV-2, perhaps which could be related to the cognitive and neurological impairment that occur in patients.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1486 / #2474

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01f. Epidemiology of Covid-19 in Patients with Neurodegenerative Diseases*

PROJECTIONS FOR PREVALENCE OF DEMENTIA IN 18 GEOGRAPHICALLY DISPERSED EUROPEAN COUNTRIES AND IMPACT OF PREVENTION STRATEGIES: A MARKOV MODELLING STUDY

POSTERS: L01F. EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES

Sara Ahmadi-Abhari[1], Piotr Bandosz[2], Martin Shipley[3], Eric Brunner[3], Mika Kivimaki[3], Abbas Dehghan[1]
[1]Imperial College London, Department Of Epidemiology And Biostatistics, London, United Kingdom, [2]Medical University of Gdansk, Department Of Preventive Medicine And Education, Gdansk, Poland, [3]University College London, Department Of Epidemiology And Public Health, London, United Kingdom

Aims: Accurate projections for dementia prevalence, and estimating the impact of public-health prevention strategies, require statistical-modelling to integrate dynamic calendar-trends in incidence of cardiovascular-disease, dementia, and mortality, and incorporate the period effect of COVID-19 deaths.
Methods: Markov models were developed for Austria, Belgium, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom. Input data were derived from official statistics for population numbers and mortality rates, including COVID-19 deaths over 2020-2022, and from the Survey for Health, Ageing and Retirement in Europe for prevalence estimates, transition-probabilities, and calendar-trends.
Results: Among 289-Million population aged 35+, the pandemic, over 2020-2022, is estimated to have resulted in loss of 16.8M (95% Uncertainty-Interval 12.0M-21.8M) person-years of life (PYL), with 12.6M directly attributable to COVID-19 deaths, including loss of 13.2M PYL free of dementia. Estimated 9·5M (95% UI 8·7M-10·3M) persons lived with dementia in 2019 rising to 10·8M by 2035, thereafter declining to 9·7M by 2050 under continuation of previous trends, accounting for COVID-19 deaths. Demographic changes due to excess COVID-19 deaths do not have a remarkable impact on future projections for dementia prevalence. The highest age-standardised prevalence was observed in Spain and Italy, and lowest in Switzerland, Sweden, and Denmark among the studied countries. If intensified public-health efforts further shift the downward trends in dementia incidence to parallel those achieved for cardiovascular-disease, there will be 1·8M fewer cases of dementia by 2050 and19·7M fewer PYL lived with dementia.
Conclusions: Dementia prevalence is likely to rise for a decade, driven by population ageing. To reduce number of dementiapatients by a fifth, prevention strategies need to be as effective as those have been for cardiovascular-disease.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1487 / #1350

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01f. Epidemiology of Covid-19 in Patients with Neurodegenerative Diseases*

IMPACT OF THE COVID-19 PANDEMIC ON MORTALITY AND LOSS TO FOLLOW-UP AMONG PATIENTS WITH DEMENTIA.

POSTERS: L01F. EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES

Hojin Choi[1], Hyuk Sung Kwon[2], Seung Hyun Kim[3], Kee Hyung Park[4]
[1]Hanyang University College of Medicine, Guri Hospital, Neurology, Guri, Korea, Republic of, [2]College of Medicine, Hanyang University, Neurology, Guri, Korea, Republic of, [3]College of Medicine, Hanyang University, Neurology, Seoul, Korea, Republic of, [4]College of Medicine, Gachon University Gil Medical Center, Incheon, Korea, Neurology, Incheon, Korea, Republic of

Aims: The coronavirus disease 2019 (COVID-19) pandemic, which began to escalate rapidly in South Korea in February 2020, has profoundly impacted healthcare, especially for vulnerable groups such as patients with dementia. We examined changes in mortality and loss to follow-up in patients with dementia using data from the Korean National Health Insurance Services research database.
Methods: Patients with dementia who visited a medical institution with a recorded dementia-related diagnostic code including Alzheimer's disease and received anti-dementia medication between February 2018 and January 2020 were included in this study. We divided the participants into two cohorts: those newly diagnosed with dementia between February 2018 and January 2019 (n = 62,631) and those diagnosed between February 2019 and January 2020 (n = 54,494). We then followed their records for a year, until January 2020 and January 2021.
Results: There was a significant increase in follow-up loss among patients newly diagnosed with dementia during the COVID-19 outbreak; the rate rose from 42.04% in 2019 to 45.89% in 2020. Conversely, we observed no significant change in mortality rates before and after the onset of the pandemic in February 2020. Female sex, younger age, fewer comorbidities, diagnosis of dementia at the Department of Neurology or Psychiatry, and high income were associated with decreased follow-up loss and mortality. Living in metropolitan areas was associated with a decreased follow-up loss.
Conclusions: This study highlights the importance of providing extra attention to dementia patients, particularly in pandemic situations, given their increased risk of losing follow-up.

AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY
International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders
March 5 - 9, 2024 | Lisbon, Portugal + Hybrid
#ADPD2024 | adpd.kenes.com

P1488 / #997

Poster Topic: *Theme L: COVID-19: Impact on Brain Neurodegenerative Diseases / L01f. Epidemiology of Covid-19 in Patients with Neurodegenerative Diseases*

THE IMPACT OF COVID-19 ON DEMENTIA DIAGNOSIS AND TREATMENT: A SWEDISH NATIONWIDE STUDY

POSTERS: L01F. EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES

Minh Tuan Hoang[1], Pol Grau Jurado[1], Shayan Mostafaei[2], Tamar Abzhandadze[1], Minjia Mo[3], Madeleine Åkerman[1], Hong Xu[3], Maria Eriksdotter[3], Sara Ptacek[3]
[1]Karolinska Institutet, Neurobiology, Care Sciences And Society, Stockholm, Sweden, [2]Karolinska Institutet, Department Of Medical Epidemiology And Biostatistics, Stockholm, Sweden, [3]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society (nvs), Karolinska Institutet, STOCKHOLM, Sweden

Aims: To compare the receipt of dementia diagnosis and drugs between pre-, during and post-COVID-19 pandemic periods.
Methods: This observational study employed data of persons with dementia (PWD) registered in the Swedish registry for cognitive/dementia disorders - SveDem (2019-2022). Time of dementia diagnosis was divided into: pre- (2019-Jan-01 - 2020-Feb-29), during (2020-Mar-01 - 2020-Dec-31) and post-COVID-19 pandemic (2021-Jan-01 - 2022-May-01). Outcomes included the basic diagnostic work-up, as is recommended by the Swedish Board of Health and Welfare, individual diagnostic tests and the use of drugs.
Results: There were 19,813 PWD selected for analysis: the pre-pandemic period (n = 8335, 42.1%), during pandemic period (n = 4149, 20.9%) and the post-pandemic period (n = 7329, 37.0%). More than 50% of PWD were living alone at dementia diagnosis in three periods. Compared to the pre-pandemic group, the during pandemic group was less likely to receive lumbar puncture (OR 0.89, 95% CI 0.80 – 0.99), neuropsychological assessment (OR 0.81, 95% CI 0.73 – 0.91), but more likely to get occupational therapy assessment (OR 1.11, 95% CI 1.03 – 1.20). The post-pandemic group had higher likelihood of receiving the basic diagnostic work-up (OR 1.14, 95% CI 1.01 – 1.29), blood analysis (OR 1.88, 95% CI 1.44 – 2.49), CT – MRI (OR 1.22, 95% CI 1.01 – 1.48) and occupational therapy assessment (OR 1.13, 95% CI 1.04 – 1.22). The use of cholinesterase inhibitors and memantine was not different between these periods.
Conclusions: Compared to the pre-pandemic period, chances of receiving the basic diagnostic work-up, blood analysis and CT-MRI were not different during the pandemic, but higher in the post-pandemic period. The prescription of anti-dementia drugs was not different between periods.