AD/PD™ 2023
ADVANCES IN SCIENCE & THERAPY
International Conference on
Alzheimer's and Parkinson's Diseases
and related neurological disorders
March 28 - April 1, 2023 | Gothenburg, Sweden

OD001 / #2390

ON-DEMAND SYMPOSIUM: TDP43- AND C9ORF72-RELATED DISEASES 01
29-03-2023 07:00 - 08:30

THERAPEUTIC RESTORATION OF STATHMIN-2 IN TDP-43 PROTEINOPATHIES

Zevik Melamed
The Hebrew University, Medical Neurobiology, Jerusalem, Israel

Aims: ALS and FTD are associated with cytoplasmic aggregation and nuclear loss of the RNA-binding protein TDP-43 in affected neurons. TDP-43 pathology is found in almost all instances of ALS (>95%) and at least 50% of FTD. We recently identified a new critical role for TDP-43 in regulating expression of stathmin-2 (STMN2), a microtubule-associated protein essential for axonal regeneration. Reduction of TDP-43 suppresses stathmin-2 levels by uncovering a cryptic exon in stathmin-2 pre-mRNA, producing a short non-functional mRNA. Here, we study the precise mechanism through which TDP-43 sustains proper STMN2 pre-mRNA processing and develop therapeutic strategies to restore STMN2 expession in neurons affected by TDP-43 pathology.
Methods: We use gene-editing to identify the regulatory elements through which TDP-43 regulates stathmin-2 pre-mRNA processing. We then use those insights and mice with STMN2 genes edited to contain human STMN2 cryptic splice/polyadenylation sequences to identify therapeutically viable antisense oligonucleotides (ASOs)
Results: TDP-43 binding to a GU-rich region within the cryptic exon 2a is shown to sterically repress usage of the cryptic splice site. Removal of the GU-domain is sufficient to activate STMN2 misprocessing, while steric binding of dCasRx corrects pre-mRNA maturation. We then use those insights and mice gene-edited to contain the non-conserved human STMN2 cryptic exon to demonstrate proof-of-concept efficacy for a ASO injected into CSF, as a therapeutically viable approach to block cryptic splicing and rescue stathmin-2 expression. Further, usage of ASOs in human iPSC-derived motor neurons restores expression of the stathmin-2 protein and rescues axonal regeneration capacity in the absence of TDP-43.
Conclusions: Our data provide evidence supporting stathmin-2 as a potential therapeutic target and establish usage of ASOs to restore stathmin-2 levels in neurodegenerative diseases - especially ALS and FTD affected by TDP-43 pathology.

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OD002 / #1346

ON-DEMAND SYMPOSIUM: TDP43- AND C9ORF72-RELATED DISEASES 01
29-03-2023 07:00 - 08:30

SINGLE MOLECULE DETECTION OF TDP-43 AGGREGATES IN BIOFLUIDS

Emma Sierecki, Beau Nijhuis, Derrick Lau, Eve Jary, Yann Gambin
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Aims: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) diagnosis can be challenging and usually reached years after symptoms onset. Both ALS and FTD lack treatments capable of interfering with the underlying pathological process, highlighting the need for early biomarkers and accurate detection of TDP-43 pathology to enroll patients in clinical trials. Techniques such as Real-Time Quaking-Induced Conversion (RT-QuIC) have demonstrated excellent sensitivity and specificity for diagnostic of neurodegenerative diseases. RT-QuIC assays exist for Synuclein and Tau with proven reliability in different biofluids. Recently, an RT-QuIC was also developed for TDP-43 in CSF, showing the presence of seeding competent fibrils of TDP-43 in ALS and FTD patients.Here, we will demonstrate single molecule detection of TDP-43 aggregates in various biofluids.
Methods: Single molecule counting reveals the actual number of aggregates in biofluids, before any amplification step. This differs from RT-QuIC assays, where cyclic elongation and mechanical breaking of fibrils is used to amplify signal, and where the original number of aggregates, or their properties, cannot be accessed. We also developed a rapid amplification assay to enhance the specific detection of TDP-43, in non-shaking conditions to maintain accurate counting of the number of active seeds. In addition, the technique enables the determination of the "fingerprints" of each aggregates by measuring size (diffusion time) and reactivity to dyes (ThT or other amyloid/aggregate marker). These single molecule counting experiments are performed on a small, plug-&-play 3D printed confocal microscope and accessible to non-specialists.
Results: We will discuss results obtained on the different "strains" of TDP-43 aggregates that can be formed in vitro and found in patients.
Conclusions: The accurate quantification of seeding competent TDP-43 aggregates in biofluids will provide a valuable tool for sub-typing of patients.

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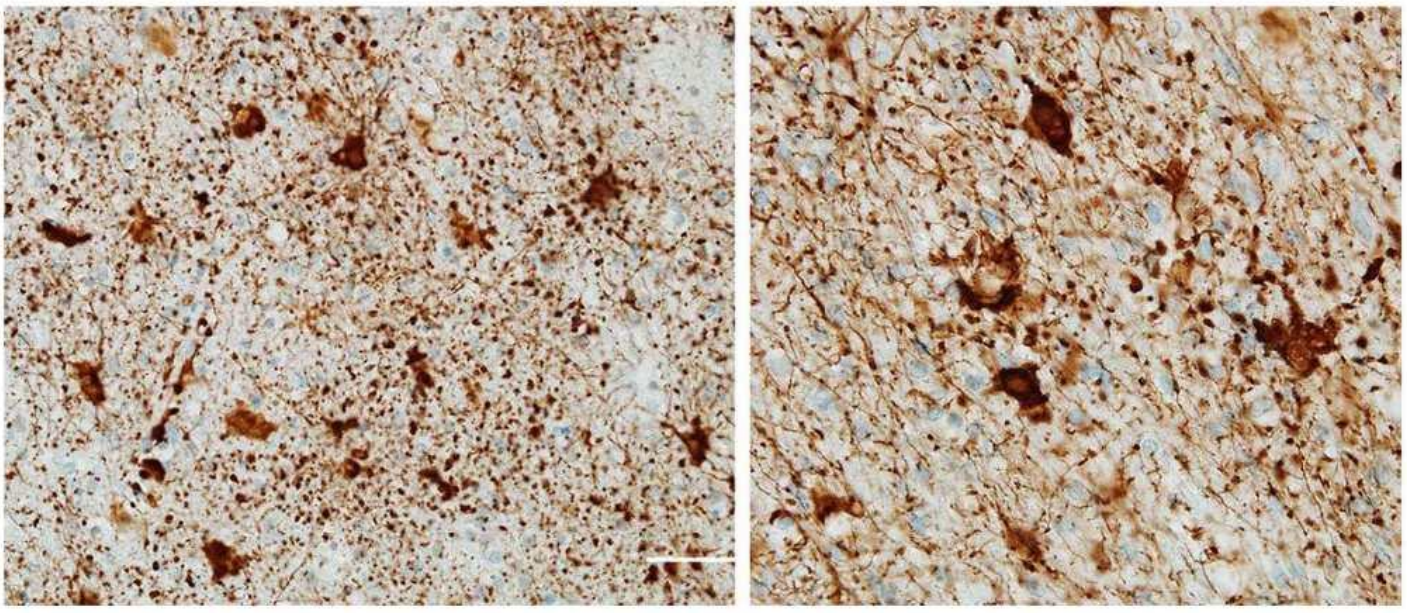
OD003 / #1064

ON-DEMAND SYMPOSIUM: TDP43- AND C9ORF72-RELATED DISEASES 01
29-03-2023 07:00 - 08:30

ASTROCYTIC DEGENERATION IN CHRONIC TRAUMATIC ENCEPHALOPATHY, FRONTOTEMPORAL DEMENTIA AND ALZHEIMER DISEASE: CANDIDATE MECHANISMS AND RELATIONSHIP TO TAU PATHOLOGY

David Brody[1], Caleb Kim[2], Eric Hsu[3], Thomas Esparza[2], Mihika Gangolli[4], Shiran Su[5], Thor Stein[6], Victor Alvarez[6], Russ Huber[6], Ann Mckee[7]
[1]Uniformed Services University of the Health Sciences, Neurology, Bethesda, United States of America, [2]Henry M Jackson Foundation, Research, Bethesda, United States of America, [3]Johns Hopkins, Neuroscience, Baltimore, United States of America, [4]NIH Clinical Center, Radiology And Imaging Sciences, Bethesda, United States of America, [5]Washington University, Neurology, St Louis, United States of America, [6]Boston University, Pathology, Boston, United States of America, [7]Boston University School of Medicine, Neurology And Pathlogy, Boston, United States of America

Aims: Objectives: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with repeated head traumas. We recently reported prominent astrogliosis and astrocytic degeneration in CTE, as well as in frontotemporal dementia (FTD) and Alzheimer Disease (AD) (Hsu et al., Acta Neuropathologica 2018). The objectives of ongoing work are a) to determine the clinical significance of astrocytic degeneration, b) to elucidate the mechanisms underlying astrocytic degeneration, c) to elucidate the relationship between astrocytic degeneration and tau pathology.
Methods: Methods: Quantitative and double-label immunohistochemistry of frontal cortex sections from patients with CTE, FTD, and AD.
Results:



Astrocytic Degeneration in CTE: GFAP Staining. Scale bar 250 microns.

Results: Of 14 patients with CTE, 10 exhibited signs of a degenerating astrocyte pathology, characterized by beaded, broken astrocytic processes (Figure: GFAP:GA5 1:1000). This astrocytic degeneration was typically found diffusely throughout white matter, although two cases demonstrated astrocytic degeneration in gray matter. Astrocytic degeneration was also observed in 2 of 3 AD and 2 of 3 FTD brains, with similar characteristics across diseases. There

was minimal to no astrocytic degeneration in six age-matched controls with no neurodegenerative disease. The extent of white matter astrocytic degeneration was strongly correlated with the level of overall astrogliosis in both the white and gray matter. However, astrocytic degeneration was not quantitatively correlated with the overall extent of tau pathology, even though some degenerating astrocytes were p-tau (AT8) immunoreactive. Double-label immunohistochemistry provided initial evidence for complement membrane attack complex deposition (C9neo), pyroptosis (N-terminal cleaved Gasdermin D), and ferroptosis [iron staining, malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)], in degenerating astrocytes in CTE.

Conclusions: Conclusions: Astrocytic degeneration represents a prominent pathological finding in human CTE, AD, and FTD. Further investigation into the mechanisms underlying astrocytic degeneration could provide new insights into potential diagnostics and targets for therapeutic intervention.

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OD004 / #2347

ON-DEMAND SYMPOSIUM: TDP43- AND C9ORF72-RELATED DISEASES 01
29-03-2023 07:00 - 08:30

ANTI-GLUA3 ANTIBODIES IN FRONTOTEMPORAL DEMENTIA

Fabrizio Gardoni[1], Maria Italia[1], Diego Scheggia[1], Elisa Zianni[1], Michela Salvade[1], Filippo La Greca[1], Antonella Alberici[2], Alberto Benussi[2], Silvana Archetti[2], Alessandro Padovani[2], Monica Diluca[1], Barbara Borroni[2]
[1]University of Milano, Disfeb, Milano, Italy, [2]University of Brescia, Department Of Clinical And Experimental Sciences, Brescia, Italy

Aims: To evaluate in a chronic mouse model of autoimmunity in frontotemporal dementia (FTD) whether and how anti-GluA3 IgG purified from FTD patients trigger synaptic dysfunction and neurodegenerative processes. Moreover, we aim at identifying the association between these events and the appearance of FTD-related neuropathological and behavioural signature.
Methods: Mice were infused with anti-GluA3 IgG isolated from FTD patients for one month through an intracerebroventricular cannula. The model was used to perform morphological and biochemical analyses and behavioural tasks. Moreover, a group of mice was treated with a well-validated AMPA receptors positive allosteric modulator (PAM, CX-1632) as a possible rescue strategy to counteract the detrimental effects mediated by anti-GluA3 IgG.
Results: Data showed that chronic anti-GluA3 IgG administration led to the appearance of FTD-related neuropathological markers and to dendritic spine loss in mice prefrontal cortex. In addition, we identified alterations in sociability and cognition that partially reflect those deficits proper of FTD GluA3+ patients. Most of these alterations were rescued by PAM administration.
Conclusions: Our model allowed to identify the specific contribution of anti-GluA3 autoantibodies to FTD neuropathology and was instrumental to the development of a personalized therapeutic strategy for GluA3+ FTD patients.

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OD005 / #1854

ON-DEMAND SYMPOSIUM: TDP43- AND C9ORF72-RELATED DISEASES 01
29-03-2023 07:00 - 08:30

AMYOTROPHIC LATERAL SCLEROSIS DUE TO MYCOTOXINS CAUSING IMMUNE PARALYSIS REQUIRING IMMUNOTHERAPY.

William Reid
Duke Medical Center, Neurology, Chapel Hill, United States of America

Aims: Treatment of Amyotrophic Lateral Sclerosis with Immunotherapy
Methods: Treatment with 1. Voraconazole, Amphotericin 2. Plasma Pheresis 3. Immunotherapy using Monoclonal Antibodies against Check Point Inhibitors. 4. Immunotherapy using Interleukin 7 and 15 5. Immunotherapy using Interferon 6. Immunotherapy using Gammaglobulin
Results: Treatment of four patients with ALS using Voraconazole and Plasma Pheresis resulting in normalization of labs and temporary recovery of motor function in 3 out of 4 patients. The labs were quantitative urine organic acids, metabolic acidosis and protoporphyrins.
Conclusions: ALS could be secondary to poisoning by neurotoxic and immunotoxic mycotoxins from the fungus, Fusarium. The likely mycotoxin would be trichothecenes such as T-2 Toxin. The likely site of infection would be the upper sinus cavity with T-2 Toxin passing into the midbrain and Pons along the Olfactory and Trigeminal Nerves. Trichothecenes especially T-2 Toxin causes progressive immune paralysis. Reversal of the poisoning would require aggressive antifungals with Amphotericin and Voraconazole and Plasma Exchange. Reversal of immune paralysis requires monoclonal antibodies against PD-1 (Programmed Cell Death-1) such as Nivolumab. In addition immune paralysis causes deficits in Interferon, Interleukin 7 and 15 and Subclass IgG deficiency requiring Gammaglobulin infusions.

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OD006 / #876

ON-DEMAND SYMPOSIUM: TDP43- AND C9ORF72-RELATED DISEASES 01
29-03-2023 07:00 - 08:30

DEVELOPMENT OF PIKFYVE INHIBITORS FOR THE TREATMENT OF ALS

Robert Scannevin, Robert Galemmo, Wendy Liang, Swati Naphade, Chao Wang, Grace Kim, Ekaterina Stomakhina, Lyn Batia, Ningzhe Zhang, Irene Choi
Verge Genomics, Inc., Research And Development, South San Francisco, United States of America

Aims: To identify novel therapeutic targets for ALS, multi-'omics data from patient tissues was analyzed in the CONVERGE™ discovery engine. This effort identified a previously unknown dysregulated gene network centered around endolysosomal biology, and further predicted that inhibition of the kinase PIKfyve would broadly rescue deficits within this pathway and ameliorate motor neuron degeneration in multiple genetic and sporadic forms of ALS. The therapeutic effect of PIKfyve inhibition has been confirmed in preclinical studies, which provides a compelling rationale for clinical investigation for the treatment of ALS.
Methods: PIKfyve inhibitors were characterized in multiple cell-free and cell-based assays to establish potency and in vitro activity. Compounds with desirable properties were further evaluated in ALS patient IPSC-derived motor neuron survival assays to prioritize compounds for in vivo profiling. PK/PD was assessed in a mouse LPS challenge model, evaluating IL12p40 levels as a biomarker of target engagement. Effects in an ALS in vivo model were assessed in rNLS8-TDP-43 mice evaluating biomarkers in multiple compartments. GLP toxicology and safety pharmacology studies were conducted in mice and dogs.
Results: Multiple potent PIKfyve inhibitors exhibited activity in heterologous cell-based assays, and demonstrated significant rescue of viability in ALS C9orf72 and TDP-43 patient-derived motor neurons. Advanced compounds had favorable PK/PD relationships in reducing IL-12p40 after LPS challenge, and also exhibited brain:plasma exposure ratios of >1. In the rNLS8-TDP-43 mouse model, PIKfyve inhibition reduced neurofilament light chain levels and rescued deficits in a lysosome-associated biomarker. The lead compound has demonstrated a favorable safety profile in GLP studies.
Conclusions: PIKfyve inhibition has been confirmed in preclinical studies to ameliorate key pathological processes in ALS-relevant models. A Verge proprietary small molecule PIKfyve inhibitor is anticipated to start clinical studies before the end of 2022.

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OD007 / #2758

ON-DEMAND SYMPOSIUM: TDP43- AND C9ORF72-RELATED DISEASES 01
29-03-2023 07:00 - 08:30

EFFECTS OF PALMITOYLETHANOLAMIDE COMBINED WITH LUTEOLINE ON HIGH FREQUENCY OSCILLATIONS AND GABAERGIC TRANSMISSION IN PATIENTS WITH FRONTOTEMPORAL DEMENTIA

Francesco Di Lorenzo[1], Martina Assogna[2], Sonia Bonnì[2], Ilaria Borghi[2], Elias Casula[2], Caterina Motta[2], Alessandro Martorana[2], Giacomo Koch[2]
[1]IRCSS Fondazione Santa Lucia, Experimental Neuropsychophysiology, Rome, Italy, [2]IRCCS Fondazione Santa Lucia, Experimental Neuropsychophisiology, Rome, Italy

Aims: Introduction: Frontotemporal dementia (FTD) is a presenile neurodegenerative disease for which there is no effective pharmacological treatment. Recently, a link has been proposed between neuroinflammation and FTD. Objective: Here, we aim to investigate the effects of palmitoylethanolamide (PEA) combined with luteoline (PEA-LUT), an endocannabinoid with anti-inflammatory and neuroprotective effects, on behavior, cognition, and cortical activity in a sample of FTD patients.
Methods: Methods: 52 patients with a diagnosis of probable FTD were enrolled. Cognitive and neurophysiological evaluations were performed at baseline and after 4 weeks of PEA-LUT 700mg×2/day. Cognitive effects were assessed by Neuropsychiatric Inventory (NPI), Mini-Mental State Examination, Frontal Assessment Battery (FAB), Screening for Aphasia in Neurodegeneration (SAND), Activities of Daily Living-Instrumental Activities of Daily Living (ADL-IADL), and Frontotemporal Lobar Degeneration-modified Clinical Dementia Rating (FTD-CDR) scale. To investigate in vivo neurophysiological effects of PEA-LUT, we used repetitive and paired-pulse transcranial magnetic stimulation (TMS) protocols assessing LTP-like cortical plasticity, short-interval intracortical inhibition, long-interval intracortical inhibition (LICI), and short-latency afferent inhibition. Moreover, we used TMS combined with EEG to evaluate the effects on frontal lobe cortical oscillatory activity.
Results: Results: Treatment with PEA-LUT was associated with an improvement in SAND, FTD-CDR and ADL/IADL scores. Neurophysiological evaluation showed a restoration of LICI, in particular at ISI 100ms, suggesting a modulation of GABA(B) activity. TMS-EEG showed a remarkable increase of TMS-evoked frontal lobe activity and of high-frequency oscillations in the beta/gamma range. Conclusion: PEA-LUT could improve functional impairment s in FTD patients through the modulation of cortical oscillatory activity and GABA(B)ergic transmission
Conclusions: Conclusion: PEA-LUT could improve functional impairment s in FTD patients through the modulation of cortical oscillatory activity and GABA(B)ergic transmission

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OD010 / #532

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

NOVEL MOUSE MODELS OF ALZHEIMER'S DISEASE CARRYING THE THREONINE 440 AMINO ACID DELETION MUTATION IN PRESENILIN-1

Peyton Fuller, Victoria Collis, Mervyn Monteiro
University of Maryland School of Medicine, Biomet And Anatomy And Neurobiology, Baltimore, United States of America

Aims: Deletion of the 440 threonine residue (D440) in presenilin-1 (PS1) was identified in 2004 as linked to a variant form of Alzheimer's disease with parkinsonism. Autopsy findings indicated cotton wool plaques, Lewy bodies and cerebral amyloid angiopathy in the afflicted brains. Biochemical studies showed that expression of the D440 mutant increases amyloid fragment accumulation and alpha-synuclein insolubility. To our knowledge animal models for the mutation have not been generated.
Methods: Four B6SJL hybrid transgenic mouse lines with Thy1.2 promoter driven expression of human PS1 cDNA carrying the D440 mutation were generated. Two of the lines express PS1 tagged with an HA epitope at the C-terminus whereas the other two, the un-tagged protein. Biochemical, pathologic and behavioral studies were performed to assess the utility of the lines to model the human disease.
Results: DNA sequencing confirmed all four lines carry the mutant D440 trangene. Expression of the transgenic PS1 protein was confirmed by immunoblotting. Although still ongoing, the behavioral results show the D440 lines have a more pronounced age-dependent decline in locomotor activity, time spent in the center of an open field box, rotarod performance, novel object recognition, detection of a change in object location, and in the speed to find and enter the escape tunnel in the Barnes Maze test compared to non-transgenic animals. Examination of their brain tissue by immunocytochemistry and immunoblotting revealed notable changes in amyloid, GFAP, IBA1 and alpha-synuclein immunoreactivity in the four lines. We will present the findings of their more complete characterizations.
Conclusions: The D440 lines may provide new models for AD research.

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OD011 / #673

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

GENOME SEQUENCING VARIATIONS IN THE OCTODON DEGUS, AN UNCONVENTIONAL NATURAL MODEL OF AGING AND ALZHEIMER'S DISEASE

Michael Hurley[1], Claudio Urra[1], Maximiliano Garduno[2], Dante Travisany[1], Marcelo Coba[3], Todd Holmes[2], Xiangmin Xu[2], Patricia Cogram[1]
[1]Institute of Ecology and Biodiversity, Genetics, Santiago, Chile, [2]University of California, Irvine, Center For The Neurobiology Of Learning And Memory, California, United States of America, [3]University of Southern California, Zilkha Neurogenetic Institute, California, United States of America

Aims: The *Octodon degus* is a long-lived diurnal rodent that spontaneously develops molecular and behavioral changes that mirror those seen in human Alzheimer's disease (AD). With age, some degu, but not all individuals, develop cognitive decline and brain pathologies like that observed in AD, including neuroinflammation, hyperphosphorylated tau and amyloid plaques, and AD co-morbidities such as macular degeneration, alterations in circadian rhythm, diabetes and atherosclerosis. Here we report the whole-genome sequencing of the degu genome, which revealed unique features and molecular adaptations consistent with AD.
Methods: 11 outbred wild captive *O.degus* Whole-Genome Sequencing: Illumina NovaSeq 6000 S4 platform at a sequencing depth of 60% by Quick Biology Inc. (Pasadena, CA 91007, USA). A single library was constructed using the TruSeq Nano DNA Kit (Illumina, CA, USA).
Results: The genome was mapped to the degu reference genome (GCF_000260255.1). We identified SNPs in 19 genes associated with AD, including in *Apoe* gene; the degu *Apoe* Mt4 can yield one of three residues at position 213, one of which affects protein structure and function. In XBP1, we identified an INDEL that deletes exon 1, which contains the bZIP domain, possibly affecting DNA-binding and dimerisation functions in the degu that carries this mutation.
Conclusions: Our study's strengths include using an outbred degu population, some of which exhibit the hallmark features of AD, to create a genetic characterisation of this model of late-onset AD. Importantly, we found novel mutations correlated with AD-like phenotypes, thereby identifying a genetic AD susceptibility in the degu. The whole-genome results suggest that, as in the human population, risk factors for AD-like phenotype like Apoe in a subpopulation of wild-type lab-outbred (but not lab-inbred) degu spontaneously develop AD-like neuropathology.

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OD012 / #1574

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

NEW ASSEMBLY AND ANNOTATION OF THE OCTODON DEGUS GENOME. A TOOL TO IMPROVE THE KNOWLEDGE OF ALZHEIMER'S DISEASE.

Dante Travisany[1], Kevin Johnston[2], Maximiliano Garduno[2], Patricio Pezo[3], Xiangmin Xu[4], Patricia Cogram[3]
[1]Universidad de las Américas (CL), Núcleo De Investigación En Data Science, Facultad De Ingeniería Y Negocios, Santiago, Chile, [2]University of California, Irvine, Center For Neural Circuit Mapping, School Of Medicine, Irvine, United States of America, [3]Institute of Ecology and Biodiversity, Genetics, Santiago, Chile, [4]University of California, Irvine, Center For The Neurobiology Of Learning And Memory, California, United States of America

Aims: We present the new genome and annotation of the degu (*Octodon degus*). This long-lived diurnal rodent can develop molecular and behavioral changes that mirror those seen in human aging. Some degu develops brain pathology, and a cognitive drop like that is observed in Alzheimer's disease and aging. Among those are neuroinflammation, hyperphosphorylated tau, amyloid plaques, macular degeneration, cataracts, alterations in circadian rhythm, diabetes, and atherosclerosis. We report a considerable improvement in the genome sequence and the new annotation that will boost this Unconventional Natural Model for Aging and Alzheimer's Disease. The annotation revealed features and molecular adaptations of aging and Alzheimer's disease.
Methods: Two individuals were taken to sequence the whole genome, a male and a female. For each PCR-Free Illumina paired-end library, PacBio HiFi and Oxford Nanopore Technology (ONT) Ultralong Reads were sequenced. A raw coverage of 25x per library per individual was obtained. Each individual was assembled independently using Wengan (Illumina + ONT) and hifiasm (HiFi Reads). Prediction and annotation of gene models were performed using Augustus, PASA, RNA-Seq Libraries, Exonerate, and Evidence modeler. Gene Models were annotated using BLAST+ UniprotKB, NR and EggNOG. BUSCO was used to assess the assembly and annotation completeness.
Results: In comparison with the public assembly (GCF_000260255.1). Our strategy generated a total of 1,610 contigs (259,905 for GCF_000260255.1) with an N50 of 11 Megabases (19,5 Kilobases GCF_000260255.1) and a L50 of 76 (36,018 GCF_000260255.1).
Conclusions: Our sequencing strategy shows an assembly and annotation that outperforms the reference available in public databases and will soon be accessible to the community. We believe that our results will demonstrate that a quality assembly and annotation will boost the Degu as a model and improve the studies of Alzheimerś disease.

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OD013 / #710

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

OVINE MODELS OF ALZHEIMER'S DISEASE

Russell Snell[1], Natasha Mckean[1], Cara Mcmurray[1], Henrik Zetterberg[2], Renee Handley[1], Skye Rudiger[3], Simon Bawden[3], Paul Verma[3], Jen Kelly[3], Richard Faull[4], Suzanne Reid[1], John Pearson[5], John Hardy[6], James Gusella[7], Michael Owen[8]
[1]University of Auckland, School Of Biological Sciences, Auckland, Auckland, New Zealand, [2]Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [3]South Australian Research and Development insitute, Livestock Sciences Division, Adelaide, Australia, [4]University of Auckland, Centre For Brain Research, Auckland, Auckland, New Zealand, [5]University of Otago, Population Health, Christchurch, New Zealand, [6]UCL, Institute Of Neurology, London, United Kingdom, [7]Harvard University, Center For Human Genetic Research, Boston, United States of America, [8]Cardiff University, Division Of Psychological Medicine And Clinical Neurosciences, Cardiff, United Kingdom

Aims: We set out to make sheep AD models. Sheep can be efficiently breed in large numbers and simply maintained in a normal farming situation. Importantly, they naturally develop plaques and tangles as they age. APP, PSEN1&2 including the APP cleavage sites are highly conserved between human and sheep, also sheep are naturally fixed for the APOE4 allele.
Methods: The edited sheep were produced by injection of CRISPR-Cas9 RNP complexes including a single strand donor DNA carrying the PSEN1 E280A or the APP Swedish mutations into single cell zygotes, and implanted. The founder lambs were genotyped by PCR and whole genome sequenced to confirm zygosity and identify off-target editing. Plasma biomarker testing Plasma Neurology 4plexE (Ab40, Ab42, NfL, GFAP) was measured by single molecule array (SIMOA) on an HD-X analyser (Quanterix).
Results: Five founder animals carrying the desired PSEN1 E280A mutation and two founders carrying the APP Swedish mutation were produced. The APP animals are both rams and are heterozygotes. Of the PSEN1 mutation carriers, two ewes are heterozygotes, one a homozygote and two rams carrying the mutation are hemizygotes with frameshift mutations on their non E280A alleles. All animals are outwardly healthy and growing normally. Plasma biomarker analysis of the PSEN1 E280A animals revealed. Aβ1–42:Aβ1-–40 peptide ratios are increased in the mutation carriers as expected. Regression analysis on genotype demonstrated genotype explained over 98% of the variation in the ratios (ANOVA P=1.2e-6).
Conclusions: We have successfully made sheep carrying both targeted mutations and are currently breeding more animals. Hemizygosity for PSEN1 does not appear to be deleterious and the increased Aβ1–42:Aβ1-–40 ratio indicative of disease progression at 5 months of age. These animals are likely to be useful for preclinical pharmaceutical testing.

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OD014 / #1379

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

UNRAVELING THE ROLE OF EXTRACELLULAR VESICLES IN ALZHEIMER'S DISEASE: FROM DISEASE PROGRESSION TO NEUROPROTECTION

Andreu Matamoros Anglès[1], Emina Karadjuzovic[1], Mohsin Shafiq[1], Behnam Mohammadi[1], Feizhi Song[1], Berta Puig[2], Hermann Altmeppen[1], Michaela Schweizer[3], Friederike Zunke[4], Markus Glatzel[1]
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Aims: Extracellular vesicles (EVs) are membranous nano/micro-structures released by most, if not all, cells. EVs carry proteins, lipids, and nucleic acids and participate in cell-to-cell communication. EVs have been related to crucial brain functions, such as myelin maintenance and neurotransmission, but their complete role is unknown. EVs emerged relevant in Alzheimer's disease (AD) and were described as biomarkers in AD patients' serum. EVs trap Aβ, which reduces Aβ-free oligomers load and Aβ-mediated toxicity, thereby exerting neuroprotective functions. Conversely, EVs enhance the propagation of Aβ and Tau aggregates, thus promoting disease progression. Here we will describe in detail the AD-EVs and characterize the main protein actors in their seemingly dual role in AD.
Methods: EVs are isolated from the forebrain of AD patients by differential ultracentrifugation and iodixanol-based density gradient. Here we use an updated non-enzymatic protocol to exclude the digestion of relevant membrane-bounded proteins on the EVs. Nanoparticle tracking analysis, western blotting, and transmission electron microscopy are used to characterize the isolated particles. Transcriptomic and proteomic work-ups analyze their protein profiles. Lastly, the role of differentially expressed proteins in brain-derived EVs biology in AD's pathophysiology is studied using hypothesis-driven experiments in human iPS cell models.
Results: Our optimized EVs' isolation protocol shows two subpopulations of EVs with a similar average mean size. The samples express the EV markers CD81, CD9, and Flotilin-1 and AD-relevant proteins, such as ADAM10 and the prion protein. TEM reveals the expected cup shape of the purified particles. Omics analyses show promising candidates that will be validated using the hiPSC-derived neuronal model established.
Conclusions: Our optimized isolation protocol drastically reduces the generation of proteolytic artifacts. These EVs will be useful to accomplish our primary goal: to achieve better mechanistic insight into EVs' function in AD, especially their neuroprotective role.

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OD015 / #2024

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

LIGATURE-INDUCED PERIODONTITIS POTENTIATED PATHOLOGICAL FEATURES AND EXACERBATED COGNITIVE IMPAIRMENT IN 3XTG-AD MICE

Rachel Pei Hsuan Wang[1], Wai Keung Leung[2], Tetsuya Goto[3], Yuen Shan Ho[4], Raymond Chuen Chung Chang[1,5]
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Aims: Periodontitis, a chronic systemic inflammatory disease, is a common oral health problem in the elderly. With increasing recognition that inflammation plays a key role in the pathophysiology of Alzheimer's disease (AD), we hypothesized that the inflammation processes associated with periodontitis would further increase the inflammatory burden and exacerbate AD pathology in an experimental mouse model of AD.
Methods: To examine the impacts of periodontitis on the onset and progression of AD, 5-0 silk ligatures were placed around the maxillary second molars of six-month-old female 3×Tg-AD mice for a total of 5 weeks. Sickness Behavior and cognitive functions were assessed using open field, spontaneous Y maze, and puzzle box tests. The brains were harvested for further immunohistochemical analysis.
Results: Ligature-induced periodontitis significantly increased periodontal bone loss, which was accompanied by increased total bacterial load and elevated gene expression levels of MCP-1, TNF-a, and IL-1b in the gums. Increased microglial immunoreactivity was observed in the brain of 3xTg-AD mice with ligature placement. Next, we examined whether the heightened neuroimmune responses would potentiate pathological features of AD. Through immunofluorescence staining analysis, significantly greater immunoreactivities of phosphorylated tau396 and % 6E10-immunoreactive area were detected in the cortex and CA1 regions of 3×Tg-AD mice with ligature placement. Lastly, findings from the behavioral tests also revealed that ligature-induced periodontitis exacerbated short- and long-term memory in 3xTg-AD mice.
Conclusions: Our study revealed that ligature-induced periodontitis potentiated pathological features and exacerbated cognitive impairment in 3xTg-AD mice. Taken together, this study provides convincing evidence that systemic inflammation serves as a connecting link between periodontitis and AD. The study was supported by Health and Medical Research Fund (HMRF 04151216) to RCCC.

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OD016 / #1137

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

THE PHARMACOLOGICAL INCREASE OF PROTEIN O-GLCNACYLATION RESCUE ALZHEIMER SIGNATURES IN DOWN SYNDROME MICE: A PROTEOMICS ANALYSIS OF MOLECULAR TARGETS

Chiara Lanzillotta, Antonella Tramutola, Simona Lanzillotta, Francesca Prestia, Fabio Di Domenico
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Aims: Disturbances of protein O-GlcNAcylation have pointed out as a possible link between altered brain metabolism and cognitive decline. We demonstrate the disruption of O-GlcNAcylation homeostasis, as an effect of altered OGT and OGA regulatory mechanism, and confirm the relevance of O-GlcNAcylation in the appearance of Alzheimer disease hallmarks in the brain of a murine model of Down syndrome (DS). Furthermore, we provide evidence for the neuroprotective effects of brain-targeted OGA inhibition (Thiamet G). Therefore, the main goal of this project is to identify brain proteins whose O-GlcNAcylation levels might result significantly modulated by the treatment, thus discovering specific pharmacological targets of thiamet G.
Methods: The neuroprotective effects of the OGA inhibitor, Thiamet G, was evaluated in DS mice by analyzing mice performances through behavioral tests in particular Novel object recognition test (NOR) and Y maze. In addition, by proteomic approach using ESI-MS/MS technique**,** we identified brain proteins whose O-GlcNAcylation levels resulted significantly modulated by the treatment.
Results: Data on DS mice supported the beneficial use of Thiamet G. The rescue of OGA activity was able to restore protein O-GlcNAcylation and reduce AD-related hallmarks and cognitive impairments. In particular, the recovery of global O-GlcNAcylation was associated with the modulation of protein specific O-GlcNAc levels and specifically occours to several components of neuronal architecture, stress response mechanisms and energy production processes.
Conclusions: In summary, our work emphasizes the central role of altered protein O-GlcNAcylation in DS neuropathology and lays the foundations to consider the rescue of protein O-GlcNAcylation as a valuable therapeutic strategy to reduce the alterations of brain metabolism and the development of AD-hallmarks.

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OD017 / #484

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

LEVERAGING GENETICALLY DIVERSE MICE TO UNDERSTAND HOW MICROGLIA IMPACT HIPPOCAMPAL NEURONAL HEALTH IN ALZHEIMER'S DISEASE

Sarah Heuer[1,2], Kelly Keezer[1], Amanda Hewes[1], Kristen Onos[1], Erik Bloss[1,2], Gareth Howell[1,2]
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Aims: Microglia activation and synaptic pruning have emerged as critical events in Alzheimer's disease (AD) that precede cognitive decline, yet the mechanisms involved are not clear. Since previous studies suggest genetic variation governs how microglia prune synapses, we are evaluating the relationship between microglia and neuronal structures in hippocampal CA1 using two genetically distinct AD mouse models that show divergent measures of microglia states and cognitive behavioral assays.
Methods: We labeled hippocampal CA1-to-frontal cortex projection neurons in young (3 month) inbred (C57BL/6J [B6], cognitively susceptible) and wild-derived (PWK/PhJ [PWK], cognitively resilient) female mice containing transgenic (*APP/PS1*) or wild-type (WT) alleles driving amyloid pathology. At 4 months, we placed 50% of the mice on diet formulated with the CSF1R inhibitor PLX5622 to deplete microglia until 8 months of age (previously determined as peak disease activity time-point). Terminally we quantitatively analyzed CA1 projection neurons for density and morphology of postsynaptic dendritic spines at basal, oblique, and tuft domains.
Results: We observed strain differences in spine density and morphology, particularly in the oblique dendritic domain. This included increased density in B6.*APP/PS1* transgenic (TG) mice compared to WT animals, but no changes in PWK mice regardless of genotype. Additionally, B6.*APP/PS1* TG mice reduced oblique spine density to WT levels with PLX5622 treatment, whereas PWK.*APP/PS1* mice did not change with PLX5622 treatment.
Conclusions: We found that genetic context is important for the CA1 excitatory neuron response to microglia depletion using one cognitively resilient and one susceptible AD mouse strain. Future work will leverage single nuclear transcriptomics to identify strain-specific genes that are altered in response to microglia depletion, providing insights into microglia-neuron interactions causing diverse AD cognitive phenotypes.

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OD018 / #775

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

EARLY CA3-CA1 SYNAPSE MISTUNING IN APPNL-F MOUSE MODEL OF ALZHEIMER'S DISEASE.

Benjamin Portal[1], Per Nilsson[2], Maria Lindskog[1]
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Aims: Despite hundred years of research, there are today no treatments available for Alzheimer's disease (AD). It is therefore urgent to identify new pharmacological targets. Whether the late phases of the disease are well described, early stages (before Aβ-plaques) remain yet to be explored. This study uses the APP^{NL-F} mice model of AD, carrying two disease-causing mutations, to investigate synaptic impairement at an early stage of the disease.
Methods: Acute hippocampal slices of six-months old mice were used for electrophysiological recordings. Field recordings in area CA1 after Schaffer collateral stimulations in area CA3 was used to investigate synaptic plasticity. Patch-clamp recordings of pyramidal cells in area CA1 to study synaptic transmission. Western-blot and immunohistochemistry were used to understand molecular changes.
Results: Six-months old APP^{NL-F} mice display an overall synaptic mistuning in the hippocampus, compared to wild-type controls. The frequency of miniature synaptic potentials was significantly reduced. Moreover, an LTP inducing protocol that was sub-thresholded in slices from wild-type mice, could still evoke LTP in slices from APP^{NL-F} mice. In line with synaptic mistuning, APP^{NL-F} mice had increased levels of NMDA receptors and ERK in the hippocampus. Interestingly, ketamine 5mg/kg i.p delivered 24h prior recording, restores part of the synaptic activity as well as the LTP inducing threshold.
Conclusions: This study shows a synaptic mistuning at early stages of the AD pathology, associated with an increase in NMDA receptors and ERK. Both of them are well known to be important for synaptic tuning and plasticity. Interestingly, such mistuning is partly corrected by non anesthetic low-dose of ketamine administered 24h prior recording. Further studies are yet required to better understand behavioral consequences of the observed neuronal impairments as well as a longer treatment with ketamine.

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OD019 / #2647

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

CETP INHIBITOR EVACETRAPIB SHOWS BENEFICIAL EFFECTS IN AN AD MOUSE MODEL

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Aims: High plasma cholesterol levels increase the risk of Alzheimer's disease (AD). The **cholesteryl ester transfer protein (CETP),** which increases cholesterol levels in low-density lipoproteins, has been associated with decreased AD risk. Thus, we **hypothesize** that CETP activity in an AD mouse model of amyloidosis will lead to cholesterol accumulation in the brain, reduced cholesterol excretion, increased production of amyloid-beta (Aß) peptides, and poor cognitive performance. Further, we propose that CETP inhibition will improve the symptoms of AD or prevent its pathology.
Methods: Wildtype (WT), McGill-Thy1-hAPP (hAPP), hCETPtg, and double-transgenic (hAPP/hCETPtg) mice fed a high cholesterol diet were injected daily i.p. with 30 mg/kg of evacetrapib or vehicle at 11-weeks of age for 10-weeks. Behaviour analyses and biochemical analyses were performed at 21-weeks of age.
Results: As expected, hAPP and hAPP/hCETPtg mice showed cognitive impairment. Interestingly, evacetrapib rescued cognition in hAPP/hCETPtg mice. Good cognition correlated positively with higher HDL and lower LDL levels, but APP and Aß levels did not correlate with cognition. A ~25% cholesterol increase was found in hAPP mice brains and ~16% more cholesterol in hCETPtg mice on vehicle as compared to WT. Intriguingly, hAPP/hCETPtg mice on vehicle also only had ~16% higher cholesterol despite expressing APP indicating that CETP dominates the cholesterol load. Importantly, hCETPtg and hAPP/hCETPtg mice on evacetrapib had even higher cholesterol levels at ~38% above WT. Thus, CETP inhibition with evacetrapib increased cerebral cholesterol content against our hypothesis and was effective in rescuing cognitive performance.
Conclusions: We show that the relationship between brain cholesterol and cognition is more complex than a linear relationship; high brain cholesterol levels alone do not impair cognition. We expect that decreasing cholesterol dysfunction by drug repurposing CETP inhibitors will ameliorate AD pathology.

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OD020 / #1768

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

EARLY ASTROCYTE-RELATED CHANGES IN THE TGF344-AD RAT

Andreia Rocha[1], Luiza S. Machado[1], Carolina Soares[1], Pamela Ferreira[2], Bruna Bellaver[2], Peter Kunach[3], Pedro Rosa-Neto[3], Diogo Souza[1], Kim Green[4], Eduardo Zimmer[5]
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Aims: Imaging and fluid biomarkers have helped to reconceptualize Alzheimer's Disease (AD) as a continuum. However, the biological interpretation of many AD biomarkers remains under investigation. In this context, animal models mimickin the AD dynamic biomarkers cascade present high translational value and can be used to refine our interpretation of biomarker findings. In light of this, we longitudinally evaluated [^{18}F]FDG-PET imaging, behavioral, cerebrospinal fluid (CSF) glial and immune biomarkers in the TgF344-AD rat, a model harboring human APP/PS1 mutations.
Methods: TgF344-AD rats and wild-type littermates were longitudinally evaluated at 3, 6, 9, and 12 months of age. Rats underwent [^{18}F]FDG-microPET scans, behavioral tasks and CSF samplings. CSF glial and immune markers were measured by multiplex-ELISA. A cross-sectional cohort was used to measure cortical glutamate uptake at the same time-points. Further examination of astrocyte proteins immunocontent was conducted at 9mo.
Results: At 3mo, 6mo and 12mo, no changes in [^{18}F]FDG metabolism were found. At 9mo, we identified a significant cortical hypermetabolism in the TgF344-AD and a decline in their alternance performance in the Y-maze task. CSF GFAP levels were elevated at 6mo and 9mo of age, while CSF S100B was decreased at 9mo. Additionally, the cortical glutamate uptake and GFAP cortical immunocontent were increased at 9mo and 12mo. CSF inflammatory markers (sTREM2, IL-6, TNF-α, IL-10) were not altered in any of the ages evaluated.
Conclusions: Our results suggest that the TgF344-AD model presents an early cortical glucose hypermetabolism, biomarker evidence of reactive astrogliosis and spatial memory impairment. At the same age, we identified abnormalities in astrocyte glutamate uptake. Due to the critical role of astrocytes in brain glucose handling, our findings suggest that astrocyte reactivity could be driving glucose hypermetabolism and memory impairment.

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OD021 / #2140

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

AGE-ASSOCIATED HIPPOCAMPAL TRANSCRIPTOMIC PROFILES IN APP/PS1 MICE

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Aims: Aging is the most significant risk factor for Alzheimer's disease (AD). However, age-linked cellular events which correlate with AD onset and progression remains incompletely understood. To unravel relationships between immunity, cell signaling, and aging composite, hippocampal tests were performed in aged transgenic APP/PS1 mice.
Methods: Functional and pathway enrichment analyses of immune response genes in hippocampus were performed at 4, 6, 12, and 20 months in APP/PS1 mice. Analyses were made with RT^2 Profiler mouse innate and adaptive immune arrays.
Results: Ingenuity pathway analysis (IPA) comparisons demonstrated significant enrichment in inflammatory, oxidative, and cellular activation pathways. These included triggering receptor expressed on myeloid cells 1 (TREM1), Th1, NF-κB, IL-17, nitric oxide production, acute phase responses, and T cell receptor signaling. Each of these pathways were reduced at 6 months while increased at 12 months. At 20 months, TREM1, pro-inflammatory factors, and NF-κB signaling pathways were increased. Gene ontology (GO) annotation examined at 12 and 20 months showed 75% enrichment of spontaneous hydrolysis of the C3 thioester linked to the complement cascade. This inflammatory signature was linked to progressive AD pathologies.
Conclusions: The results demonstrate immune, inflammatory, and oxidative stress signatures associated with progressive AD pathologies.

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OD022 / #596

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

RUNNING EXERCISE ENHANCES THE STRUCTURE AND FUNCTION OF MENINGEAL LYMPHATIC SYSTEM AND DECREASES AMYLOIDOSIS IN 5XFAD MICE

Onanong Mee-Inta[1], Chin-Fang Hsieh[2], Chih-Chung Huang[2], Ping-Ching Wu[2], Yu-Min Kuo[3]
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Aims: The meningeal lymphatic system, a route for waste products transported out from the brain, has been implicated in the pathogenesis of Alzheimer's disease (AD). Exercise is known to delay AD progression. Whether exercise affects the function of the meningeal lymphatic system remains unclear.
Methods: 5xFAD mice, a mouse model for AD amyloidosis, were subjected to running wheel exercise from 3- to 6-month-old, representing the initial and accumulating phases of amyloidosis. The flow of the meningeal lymphatic system was real-time monitored by injecting the FePt/PLGA nanoparticles into the lateral ventricles and detecting their signals at the deep cervical lymph nodes by high-frequency ultrasound.
Results: The amounts and speeds of the FePt/PLGA nanoparticles traveling from the lateral ventricles to the deep cervical lymph nodes decreased as the age of 5xFAD mice increased from 3 to 6 months. Such decreases were not evident in wild-type littermates. Bilateral ligation of the afferent lymphatic vessels of the deep cervical lymph nodes increased amyloid plaque loads of 5xFAD mice. Compared to the same age (6-month-old) sedentary mice, the size and function (i.e. amount and speed of the FePt/PLGA nanoparticles) of the meningeal lymphatic vessels were increased after 3 months of running exercise. The amounts of amyloid plaque loads were decreased in the exercise group.
Conclusions: Running exercise can be an alternative therapeutic strategy to delay amyloidosis by enhancing the structure and function of the meningeal lymphatic system.

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OD023 / #650

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

IN VIVO VALIDATION OF LATE-ONSET ALZHEIMER'S DISEASE GENETIC RISK FACTORS IN MOUSE MODELS

Michael Sasner[1], Adrian Oblak[2], Kevin Kotredes[1], Dylan Garceau[1], Cynthia Ingraham[2], Bridget Perkins[2], Christoph Preuss[1], Ravi Pandey[3], Asli Uyar[3], Bruce Lamb[2], Gareth Howell[1], Greg Carter[1]
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Aims: Genome-wide association studies have identified over 70 genetic loci associated with late-onset Alzheimer's disease (LOAD), but few candidate variants have been functionally assessed for disease relevance and mechanism of action. One goal of the MODEL-AD program is to develop and characterize novel LOAD mouse models for preclinical testing by combining these common, low-risk genetic variants.
Methods: Candidate genetic risk variants were informatically prioritized and individually engineered into a LOAD-sensitized mouse model that carries the AD risk variants APOE4 and Trem2*R47H. Potential disease relevance of each model was assessed by comparing brain transcriptomes measured with the Nanostring Mouse AD panel at 4 and 12 months of age with human study cohorts.
Results: We created novel LOAD models for 12 coding and loss-of-function risk variants. Transcriptomic effects from multiple genetic variants recapitulated a variety of gene expression patterns observed in human LOAD cohorts. Specific models matched to emerging molecular LOAD sub-types. We have prioritized variants in *Plcg2*, *Abca7* and *Mthfr* loci for deeper analysis.
Conclusions: These results provide an initial functionalization of 12 candidate risk variants and identify potential preclinical models for testing targeted therapeutics. Ongoing studies include: comprehensive phenotyping of a subset of these models out to 24 months of age, including transcriptomics and proteomics, neuropathology, biomarkers and *in vivo* imaging; creation of combinations of risk alleles based on initial transcriptomics signatures; incorporation of humanized Aβ and tau alleles; and use of environmental risk factors such as high-fat diet.

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OD024 / #2663

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

SINGLE CELL GENOMICS AND EPIGENOMICS IN AN ALZHEIMER'S MODEL AND ELOVANOIDS AS EPIGENETIC MODULATORS AT DISEASE ONSET

Nicolas Bazan[1], Surjyadipta Bhattacharjee[1], Gethein Andrew[1], Marie-Audrey Kautzmann[1], Marianne Schultzberg[2]
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Aims: We are identifying cell-specific responses activated at the onset of AD and PD and exploring elovanoids (ELVs; stereospecific dehydroxylated C32:6,n-3 and C34:6,n-3) as guardians sustaining telomere integrity, senescence programming, and epigenome modulation, including DNA methylation in uncompensated oxidative stress (UOS), erastin (ferroptosis) or oligomeric amyloid-beta (OaB) peptide. Additionally, we identified genomic, epigenomic, and CpG islands perturbations at the single cell level in an AD mouse model.
Methods: We used human neuronal/glial in cultures as well as 2-month-old App-KI (*App*$^{NL-G-F}$). DNA methylation profiles were measured using Illumina Infinium bead chip array, and single cell transcriptomics analyzed with 10xGenomics multiome (sn-ATACSeq + sn-RNASeq).
Results: ELVs act as epigenetic regulators reflected in 5-methyl-cytosine that, in turn, is modified iteratively by the ten-eleven translocation family of proteins to produce oxidation products 5-hydroxymethylcytosine and 5-formylcytosine. We explored UOS, erastin to perturb ferroptosis, or OaB in human neurons. We found that ELVs (200 nM) protect dendrites, thwart senescence-associated secretory phenotype gene programming, and restore hyperphosphorylation at Tau: Thr181, Thr217, Thr231, and AT8 (Ser202, Thr205). Moreover, ELVs counteract DNA methylation, histone methylation/acetylation at H3K9, and H3K27 and protect telomere length attrition. Moreover, with methylation bead chip array, we found differentially methylated CpGs between WT and App-KI cortex and hippocampus. Single cell transcriptomics also reveal marked changes in gene expression and differential up/downregulation of neuronal and astrocytic genes between WT and App-KI cortex and hippocampus. The chromatin accessibility peaks were different among various genes in cell clusters in WT and APP-KI hippocampus.
Conclusions: ELVs counteract cell damage; are neuroprotective; modulate transcriptome architecture to induce neuronal cell survival; modulate the epigenomic landscape and downregulate senescence gene programming, autophagy, extracellular matrix remodeling, and inflammaging.

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OD025 / #1754

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

AGE, SEX, AND APOE GENOTYPE MODIFY THE PROGRESSION OF SARS-COV-2 INFECTION AND ENSUING NEUROINFLAMMATION IN MOUSE MODELS

Ling Li[1], Venkatramana Krishna[2], Holly Korthas[1], Susanna Var[3], Allison Chang[4], Walter Low[3], Maxim Cheeran[2]
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Aims: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes the worldwide Covid-19 pandemic. While SARS-CoV-2 can infect people of all ages and both sexes, senior populations are at greatest risk of severe disease and worse outcomes and sexual dimorphism in Covid-19 has been reported. Covid-19 causes damage to multiple organ systems, including the brain. Neurological symptoms are widely observed in patients with Covid-19, with many survivors suffering from persistent neurological impairment, potentially accelerating Alzheimer's disease (AD). Further, people carrying the APOE4 gene, the greatest genetic risk factor for late-onset AD, are more susceptible to SARS-CoV-2 infection than APOE3 carriers. This study aims to investigate the mechanisms underlying the impact of age, sex and APOE genotype on outcomes of SARS-CoV-2 infection using mouse models.
Methods: Wild-type C57BL/6 and humanized APOE4/APOE3 mice were subjected to intranasal inoculation of SARS-CoV-2 lineage B.1.351, followed by daily body weight monitoring. At 7 dpi, viral burden and inflammatory cytokine/chemokine responses in the lung and brain were determined by quantitative RT-PCR, followed by immunohistochemical and transcriptomic analyses.
Results: Older age, male sex, and APOE4 genotype increased lung viral loads and severity of SARS-CoV-2 infection in mice. No viral RNA was detected in the brains of infected mice but IL-6 and CCL2 mRNA increased significantly, particularly in brains of old and APOE4 mice. Immunohistochemical and transcriptomic analyses are underway to identify molecular networks underlying the impact of SARS-CoV-2 infection and its interactions with age/sex and APOE on neuroinflammation and related pathways.
Conclusions: These findings demonstrate that SARS-CoV-2 infection triggers neuroinflammatory responses despite the lack of detectable virus in the brain. Furthermore, age, sex, and APOE genotype modify the progression and outcome of SARS-CoV-2 infection.

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OD026 / #2795

ON-DEMAND SYMPOSIUM: ANIMAL MODELS FOR AD
29-03-2023 07:00 - 08:30

LONGITUDINAL TRANSCRIPTOMIC SIGNATURES ACROSS GENETICALLY DIVERSE MOUSE MODELS OF ALZHEIMER'S DISEASE STRATIFY BY SPECIFIC IMMUNE AND METABOLIC PROCESSES

Asli Uyar, Kelly Keezer, Michael Sasner, Greg Carter, Gareth Howell, Kristen Onos
The Jackson Laboratory, Research, Bar Harbor, United States of America

Aims: Common mouse models of Alzheimer's Disease (AD) generated on a single inbred strain do not recapitulate the spectrum of molecular and neuropathological phenotypes observed in the disease. To better represent phenotypic diversity in AD, we introduce genetically diverse mouse strains harboring the *APOE4* allele and amyloidogenic mutations. In this longitudinal study, we aimed to dissect transcriptomic signatures associated with amyloid and late-onset risk factors throughout the course of aging and within the context of genetic diversity.
Methods: Cohorts of mice carrying the mutant APP/PS1 transgene with or without humanized APOE4 were generated on C57BL/6J (B6), WSB/EiJ (WSB) and PWK/PhJ (PWK) strains. Brains were collected at multiple age points (4, 8, 14 and 18-months) for RNA-seq transcriptomic profiling and neuropathological assessment. Data analysis focused on the age-, sex-, strain-, amyloid- and APOE-status for differential gene expression, pathway enrichment and human-relevant comparisons. Neuropathology assessed the presence and severity of cerebral amyloid angiopathy (CAA) and parenchymal amyloid deposition, neuronal cell counts and microglia activation states.
Results: There were significant strain differences detected as early as 4 months across the panel. This was reflective of neuroimmune response in B6 and PWK, and metabolic alterations in WSB strains. WSB.*APP/PS1* mice showed an accelerated aging signature and consistent with neuropathology, a downregulation in genes enriched for synaptic signaling across multiple neurotransmitter systems. In contrast to B6 and WSB, APOE4 caused the greatest transcriptomic change in PWK.
Conclusions: These findings highlight genetic diversity is a key determinant of phenotypic heterogeneity across multiple pathways in mouse models of AD. Stratification of gene expression changes across this panel will allow better alignment to disease subtypes in human AD patient populations, and help to identify the appropriate model for preclinical studies.

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OD027 / #1467

ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

THALAMOCORTICAL DYSRHYTHMIA IN PATIENTS WITH DELIRIUM: A MULTICENTER-COHORT STUDY

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Aims: Delirium is an acute clinical syndrome, characterized by confused thinking and reduced awareness of the environment due to fluctuations in vigilance, attention, and other cognitive functions possibly related to thalamo-cortical dysrhythmia (TCD). It is particularly prevalent during hospitalization, especially in elderly. In elderly patients with intact cognition, delirium during the hospitalization may be due to TCD detected by on-going electroencephalographic (EEG) activity. The study aim was to identify compressed spectral array (CSA) markers of resting-state electroencephalogram (rsEEG) rhythms related to delirium.
Methods: 65 patients were admitted in 7 Italian Neurology or Internal Medicine Clinics during the year 2021 and experienced an episode of delirium (delirium group). The patients were matched with a group of patients admitted during the same period (no-delirium group). The presence of delirium was revealed by the administration of 4AT scale and according to DSM-5. Comorbidities were evaluated by Charlson Comorbidity index. All patients underwent a rsEEG registration and spectral makers were compared between the two groups: power density at delta, theta, pre-alpha, and alpha frequency bands, dominant frequency (DF), and dominant frequency variability (DFV).
Results: All 65 delirium patients (76.9 years ±12 standard deviation, SD; 49% females) showed abnormal CSA patterns. In no-delirium patients (74.6 years ±12 SD; 39% females), a minority (28.6%) presented abnormal CSA patterns. Delirium group had an EEG mainly characterized by lower mean DF and higher DFV at the pre-alpha/theta frequencies (< 8 Hz). These effects were topographically widespread.
Conclusions: Delirium may be strictly related to TCD, known to affect vigilance and awareness, and reflected by CSA markers of on-going EEG activity.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

ALZHEIMER'S DISEASE IS ASSOCIATED WITH A LOSS OF GLUCOSE BUT NOT KETONES CEREBROVASCULAR TRANSPORTERS

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Aims: The brain is a highly demanding organ, utilizing glucose and ketones as main sources of energy. GLUT1 and MCT1, respectively, transport glucose and ketones across the blood-brain barrier (BBB). While reduced glucose uptake by the brain is one on the earliest signs of Alzheimer's disease (AD) detected by positron emission tomography scanning, no changes in the uptake of ketone bodies have not been evidenced yet.
Methods: We used microvessel-enriched brain samples from the parietal cortex of 60 participants of the Religious Orders Study classified as Controls, mild-cognitive impairment (MCI) or AD.
Results: We first showed that GLUT1 and MCT1 are concentrated in the cerebral vasculature in humans and mice and colocalized with vascular basement membrane protein. Participants clinically diagnosed with AD had significantly lower cerebrovascular levels of GLUT1, whereas MCT1 remained unchanged. GLUT1 reduction was associated with lower cognitive scores for global cognition, episodic and semantic memory, and perceptual speed. No such association were found for MCT1, except a negative association with working memory. Cerebrovascular levels of GLUT1 were negatively associated with neuritic plaques and APPβ-CTF, whereas MCT1 was positively associated with cerebrovascular ApoE. Finally, while GLUT1 levels correlated inversely with neuritic plaque counts, both transporters were not significantly associated with age at death or tau pathologies.
Conclusions: These results suggest that, while a deficit of GLUT1 may underlie the failed transport of glucose to the brain in AD, no such an impairment occurs for MCT1. These results support the use of ketones bodies as an alternative energy source for the aging brain.

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OD029 / #1463

ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

B VITAMINS PREVENT IRON-ASSOCIATED BRAIN ATROPHY AND DOMAIN-SPECIFIC EFFECTS OF IRON, COPPER, ALUMINUM AND SILICON ON COGNITION IN MILD COGNITIVE IMPAIRMENT

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Aims: Metals, silicon, and homocysteine are linked to Alzheimer's disease. B-vitamin therapy lowers homocysteine, slows brain atrophy and cognitive decline in mild cognitive impairment (MCI). Our aims were to examine metals and silicon as predictors of cognition/brain atrophy in MCI, their interaction with homocysteine and cysteine, and how B-vitamins affect these relationships.
Methods: Participants with MCI (n=266, 77.6-year-old, 60.7% female) in VITACOG trial were randomized to receive daily folic acid (0.8 mg)/vitamin-B_{12} (0.5 mg)/vitamin-B_6 (20 mg) (n=133) or placebo for two years. At baseline and end-of-study cranial MRIs were obtained from 168 participants, cognition analyzed by neuropsychological tests, and serum iron, copper, arsenic, aluminum, silicon quantified by inductively coupled plasma mass spectrometry in 196 participants. Data were analyzed by bivariate and multiple regression.
Results: Baseline iron and cysteine independently predicted brain atrophy rate in MCI patients, and modified effects of homocysteine on brain atrophy rate. Baseline copper, aluminum, and silicon were not associated with brain atrophy rate. At baseline, iron, copper, aluminum, and silicon were significantly associated with cognition in one or more domains: semantic memory, verbal episodic memory, attention/processing speed, and/or executive function. At the end-of-study, baseline iron, copper, aluminum, and silicon predicted cognition in at least one domain: semantic memory, verbal episodic memory, visuospatial episodic memory, attention/processing speed, and global cognition. Baseline iron and silicon predicted better cognition, while aluminum and copper predicted worse cognition at follow-up in the palcebo but not in the B-vitamin therapy group.
Conclusions: Disparate effects of serum iron, copper, aluminum, silicon, and homocysteine on brain atrophy and/or cognition in MCI patients suggest that cognitive impairment is independent of brain atrophy. Associations of iron with brain atrophy/cognition and of other elements with cognition were abrogated by B-vitamin therapy.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

PROTEOMIC CHARACTERIZATION OF NEUROMELANIN GRANULES IN HEALTH AND DISEASE

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Aims: Neuromelanin granules (NMGs) are organelle-like structures present in the human *substantia nigra* (SN) *pars compacta*. Besides neuromelanin, NMGs contain proteins, lipids and metals. Since especially NMG-containing dopaminergic neurons are lost in Parkinson's disease (PD) and dementia with Lewy bodies (DLB), NMGs are thought to play a role in neurodegenerative processes. Until now, this role is not completely understood, as well as the mechanism of NMG formation.
Methods: We therefore set up a proteomic study to identify differences in the proteomic profile of NMGs from DLB cases (n=5) compared to healthy controls (CTRL, n=5). NMGs and surrounding SN tissue were isolated using laser microdissection and resulting samples were afterwards prepared for untargeted mass spectrometry. After statistical evaluation, proteins were selected for validation, which was performed via targeted mass spectrometry.
Results: Of 3,090 identified proteins, 81 proteins were found to be significantly different in abundance between NMGs of DLB and CTRL. Among them, alpha-synuclein (p=0.001) and protein S100A9 (p=0.019) displayed a higher abundance in NMGs of DLB patients. In addition, proteins related to stress granules (SGs) were higher abundant in NMGs of CTRL patients, indicating a link between NMGs and SGs which may be impaired in DLB. Nevertheless, several endosomal and lysosomal proteins showed no changes in abundance in NMGs of both conditions, potentially indicating a conserved mechanism of NMG generation.
Conclusions: Our results revealed for the first time a relationship between NMGs and SGs that will provide the basis for further studies and open new perspectives in NMG research. Furthermore, insights into NMG formation and the involvement of NMGs in neurodegenerative processes were presented, which will be investigated in postmortem tissues from PD cases in the future.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

RECRUITMENT OF APOLIPOPROTEIN E FACILITATES HERPES SIMPLEX VIRUS 1 RELEASE

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Aims: Interactions between human apolipoprotein E (ApoE, isoform 4) and herpes simplex virus type 1 (HSV1) have been shown to associate with higher risk of Alzheimer's disease (AD). Here, the effects of ApoE on the HSV1 infectious life cycle are investigated at molecular levels *in vitro*.
Methods: The effects of ApoE on HSV1 infection were studied by plaque assay and/or qPCR based methods on cultured cell lines exposed to purified ApoE. The interaction kinetics of single HSV1 particles with the plasma membrane were quantified using TIRF microscopy and cell-free plasma membrane models.
Results: Analysis of HSV1 growth shows that HSV1 production is promoted in presence of any of the three ApoE isoforms, with ApoE3 or 4 exhibiting the strongest pro-viral effect. After investigating the effects of ApoE on different stages of HSV1 infection, we found that ApoE facilitates HSV1 release from the cell surface. Subsequent results reveal that ApoE not only accumulates at the cell periphery with HSV1 infection, but also associates with HSV1 particles, indicating that the presence of ApoE at cell surface or in association with HSV1 particles promotes virus detachment. This hypothesis was tested by quantifying interaction kinetics and apparent affinity between of HSV1 and the plasma membrane. Our kinetic data shows that the presence of ApoE, on the cell membrane or in association with virus particle, leads to higher dissociation rate constants (k_{off}), but unchanged association behavior (k_{on}); this results in overall higher dissociation constants (K_D), which is in line with the promoted virus release.
Conclusions: our results provide new insights into the roles of ApoE during HSV1 infections, which is worth to be considered when studying their involvement during AD development.

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OD032 / #1369

ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

A DOUBLED RISK OF DEMENTIA WITH HERPES SIMPLEX VIRUS INFECTION – PROSPECTIVE INVESTIGATIONS IN A CONTEMPORARY COHORT

Erika Vestin[1], Gustaf Boström[1], Jan Olsson[2], Fredrik Elgh[2], Lars Lind[3], Lena Kilander[4], Hugo Lövheim[5], Bodil Weidung[1]
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Aims: Accumulating evidence indicates that herpes simplex virus (HSV) plays a role in Alzheimer's disease (AD) pathogenesis. We investigated risk of AD and dementia with presence of antibodies against herpesviruses in relation to interactions with *APOE4*-carriership and effects of anti-herpes treatment, in a contemporary cohort of elderly Swedes followed for 15 years.
Methods: The study included 1002 dementia-free 70-year-olds living in Uppsala, Sweden in 2001-2005. Serum samples were analyzed for presence of anti-HSV, anti-HSV type 1 (HSV-1) and anti-cytomegalovirus (CMV) IgG, presence of anti-HSV IgM, and levels of anti-HSV and anti-CMV IgG. Dementia diagnoses and anti-herpes drug prescriptions were collected from medical records. Cox-proportional hazard regression models were applied.
Results: The AD and dementia incidences were 3.6% and 7.1%. Also, 82% were anti-HSV IgG positive, of which 6% received anti-herpes treatment. Anti-HSV IgG was associated with increased all-cause dementia risk (adjusted hazard ratio = 2.26, p = .031), but not with AD. Presence of anti-HSV IgM or anti-CMV IgG, levels of anti-HSV IgG or anti-CMV IgG or use of anti-herpes drugs were not associated with AD or dementia, nor were the interactions between anti-HSV IgG and either *APOE4* or anti-CMV IgG. Similar results were found when replacing HSV with HSV-1.
Conclusions: Latent infection with HSV, but not CMV, may double the risk of incident dementia in elderly people. Previously shown interactions with CMV- or *APOE4*-carriership were not replicated. Potential AD or dementia risk reduction with anti-herpes treatment, or effects of reactivation (defined by anti-HSV IgM presence or elevated anti-HSV IgG levels), may not be apparent in contemporary cohorts, where treatment among risk groups may be common.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

ACCELERATION OF ALZHEIMER'S DISEASE PHENOTYPE FOLLOWING SUBACUTE EXPOSURE TO WORLD TRADE CENTER DUST

Ruth Iban Arias[1], Kyle Trageser[1], Eun-Jeong Yang[1], Elizabeth Griggs[1], Aurelian Radu[1], Sean Naughton[1], Md Al Rahim[1], Tatsunori Oguchi[1], Giuseppe Evangelista[1], Urdhva Raval[1], Lung-Chi Chen[2], Giulio Maria Pasinetti[1,3]
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Aims: The terrorist attacks on September 11th, 2001, on the World Trade Center (WTC) led to intense fires and a massive dense cloud of toxic gases and suspended pulverized debris. There is a correlation between chronic exposure to WTC dust with the acceleration of brain aging leading to emerging health conditions in the central nervous system (CNS). We hypothesize that WTC dust exposure affects the immune cross-talking between the periphery and CNS that may induce brain permeability ultimately promoting AD-type phenotype.
Methods: 5XFAD and WT mice were intranasally administered with 125µg/dose of WTC dust 10-53µm collected at Ground Zero on the afternoon of 9/11/2001. Three experimental groups were used: high exposure to WTC dust: mice exposed to 9 dust inhalations in 3 weeks; low exposure: mice exposed to 3 dust + 6 vehicle inhalations, and no exposure, a control group of mice exposed to 9 vehicle inhalations. Y-maze assay and novel object recognition behavioral tests were performed for working memory deficits, and, learning and recognition memory, respectively. Transcriptomic analysis in the blood and hippocampus was performed and confirmed by RT qPCR.
Results: Mice chronically exposed to WTC dust exhibited a significant impairment in spatial and recognition short and long-term memory. The transcriptomic analysis in the hippocampus and blood revealed significant changes in genes related to neuroinflammation, and blood-brain-barrier tight junction integrity. Ongoing studies to confirm the chemical elements found in the brain following exposure and the AD-type β-amyloid (Aβ)-neuropathology will be also presented.
Conclusions: The study supports the hypothesis that sub-acute exposure to WTC dust may promote cognitive deterioration and possibly accelerates AD-type neuropathology in a mouse model genetically predisposed to develop AD.

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OD034 / #2364

ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

THE IMPACT OF COVID-19 LOCKDOWN ON MORTALITY RATE IN MEMORY CLINIC PATIENTS

Els Bakker[1], Marissa Zwan[2], Freek Gillissen[1], Femke Bouwman[3], Philip Scheltens[4], Wiesje Van Der Flier[5], Ingrid Van Maurik[1]
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Aims: People with (pre-)dementia were particularly at risk for mortality during the COVID-19 pandemic due to severe outcome of a COVID-19 infection and the negative consequences of restrictive measures. Here we study whether patients during the COVID-19 pandemic had a higher mortality rate compared to historical controls.
Methods: In this case-control study, we from the Amsterdam Dementia Cohort: 1) Pandemic patients with a baseline visit between January 2017 and December 2018 and 2) Historical controls with a baseline visit between January 2015 and December 2016. Both groups were followed for three years (pandemic patient until 2021 and historical controls until 2019). Absolute standardized mean differences were analyzed in order to determine whether groups well balanced in terms of demographics and cognition at baseline. Cox regression analyses was performed to compare the (all-cause) mortality rate during COVID-19 pandemic with historical controls. Age, sex, diagnosis, MMSE score, education level, and comorbidity were added as covariates to the model.
Results: Mean age of the pandemic patients was 63 ± 9 years, n = 423 (41%) were female and mean MMSE score was 24.5 ± 5.0. The mean age of the historical control patients was 63 ± 8 years, n = 404 (43%) were female and MMSE score was 24.2 ± 5.2. The absolute standardized mean differences were under 0.1 for all selected covariates and groups were considered balanced. Pandemic patients had higher risk for mortality than historical controls (HR [95%-CI] = 1.27 [1.02-1.59]). Results remained significant after adjusting for covariates (HR [95%-CI] = 1.37 [1.09-1.72]).
Conclusions: Memory clinic patients have increased risk on mortality during times of COVID-19 lockdown compared to historical controls. This indicates that COVID-19 lockdown regulations have accelerated disease.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

DORSAL RAPHE NEUROPATHOLOGY IN THE PRODROMAL SYMPTOMS OF NEURODEGENERATIVE DISEASE

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Aims: A common feature of neurodegenerative disease (ND) is the presence of protein aggregates in brainstem nuclei including the dorsal raphe nucleus (DRN), which may be one of the underlying causes of prodromal sleep disorders and neuropsychiatric symptoms (NPS). Our goal was to assess the prevalence of protein aggregates in the DRN of older adults with normal cognitive function that may be at risk for ND, then determine whether inducing tau pathology in this region could recapitulate the prodromal symptoms of ND.
Methods: To assess the prevalence of protein aggregates in the DRN, serial sections from 14 control and 10 Alzheimer's disease (AD) cases were immunostained for tryptophan-hydroxylase 2 (Tph2), ptau(S202/T205), pS129-α-synuclein, and pS409/410-TDP-43. Images were captured with a brightfield microscope. To examine the role of tau pathology in the DRN in prodromal symptoms, an AAV vector encoding P301Ltau was microinjected into the DRN of C57BL/6J mice, a subset of which were implanted with EEG/EMG electrodes. Mice were then assessed for depressive-like behaviors or underwent continuous EEG/EMG recordings for 48 hours.
Results: Of 7 controls with confirmed DRN, 4 stained positive for ptau, 1 for psyn and none for pTDP-43. All 10 AD cases contained DRN and 9 were positive for ptau, 3 for psyn, and 3 for pTDP-43. P301Ltau expression in the DRN induced depressive-like behaviors, reduced REM sleep after 4 weeks, and increased non-REM sleep after 16 weeks.
Conclusions: Tau pathology is present in the DRN of a subset of cognitively normal adults and may precipitate prodromal symptoms that presage ND. Screening older adults for DRN tauopathy in addition to late-onset depression and sleep disorders may be an effective strategy for early diagnosis.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

CASP8 GGGAGA REPEAT EXPANSIONS PRODUCE POLY-GLYCINE-ARGININE CONTAINING PROTEINS THAT ACCUMULATE IN ALZHEIMER'S DISEASE BRAINS

Lien Nguyen[1], Ramadan Ajredini[1], Shu Guo[1], Lisa Romano[1], Tao Zu[1], Monica Bañez Coronel[1], Georgios Vasilakos[1], Chase Kelley[1], Alexis Tays[1], Javier Redding-Ochoa[2], Olga Pletnikova[3], Paul Ranum[4], H. Brent Clark[5], Alan Renton[6], Alison Goate[7], Kiruphagaran Thangaraju[1], Beverly Davidson[4], Anthony Yachnis[8], Todd Golde[9], Xiang Lou[10], Stefan Prokop[8], Eric Wang[1], Juan Troncoso[2], Laura Ranum[11]
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Aims: Background: The genetic causes of most sporadic AD (sAD) cases are unclear. In a related abstract (Ranum et al.), we showed poly-glycine-arginine (polyGR) aggregates accumulate in sAD autopsy brains and correlate with pTau levels. Additionally, we identified an intronic GGGAGA repeat expansion in *CASP8* (*CASP8*-GGGAGA^{exp}) as a novel AD risk factor. **Objectives:** To test if the *CASP8*-GGGAGA^{exp} produces repeat-associated non-AUG (RAN) proteins that contribute to polyGR aggregates found in sAD.
Methods: We generated minigenes containing 6 upstream stop codons, unique *CASP8* sequence upstream of the repeat, the *CASP8*-GGGAGA^{exp}, and 3'-epitope tags (FLAG, HA or Myc) in each reading frame (6xStop-CASP8-RE-3T). We used these minigenes to test if the *CASP8*-GGGAGA^{exp} expresses RAN proteins and if this expansion is toxic. Additionally, we generated α-CT-f1S and α-CT-f3S antibodies against unique C-terminal sequences of putative *CASP8*-RAN proteins to test if the *CASP8*-GGGAGA^{exp} produces polyGR-containing protein aggregates in *CASP8*-GGGAGA^{exp} (+) AD autopsy brains.
Results: Immunofluorescence (IF) and western blot show polymeric RAN proteins are expressed from 6xStop-CASP8-RE-3T minigenes in all three reading frames in transfected HEK293T cells and RAN protein levels are increased by thapsigargin-induced stress. Expression of the 6xStop-CASP8-RE-3T constructs increased cell death and decreased cell viability in T98 cells ($p < 0.0001$). Moreover the *CASP8*-RAN C-terminal antibody, α-CT-f3S, detected fibril-like/aggregates in hippocampal regions in *CASP8*-GGGAGA^{exp}(+) AD but not in *CASP8*-GGGAGA^{exp}(+) unaffected controls, or *CASP8*-GGGAGA^{exp}(-) AD or control autopsy brains. Double IF shows polyGR staining co-localizes with α-CT-f3S staining in frontal cortex from *CASP8*-GGGAGA^{exp}(+) AD cases.
Conclusions: We show the *CASP8*-GGGAGA^{exp} is toxic to cells and produces polyGR-containing proteins that accumulate in *CASP8*-GGGAGA^{exp}(+) AD brains. Stress increases *CASP8* RAN protein levels, which may in turn increase the susceptibility of *CASP8*-GGGAGA^{exp} carriers to develop AD.

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OD037 / #2295

ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

RECLASSIFICATION OF MANIFEST DISEASE DIAGNOSES USING ALZHEIMER'S DISEASE BIOMARKERS IN THE GOTHENBURG MILD COGNITIVE IMPAIRMENT STUDY

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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, is diagnosed based on medical history, 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) are analyzed for the patients, although these are not used for diagnosis. The International Working Group (IWG) for New Research Criteria for the Diagnosis of AD has proposed a conceptual framework for to use these biomarkers in the diagnosis of AD, i.e. the IWG-2 criteria. In short, patients with typical AD and mixed AD/SSVD should display decreased Aβ 1–42 together with increased t-tau or p-tau in CSF. In this project, we compared the clinical diagnoses of patients with manifest disease with diagnoses set according to the IWG-2 criteria.
Methods: In total, 94 AD patients, 52 mixed AD/SSVD patients and 27 SSVD patients were available at baseline with complete CSF biomarker data. The applied cut-offs for abnormality were t-tau > 350 ng/L, p-tau181 > 59 ng/L, and Aβ1-42 < 530 ng/L.
Results: Using the IWG-2 criteria, 74.2% of patients diagnosed with AD had pathological AD biomarkers. Moreover, the clinical diagnosis of 73.1% of the mixed AD/SSVD patients was confirmed using IWG-2 criteria. Finally, 72.8% of SSVD patients were confirmed as being SSVD, having non-pathological AD CSF biomarkers.
Conclusions: This indicates that clinical diagnostic methods show a correlation with a diagnosis based on the IWG-2 criteria.

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OD038 / #2075

ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

PREDICTING CONVERSION FROM SUBJECTIVE COGNITIVE DECLINE TO MILD COGNITIVE IMPAIRMENT OR DEMENTIA THROUGH BRAIN ATROPHY PATTERNS

Ondřej Lerch[1,2], Daniel Ferreira[3], Erik Stomrud[4,5], Danielle Van Westen[4,6], Jakub Hort[1,2], Oskar Hansson[7,8], Eric Westman[9,10]
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Aims: Alzheimer's disease (AD) is a progressive neurogenenerative disease where pathophysiological changes begin years or even decades before the onset of clinical symptoms. Analysis of brain atrophy patterns using structural magnetic resonance imaging (MRI) and multivariate data analysis are an effective tool in identifying patients with subjective cognitive decline (SCD) at high risk of developing AD dementia. The majority of currently available predictive models were trained using patients in advanced stages of AD, which we hypothesize may not be optimal for subjects at an early stage like SCD. In this study, we compared the accuracy of the SCD prediction using the standard model trained on patients with AD dementia versus a new model trained on β-amyloid (Aβ) positive amnestic mild cognitive impairment (aMCI) patients.
Methods: We used structural MRI data of 504 patients from the BioFINDER study (Aβ-negative cognitively normal (CN)=220; SCD=139; Aβ-positive aMCI=106; AD dementia=39). We applied multivariate data analysis to create two predictive models trained using either aMCI or AD-dementia individuals. Models were applied to SCD individuals to classify their atrophy patterns as either high-risk "disease-like" or low-risk "CN-like". Clinical trajectory and model accuracy were evaluated using 8 years of longitudinal data.
Results: Both models reached high cross-validated sensitivity (96.7-100%) and specificity (80.22-100%). However, the aMCI-based model reached a higher area under curve (AUC = 0.72) to predict conversion from SCD to MCI or dementia, in comparison with the AUC of the dementia-based model (AUC = 0.57).
Conclusions: When predicting conversion from SCD to MCI or dementia using structural MRI data, prediction models using patterns of brain atrophy based on individuals with milder levels of atrophy (i.e. aMCI) may offer superior clinical value compared to standard dementia-based models.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

PREDICTING AMYLOID-BETA PATHOLOGY IN THE GENERAL POPULATION

Phuong Thuy Nguyen Ho[1], Joyce Van Arendonk[1,2], Rebecca Steketee[1], Frank Van Rooij[2], Gennady Roshchupkin[1,2], M Ikram[2], Meike Vernooij[1,2], Julia Neitzel[1,2,3]
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Aims: We developed prediction models for amyloid-beta (Aβ) positivity and validated our models in non-demented older adults representative of the general population to support primary care decisions regarding confirmatory biomarker testing for Alzheimer's disease (AD).
Methods: Model development was performed in the Anti-Amyloid Treatment in Asymptomatic Alzheimer (A4) Study (n=3,823), the largest dataset with amyloid positron emission tomography (PET), while independent external validity was assessed in the Rotterdam Study (n=434), an ongoing longitudinal population-based cohort study. We considered apolipoprotein (*APOE)* genotyping and 18 non-genetic predictors containing demographics, lifestyle, objective and subjective measures of cognition and daily functioning.
Results: We developed two Aβ prediction models, without and with *APOE* ε4 carrier status. The model without *APOE* performed robustly across datasets and when considering non-genetic predictors from three different Rotterdam Study visits (on average 13 years or 7 years before or 2 year after PET). Importantly, the performance of the model with *APOE* improved in the Rotterdam Study validation dataset compared to the A4 training dataset (Fig.

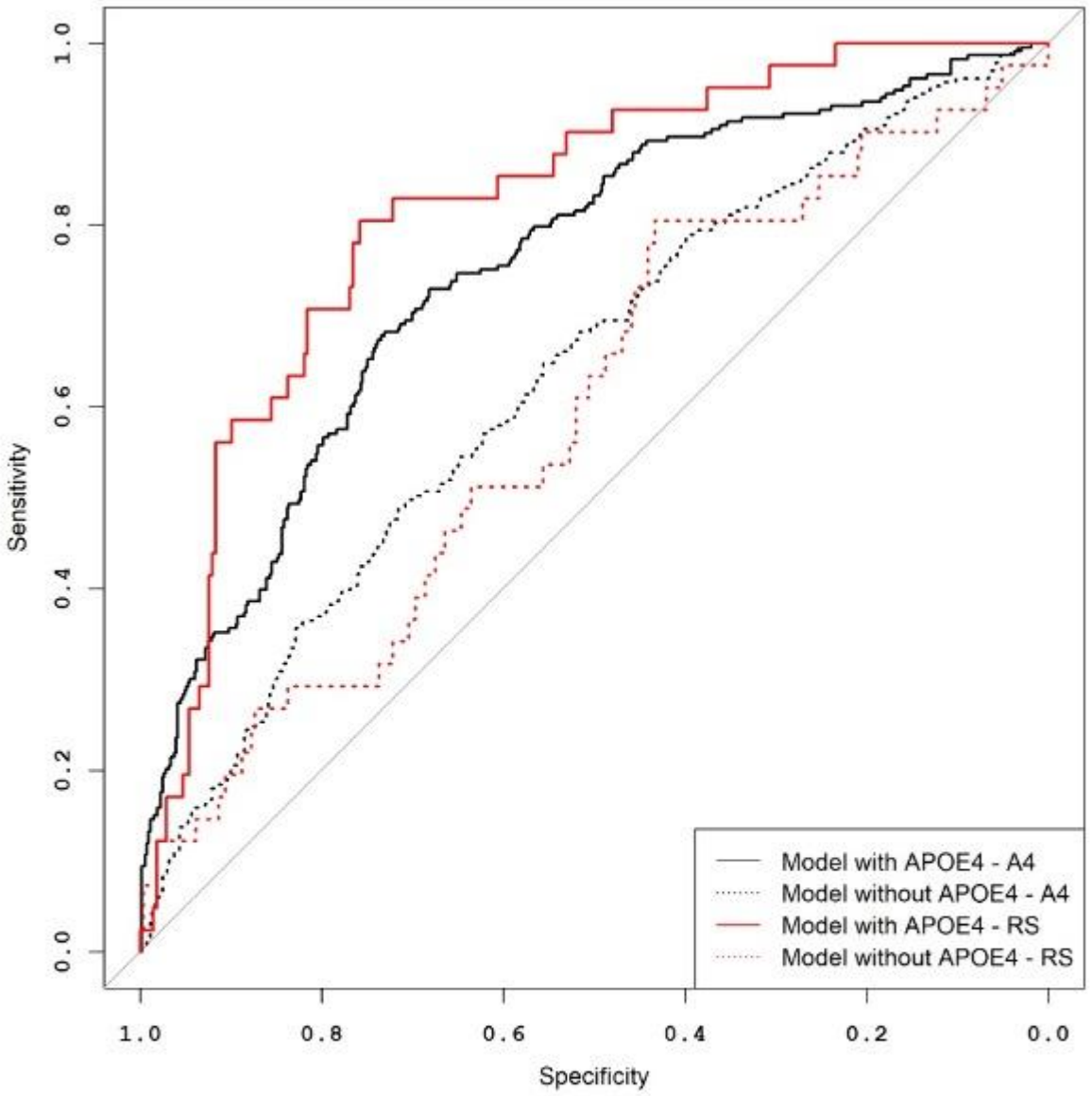

Fig. 1 Receiver operating characteristic (ROC) curves of the two prediction models, with and without *APOE* ε4 carrier status, on the A4 test dataset (black) and the Rotterdam Study validation dataset (red)

1).

Conclusions: This study provides evidence that models developed in a large clinical sample predict Aβ positivity in the general population comparably well or better and that they may therefore serve as inexpensive, non-invasive screening tools in primary care before patients are referred to specialized memory clinics for more elaborate AD biomarker tests.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

METHYLOMIC-BASED MOLECULAR SUBTYPING OF ALZHEIMER'S DISEASE

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Aims: Accumulating evidence shows that the heterogeneity and temporal complexity of Alzheimer's Disease (AD) contributes to the lack of effective treatment. Advances in omics technologies along with development of efficient analytical pipelines, provide a unique opportunity to investigate the drivers of heterogeneity at multiple molecular levels. In this study, we used DNA methylation data quantified in postmortem prefrontal cortex to identify the molecular subtypes and the distinct molecular features driving the disease heterogeneity in AD.
Methods: We used DNA methylation data generated in postmortem prefrontal cortex in three independent biobanks of Brain for Dementia Research (Discovery; n = 415), the Mount Sinai Brain Bank (n = 250) and The Religious order Study and the Memory and Aging Project (n = 710). Unsupervised clustering methods including network-based, Bayesian and Ensemble approaches were applied to the data quantified in the discovery cohort using the Illumina EPIC arrays. Following each clustering method, distinct methylomic features related to the identified subtypes were captured using classification models such as sparse partial least squares discriminant analysis. The most accurate models comprising the distinct features were used to classify the samples within the two other independent cohorts.
Results: We identified multiple well-defined clusters of samples in the discovery cohort. We achieved good prediction values in the test data to classify the subtypes using the distinct methylation features related to the identified subtypes (AUC: 0.86 – 0.96). The best performing classification model was applied on two independent cohorts and similarly classified samples across different cohorts were extensively characterized using relevant clinical and pathological information.
Conclusions: We used state-of the-art methods to undertake the first systematic, DNA methylomic-based subtyping of AD. This is a vital step to unravel the heterogeneity of the disease

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

THE NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA AGITATION, ANXIETY, DISINHIBITION AND SLEEP DISTURBANCE ARE ASSOCIATED WITH ELEVATED PLASMA CONCENTRATIONS OF KYNURENIC ACID

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Aims: The tryptophan metabolite kynurenic acid may play an active part in the pathophysiology of Alzheimer's Disease (AD). Past studies of kynurenic acid concentrations in cerebrovascular fluid and blood plasma in patients with AD compared with control subjects have been inconclusive, but there is support for increased levels of kynurenic acid in patients with some psychiatric disorders. It would be useful to investigate kynurenic acid concentrations in patients with neuropsychiatric symptoms in dementia (NPSD), considering the overlapping symptoms between psychiatric and cognitive disorders.
Methods: The study is based on 90 patients with NPSD in Stockholm in 2003-2005. Primary caregivers were assessed with the Neuropsychiatric Inventory (NPI) and the Cohen-Mansfield Agitation Inventory (CMAI). Blood plasma concentrations were measured with mass spectrometry. Correlations were assessed with Spearman's rank correlation coefficients. The median NPI score was 47 (IQR 30-68) and the median age was 79 (IQR 74-83). There were 55 people with AD including mixed forms (61.1%), 16 with vascular dementia (17.8%), 11 with mild cognitive impairment (12.2%), and 59 women (65.6%).
Results: Kynurenic acid plasma concentration was correlated with the NPI items agitation/aggression (0.232, CI 0.023 to 0.421), anxiety (0.236, CI 0.028 to 0.425), disinhibition (0.219, CI 0.010 to 0.410), and sleep (0.315, CI 0.110 to 0.494), and the CMAI item verbal/non-aggressive (0.248, CI 0.040 to 0.436). Tryptophan plasma concentration was correlated with the NPI item depression/dysphoria (-0.302, CI -0.483 to -0.097). Kynurenic acid and tryptophan plasma concentrations were not significantly associated with Mini-Mental State Examination score, age or sex.
Conclusions: The NPSDs agitation, anxiety, disinhibition and sleep disturbance are associated with elevated blood plasma concentrations of kynurenic acid, and depressive symptoms are associated with lower concentrations of tryptophan.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

ELECTROPHYSIOLOGICAL EXCITATORY TO INHIBITORY RATIO IN HIPPOCAMPUS AND TEMPORAL CORTEX IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

Pietro Scaduto, William Russell, Agenor Limon
UTMB, Neurology, Galveston, United States of America

Aims: Individuals at distinct stages of Alzheimer's disease (AD) show abnormal electroencephalographic activity which has been linked to network hyperexcitability and cognitive decline. Using electrophysiology and proteomics of human synapses from the hippocampus and temporal cortex of control, mild cognitive impaired (MCI) and AD individuals we aimed to determine the global synaptic balance in hippocampus and temporal cortex at distinct stages of neuropathology.
Methods: Electrophysiological synaptic E/I ratios in post-mortem samples from the temporal cortex of individuals with MCI (n = 6) or AD (n = 6) compared to non-demented controls (n = 6), and the hippocampus (MCI, n = 8; AD n = 11, CTRL = 8) were assessed by microtransplantation of synaptic membranes (MSM). Proteomics of synaptosomes from temporal cortex were analyzed in the context of their electrophysiological responses using Electrophysiologically-anchored Dataset Analysis (EDA)
Results: We found that the higher the amplitude of $GABA_AR$s currents the better the cognitive performance score (R^2=0.152; p=0.044). A similar association was observed for AMPARs currents (R^2=0.133; p=0.06). The eE/I ratio was significantly higher in the TCx of AD subjects and was negatively associated with the MMSE in the TCx (R^2= 0.205; p=0.059) but not in the hippocampus. The synaptoproteome revealed the impact and directionality of protein alterations and neuropathology on the amplitude of synaptic receptors responses and cognitive MMSE scores.
Conclusions: These findings indicate that early shifts of the E/I balance contribute to the loss of cognitive capabilities in the continuum of AD symptomatology.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

AETIOLOGICAL AND PARACLINICAL PARTICULARITY OF CEREBRAL HEMORRAGE IN THE PATIENT WITH MULTIPLE RISK FACTORS

Antonia Ioana Vasile, Cristina Nica, Alexandru Rusu
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Aims: Cerebral venous sinus thrombosis represents 1% of all strokes. The factors favoring this status are: intracranial tumors, neoplasms, systemic diseases, use of contraceptives, congenital coagulopathies, dehydration, pregnancy and chemotherapy drugs. We present the clinical case of a 53-year-old patient , diagnosed hypertension, obesity, right breast neoplasm chemo-treated. The patient is admitted for altered state of consciousness, right homonymous hemianospia, right hemiparesis and predominantly receptive mixed aphasia.
Methods: Imaging examination revealed: left temporal-parietal hemorrhagic collection with perilesional edema that has mass effect on midline structures (8mm displacement to the right). The repeated CT scan shows suspicion of a hemorrhagic venous infarction in the territory of the Labbe vein and the venous timing of the cerebral angiography confirms it.
Results: The particularity of the case comes from the differential diagnosis. Hypertension is a risk factor for intracerebral hemorrhage. On the other hand, the procoagulant status associated with the neoplasm and chemotherapy are favorable factors for venous hemorrhagic infarction. In the presented conditions, a possible secondary cerebral determination with associated bleeding, as well as a previously unknown pre-existing condition (such as an arteriovenous malformation) decompensated by the patient's complex biological condition was also discussed.
Conclusions: The vein of Labbe drains the lateral temporal lobe and drains into the transverse sinus. It is important to make the differential diagnosis with thrombosis of Labbe's vein in the case of a temporally localized hemorrhage in order to initiate anticoagulant treatment as quickly as possible.

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ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

ORGANIC DELUSIONAL DISORDER ON THE BACKGROUND OF CARDIOVASCULAR COMORBIDITIES

Antonia Ioana Vasile[1], Cristina Nica[1], Simona Corina Trifu[2]
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Aims: Cardiovascular diseases are the main cause of death worldwide. A significant number of psychiatric patients associate cardiovascular pathologies which can act as a trigger for a decompensation. We present the case of a 76 years old patient, with no psychiatric history, with several comorbidities (3 ischemic strokes, 5 stents, 2 coronary bypass surgeries, insulin-dependent diabetes mellitus) developed psychiatric symptoms after surgery mitral valve replacement.
Methods: In the first month after the intervention, the family reported a change in the patient's behavior and personality, stating that he had become "unrecognizable". The admission was made after the patient broke the windows of his home and became aggressive towards his family - following delusional concerns about an affair between his wife and his son-in-law. Thus he has been admitted non-voluntary to psychiatry. We used psychiatric evaluation, application of clinical scales, internal medicine consultation, cardiological and neurological consultation, carotid doppler, cerebral MRI, EEG.
Results: Symptomatology affected both cognitive and affective function, with the patient's mood ranging from severe dysphoria to emotional incontinence with uncontrollable episodes of crying or anger suggesting a pseudobulbar aspect. A psychological assessment tested his intellectual impairment and personality changes, the features highlighting an impulsive-excitable personality superimposed on multiple somatic comorbidities and a neurocognitive impairment.
Conclusions: The delusional thinking impaired his functioning suggesting a diagnosis of organic delusional disorder superimposed on the pathology of cognitive impairment.

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OD045 / #1583

ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

ALZHEIMER'S DISEASE RISK PRS IS ASSOCIATED WITH DEMENTIA AND MEMORY PHENOTYPES IN DOWN SYNDROME

Priyanka Gorijala[1,2], Victoria Fernandez[1,2], Yun Ju Sung[1,2,3], Kan-Hsien Fan[4], M. Muaaz Aslam[4], Eleanor Feingold[4], Laura Xicota[5], Lam-Ha Dang[5,6], Courtny Delacuesta[5], M. Ilyas Kamboh[4], Joseph.H Lee[5,6], Carlos Cruchaga[1,2,7]
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Aims: To determine genetic overlap of early and late onset forms of sporadic and familial Alzheimer's disease (AD) and Down syndrome (DS). We hypothesize that the polygenic risk score (PRS) for AD is associated with age at onset (AAO) of dementia or memory related phenotypes in DS.
Methods: We constructed PRS using GWAS from Bellenguez et al (2022) in five different cohorts: DS (n=282), sporadic early-onset AD (sEOAD, n=395), sporadic late-onset AD (sLOAD, n=2259), familiar early-onset AD (fEOAD, n=196), familial late-onset AD (fLOAD, n=1413). Unrelated European ancestry samples (4545 cases and age-matched controls) were selected for analysis. To understand AD risk beyond APOE, PRS including and excluding APOE region were calculated using PRSiceV2.3. We tested association of PRS with the clinical status in each cohort, and AAO of dementia, CSF and memory related phenotypes in DS.
Results: We found association of the PRS with sEOAD, fLOAD and sLOAD, but not with fEOAD, whereas DS showed inverse association. This replicates our previous findings. Among the memory phenotypes tested in DS, DSMSE memory and total scores were significant with and without APOE PRS. NTG-EDSD memory score, DLD cognitive score showed association only when age was included in the model. Cox survival analysis showed no association of AAO of dementia and MCI in DS with PRS. ROC models were not sensitive enough to predict consensus cognitive/memory and health history of dementia status in DS. CSF Aβ40, Aβ42 showed significant association with APOE PRS.
Conclusions: Our analysis indicates that the PRS for AD is inversely associated with DS status beyond APOE. This study shows that PRS association with memory related phenotypes in DS may be used to identify high-risk individuals that may develop memory problems early in life.

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OD046 / #2548

ON-DEMAND SYMPOSIUM: VULNERABILITY AND RISK FACTORS, HETEROGENEITY. PROGRESSION NEURODEGENERATION AND PATHOLOGY
29-03-2023 07:00 - 08:30

MULTIFACTOR DIMENSIONALITY REDUCTION ANALYSIS TO EVALUATE THE ASSOCIATION OF DOPAMINE BETA-HYDROXYLASE (DBH) POLYMORPHISMS WITH SUSCEPTIBILITY TO DEMENTIA (SADEM STUDY).

Teresa Juárez Cedillo
Insituto Mexicano del Seguro Social, Unidad De Investigación En Epidemiología Clinica, Mexico, Mexico

Aims: The aim of this study was to evaluate the association between single-nucleotide polymorphism (SNP) in the dopamine b-hydroxylase (DBH) gene (rs1611115) and their interactions with environmental factors and the dementia risk**.**
Methods: Material and methods: We examined the genotype of the gene DBH (rs1611115) polymorphism in patients with dementia and healthy. The interaction and the impact of DBH (rs1611115) polymorphism on dementia was examined through multifactor dimensionality reduction (MDR) analysis and the results were verified by Chi-square test. Hardy-Weinberg equilibrium (HWE) was also checked by chi-square test. The relative risk was expressed by odds ratio (OR) and 95%.
Results: Results: Total 221 dementia patients and 534 controls met the inclusion criteria of MDR analyses. The results of the MDR analysis showed that the development of dementia was positively correlated with interaction between the TT genotype of the DBH1 locus rs1611115 TT and diabetes, hypertension, alcohol consumption (OR =6.5: 95%CI = 4.5-9.5), originating further cognitive damage.
Conclusions: Conclusion: These findings provide insight are positive correlation between the metabolism and cardiovascular disorders and the presence of the T allele by means of a recessive model of DBH rs1611115 polymorphism with the suspensibility of dementia.

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OD047 / #772

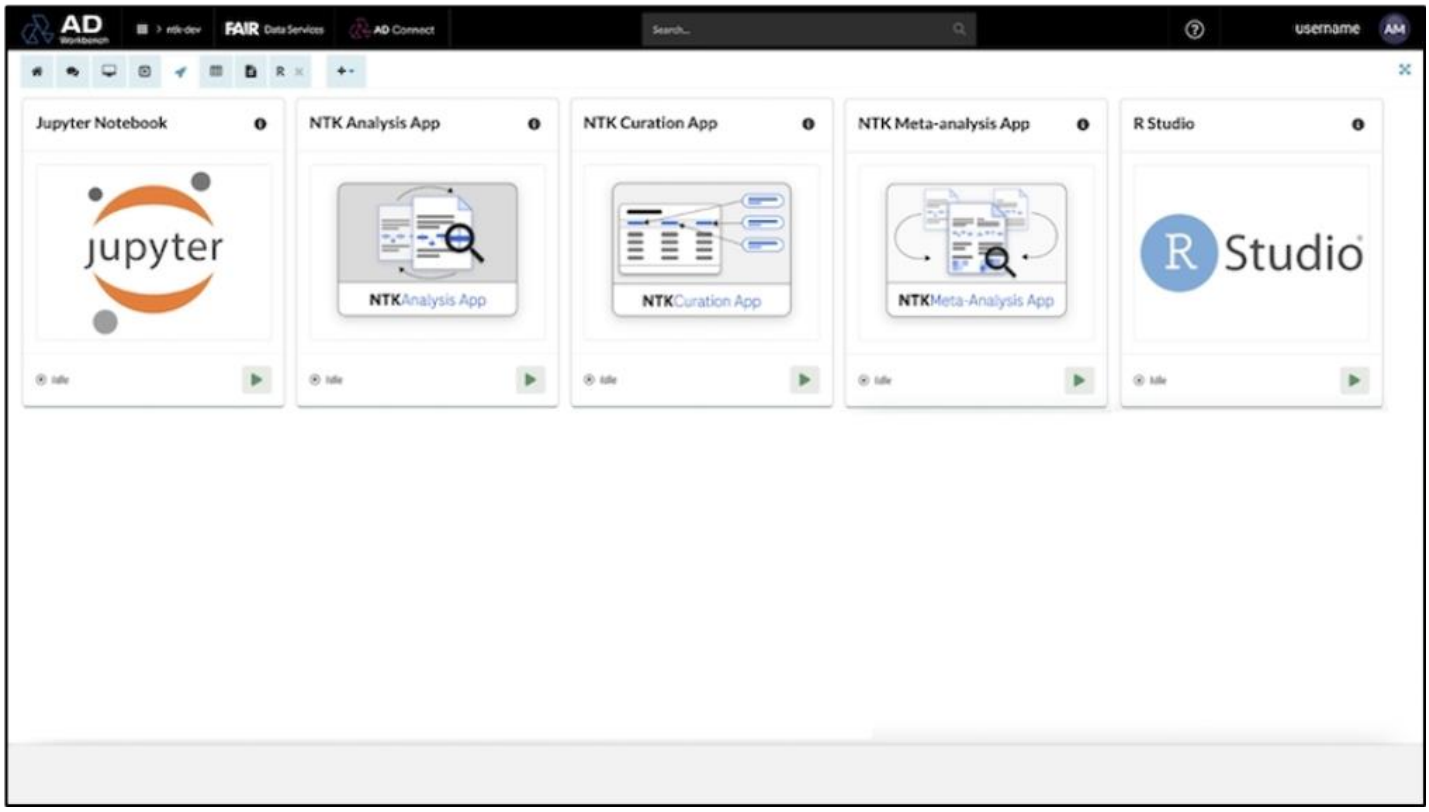
ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

THE AD WORKBENCH NEUROTOOLKIT APPLICATION (NTKAPP) SUITE OF CLOUD-BASED TOOLS FOR SECURE COLLABORATIVE RESEARCH IN ALZHEIMER'S DISEASE

Chad Logan[1], Alina Bauer[2], Stefan Bentink[3], Eugen Rosenfeld[4], Alexandru Maxim[4], Remus Tomsa[4], Caitlin P. Mchugh[5], Matthew H. S. Clement[6], Ivonne Suridjan[7], Margherita Carboni[7]
[1]Roche Diagnostics GmbH, Phcs Biostatistics & Data Management, Diessen am Ammersee, Germany, [2]Roche Diagnostics GmbH, Phcs Biostatistics & Data Management, Penzberg, Germany, [3]Roche Diagnostics GmbH, Clinical Biostatistics, Penzberg, Germany, [4]Nagarro, Nagarro, Bucharest, Romania, [5]Alzheimer's Disease Data Initiative (ADDI), Bioinformatics, Kirkland, United States of America, [6]Alzheimer's Disease Data Initiative (ADDI), Director Of Partnerships & Scientific Strategy, Kirkland, United States of America, [7]Roche, Roche Diagnostics International Ltd, Rotkreuz, Switzerland

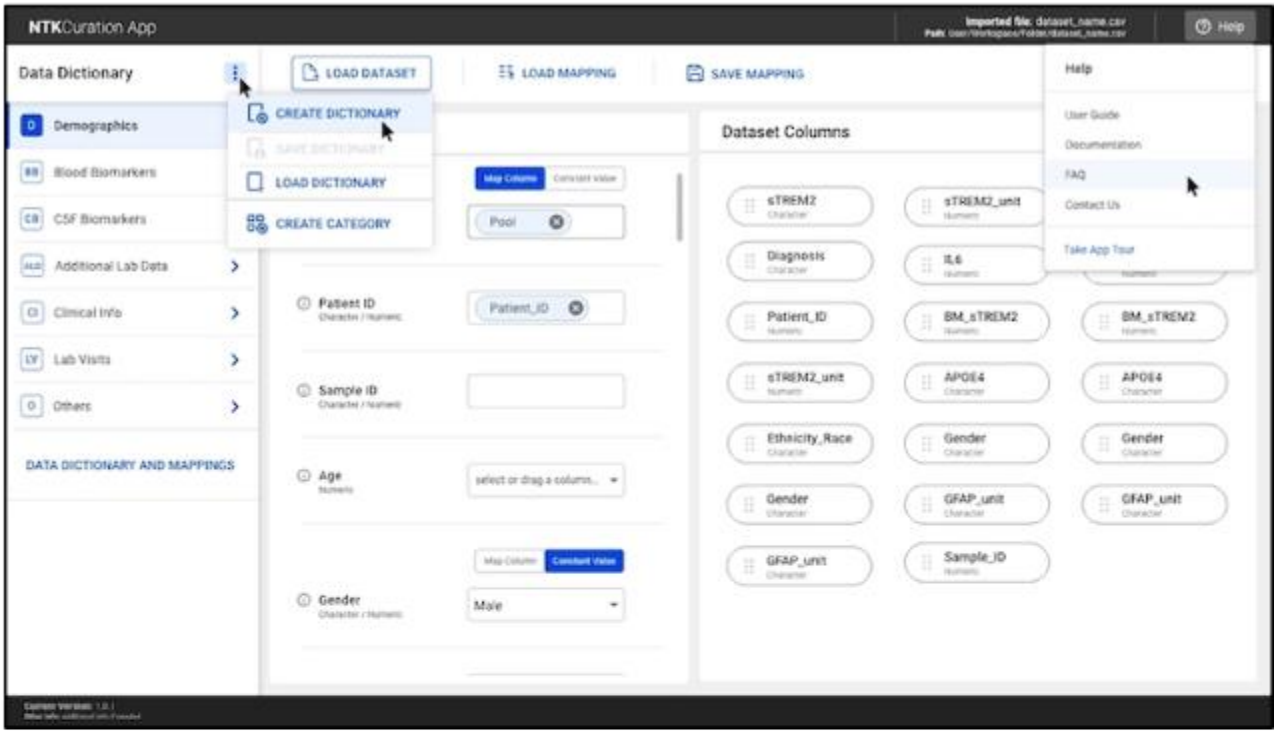
Aims: Roche Diagnostics and the non-profit organization Alzheimer's Disease Data Initiative (ADDI) have co-developed the NeuroToolkit Application (NTKapp); a suite of tools for data harmonization, standardized statistical analysis, meta-analysis, and results sharing among academic and industry researchers using ADDI's AD Workbench, a secure cloud-based research environment that offers storage and compute to researchers. The application is designed to promote collaborative and federated analyses aimed at identifying and assessing potential clinical utility of novel biomarkers of interest in AD and other neuronal diseases.
Methods: The AD Workbench is a Microsoft Azure based platform hosted on the Aridhia Digital Research Environment (DRE). Datasets can be standardized based on user-defined data dictionaries using a data curation application. A user-friendly data analysis application has been developed for creation and execution of standardized statistical analyses and for comparing and sharing analysis results within and across workspaces. Analysis code and results may also be exported for replication, use in cross-cohort comparisons or meta-analyses without users needing to share private discrete data directly with external collaborators or other AD-workbench users.
Results: Please see screenshots of the
NTKApp:

1. AD Workbench NTK Application Suite



2. NTKCuration App

A



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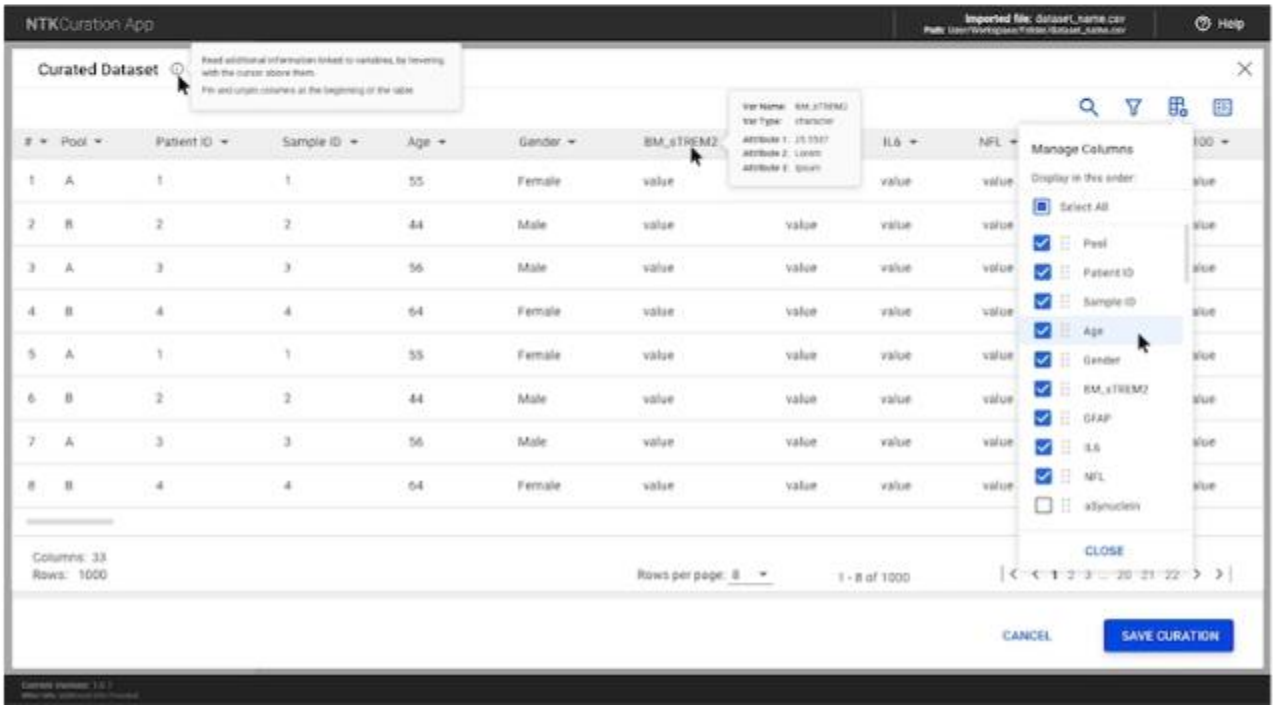

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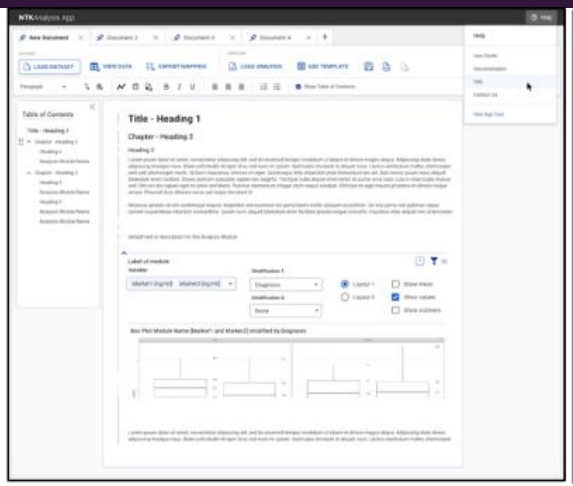
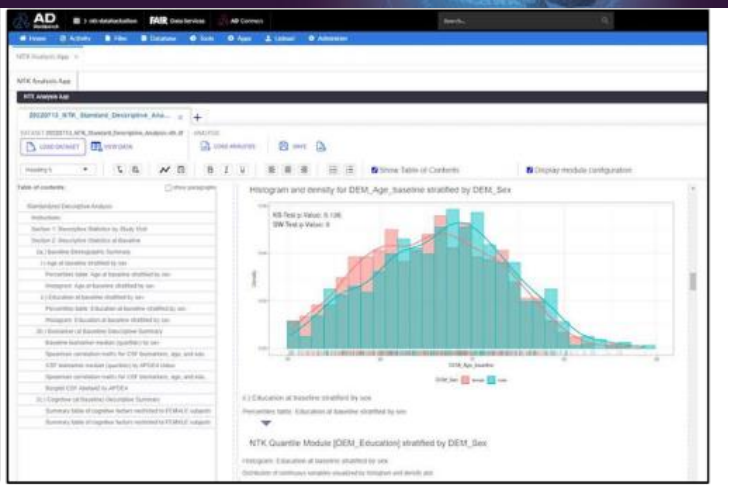
3. NTKAnalysis App





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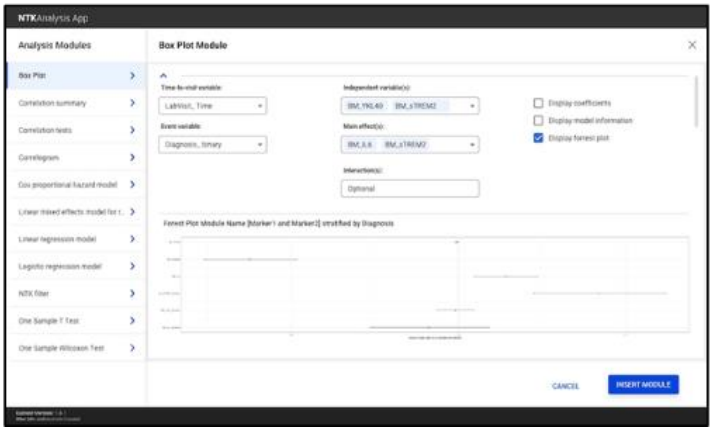

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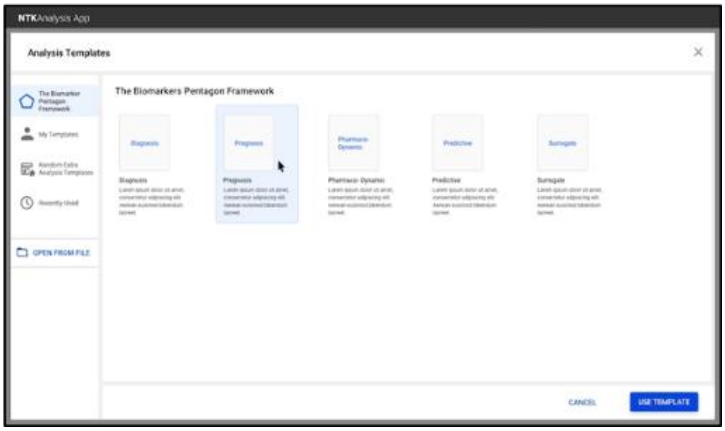
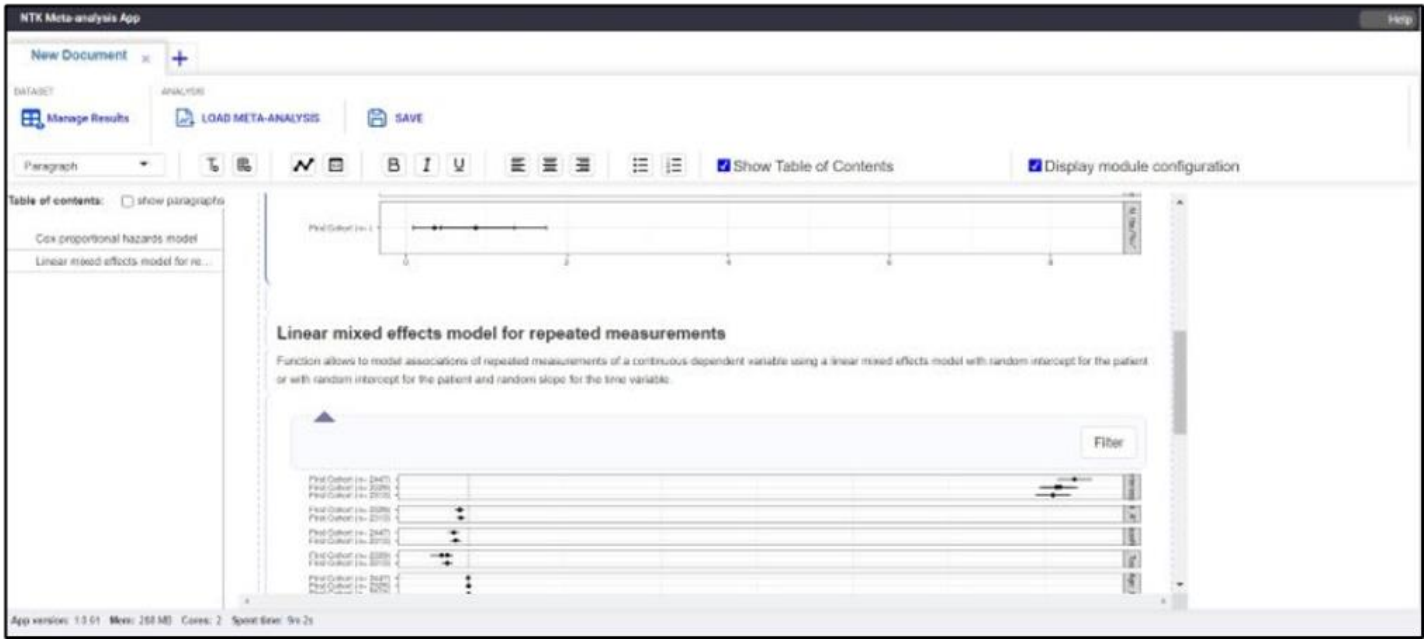


4. NTKMeta Analysis



Conclusions: The NTK-app prototype developed in 2021 was well received by the NTK community and an updated version was publicly beta-tested in July 2022 via a data hackathon challenge where the app was used to analyze data from the European Prevention of AD (EPAD) cohort. A scalable and modular first version of the NTK-app was released

via AD Workbench in September 2022. Continuous updates will be performed to expand capabilities for collaboration and federated analysis based on user and partner engagement and feedback.

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OD048 / #1987

ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

MULTI-TASK LEARNING AND ENSEMBLE APPROACH TO PREDICT COGNITIVE SCORES FOR PATIENTS WITH ALZHEIMER'S DISEASE

Daren Ma[1], Christabelle Pabalan[2], Abhejit Rajagopal[1], Yannet Interian[2], Ashish Raj[1]
[1]UCSF, Department Of Radiology, San Francisco, United States of America, [2]University of San Francisco, College Of Arts And Sciences, San Francisco, United States of America

Aims: Alzheimer's Disease severely harms the patients' cognitive abilities. Assessment of current and future cognition is an integral component of a diagnosis of dementia, and therefore an important clinical and scientific goal. Unfortunately, subjective, time-consuming and operator-sensitive clinical surveys or neuropyschiatric batteries remain the only viable methods of assessing cognition. Given that MRI is the most prevalent, cost-effective, and clinically important imaging modality, it may be considered a suitable predictor of cognition. We aim at predicting the subjects' ADAS-Cog scores using deep learning approaches given the rich MRI scan data from the ADNI group.
Methods: We designed a multi-task UNet model to predict the subjects' current and future ADAS-Cog scores, taking as input baseline T1-weighted MRI and demographic risk factors. The model solves two adjacent tasks: image segmentation into tissue types; and prediction of cognition. We achieved a high-accuracy brain segmentation for our first task, and took the underlying features, namely the middle-layer model parameters, as the imaging input of the cognition regressor along with tabular demographic data and segmented tissue volumes. We also applied feature map analysis to verify the effectiveness of each convolution step in the UNet format.
Results: We achieved excellent accuracy in baseline ADAS-Cog score predictions. The dice score in our segmentation tasks are 0.9813, and the testing R-squared metric for the ADAS-Cog scores are over 0.80. Details explanations are attached to the
figure.

Table 1. Model Results for Segmentation and ADAS-Cog11 prediction

Model	*MSE*	*DiceScore*	*Cross – Validation R^2 Range*	*Testing R^2*
Gradient Boosting Regressor (Tabular)	45.16	-	0.49 - 0.53	0.50
Single-Task CNN Model	39.99	-	0.33 - 0.57	0.48
Multi-Task UNet Model	52.05	0.9798	0.44 - 0.65	0.60
Multi-Task UNet Model with SVM-R	48.23	0.9798	0.48 - 0.72	0.59
Ensemble Model using MLP	34.13	0.9813	0.66 - 0.72	0.68
R-squared Ensemble Model	**23.49**	**0.9813**	**0.67 - 0.82**	**0.80**

In **Table 1**, we report the performance of different modeling approaches. We applied the 5-fold cross validation among the training set, and compared their prediction power on the set-aside testing set. It's apparent that the Ensemble model gave us the best results.

Figure 2. Scatter plots of performance of the ensemble model in predicting baseline ADAS-Cog11

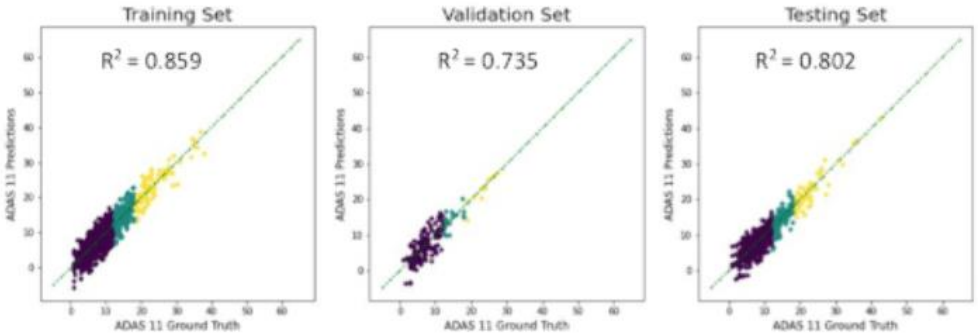

Fig 2 shows the scatter plots of performance of the ensemble model in predicting baseline ADAS-Cog11, separately for subjects within the in-sample training set, validation set and out-of-sample test set. The legend reflects three cognition groups of the subjects: Healthy Control, MCI, and Dementia. All sets give excellent correlation with real data.

Conclusions: This study constitutes the best-reported performance of any comparable approaches and opens the door towards machine learning based tracking of AD progression. Through further feature map analysis made on the receptive

fields, we managed to impart much-needed model interpretability, critical for real-world clinical practice. We're also looking forward to extend this to time-series forecast.

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OD049 / #1159

ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

COMPUTER ASSISTED HAND MOVEMENT ANALYSIS-BASED POTENTIAL SCREENING METHOD FOR MILD COGNITIVE IMPAIRMENT

Dalida Berente[1,2], Andras Horvath[1,3], Anita Kamondi[1,4]
[1]National Institute of Mental Health, Neurology and Neurosurgery, Neurocognitive Research Center, Budapest, Hungary, [2]Semmelweis University, School Of Phd Studies, Budapest, Hungary, [3]Semmelweis University, Department Of Anatomy Histology And Embryology, Budapest, Hungary, [4]Semmelweis University, Department Of Neurology, Budapest, Hungary

Aims: Alzheimer's disease (AD) is the most common cause of major neurocognitive disorders (NCDs) in the elderly. NCDs in our aging population pose a significant socioeconomic burden on our society. However, ideal screening methods for large patient groups with NCDs are yet to be developed. Latest results suggest that decline in visuomotor function appears in the early stages of the disease which may have screening potential. Our objective was to develop an automated, electronic screening tool for Mild Cognitive Impairment (MCI) the prodromal phase of NCDs.
Methods: 68 individuals took part in our study: 46 healthy controls and 22 patients with clinically defined MCI. They underwent detailed neurological and neuropsychological evaluation, MRI acquisition and used a computer-based screening algorithm called Precognize. Detailed statistical analysis was performed for all data.
Results: Significant differences were found between HC and MCI groups in mouse movement characteristics derived from Precognize, including entropy, distance and duration of mouse movements. Entropy of the mouse movements showed the most significant difference between the two groups (left hand: $F=5.24$; $p=0.001$ right hand: $F=8.46$; $p<0.001$). Correlation analysis between motor data and neuropsychological test scores revealed that negative correlation was strongest between mouse movement parameters and Addenbrooke's Cognitive Examination total score (average r: -0.37, all p's<0.05) while positive correlation was strongest between motor parameters and Clinical Demenatia Rating scale score (average r:-0.36, all p's<0.001). Age, gender and anxiety did not influence the motor parameters (all p's>0.05).
Conclusions: Based on our results, hand movement analysis might serve a screening purpose as the Precognize system shows promising potential for the early recognition of MCI. Our findings are promising for the future development of an automatic, digital screening method for MCI.

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ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

COMPUTER AND SMARTPHONE-ADMINISTERED VERSIONS OF THE COGSTATE BRIEF BATTERY ARE EQUIVALENT ON PERFORMANCE ACCURACY BUT NOT PERFORMANCE SPEED

Christopher Edgar[1], Hannah Cummins[2], Lisa Bransby[2], Laura Bird[2], Veronika Simic[3], Paul Maruff[3], Yen Ying Lim[2]
[1]Cogstate Ltd, Cogstate Ltd, London, United Kingdom, [2]Turner Institute for Brain and Mental Health, School Of Psychological Sciences, Monash University, Clayton, Australia, [3]Cogstate Ltd, Cogstate Ltd, Melbourne, Australia

Aims: The use of smartphones to assess cognition holds potential in increasing access to assessment and for use in novel experimental designs such as in ecological momentary assessment. The Cogstate Brief Battery (CBB) is a well-validated computerised test battery, whose simple design and response requirements make it suitable for smartphone administration. The aim of this study was to compare performance speed and accuracy between computer and smartphone CBB in healthy adults. We also explored whether different smartphone operating systems impacted performance.
Methods: A convenience sample of healthy young adults (n=60), $M(SD)_{age}$ =24.5(6.0), completed three assessments of the computer and smartphone CBB in a randomized crossover study. The CBB comprises of tests of psychomotor function (Detection; DET), attention (Identification; IDN), visual learning (One Card Learning; OCL), and working memory (One Back; OBK).
Results: No CBB data was lost or incomplete. All CBB tests showed comparable test-retest reliability across both smartphone (ICC 0.61-0.88) and computer (ICC 0.62-0.85) administrations. Performance speed on the DET, IDN and OBK tests was slower on the smartphone than computer (d's ranging between 0.40-0.53). Performance accuracy on each test was equivalent across smartphone and computer (d's ranging between 0.08-0.18). Of the sample, 58% reported using an iPhone compared to Android. Accuracy of CBB performance did not differ between smartphone operating systems, whereas performance speed was generally faster on iPhone compared to Android for OCL (d=0.67) and OBK (d=0.50).
Conclusions: The results indicate that smartphone CBB has high acceptability, good reliability, and that accuracy of performance was equivalent between smartphone and computer versions. However, the smartphone CBB generally, and the smartphone operating system do influence performance speed. This study highlights important considerations for the use of smartphone-administered cognitive tests.

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OD051 / #2087

ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

SEX DIFFERENCES IN A COMPUTERIZED COGNITIVE ASSESSMENT (A PREDICTIVE DIGITAL BIOMARKER FOR ALZHEIMER'S DISEASE)

Julie Novakova Martinkova[1,2], Robbert Harms[3], Alberto Ferrari[1,3], Maria Florencia Iulita[1,3], Jakub Hort[2], Carmela Tartaglia[1,4], Cassandra Szoeke[1,5], Maria Teresa Ferretti[1], Antonella Santuccione Chadha[1,3]
[1]Women's Brain Project, Women's Brain Project, Guntershausen, Switzerland, [2]Charles University and Motol University Hospital, Department Of Neurology, Prague, Czech Republic, [3]Altoida Inc., Altoida Inc., Washington, United States of America, [4]University of Toronto, Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [5]Faculty of Medicine, Dentistry and Health Science, University of Melbourne, Centre For Medical Research, Melbourne, Australia

Aims: Digital biomarkers enable non-invasive longitudinal observations of at-risk populations, and may offer high sensitivity to predict disease progression. Alzheimer's disease (AD) is characterized by cognitive impairment, with potential motor dysfunction. The Altoida Digital Neuro Signature (DNS) was previously described to have high predictive ability (up to ROC-AUC 0.92) for conversion from mild cognitive impairment (MCI) to AD dementia. Since sex differences have been described in AD, we explored whether this digital biomarker was able to distinguish differences in performance between sexes.
Methods: We examined the sex-discerning ability of the DNS on a combined population/memory clinic cohort of n=568 individuals (55% women) spanning the spectrum of AD (healthy, MCI, AD dementia). Participants underwent testing using the DNS, which simulates complex activities of daily living through augmented reality tasks, complemented with motoric function tests and two speech tasks. In a subset of healthy subjects (n=348), we used recorded features to train a sex classifier (male/female), and subsequently used fivefold cross-validation to estimate its performance, and the Shapley Additive exPlanations method to estimate feature contribution.
Results: The classifier achieved an AUC of 0.75 (SD +- 0.06) for discriminating between sexes. The performance differed between the heathy (AUC 0.74), MCI (AUC 0.66) and AD dementia (AUC 0.60) subgroups. For individual features, higher acceleration variances were indicative of males, while lower were indicative of females. Contributing groups of features represented steady hand microtremors and coarse scale hand motion variance.
Conclusions: Exploration of sex differences in digital biomarkers for AD is warranted, including exploration in diverse diagnostic subgroups. Further study of sex differences in digital biomarkers' predictive ability could help identify sex-specific markers of progression; this analysis is currently underway.

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OD052 / #649

ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

EXPLAINABLE ARTIFICIAL INTELLIGENCE IDENTIFIES AN AQP4 POLYMORPHISM-BASED RISK SCORE ASSOCIATED WITH BRAIN AMYLOID BURDEN

Simone Beer[1], David Elmenhorst[1,2], Gérard Bischof[1,2], Alfredo Ramirez[3,4,5], Andreas Bauer[1], Alexander Drzezga[1,2,4]
[1]Forschungszentrum Juelich, Institute Of Neuroscience And Medicine (inm-2), Juelich, Germany, [2]Faculty of Medicine and University Hospital Cologne, University of Cologne, Department Of Nuclear Medicine, Cologne, Germany, [3]Faculty of Medicine and University Hospital Cologne, University of Cologne, Division Of Neurogenetics And Molecular Psychiatry, Department Of Psychiatry And Psychotherapy, Cologne, Germany, [4]German Center for Neurodegenerative Diseases (DZNE), German Center For Neurodegenerative Diseases (dzne), Bonn, Germany, [5]University of Cologne, Excellence Cluster On Cellular Stress Responses In Aging-associated Diseases (cecad), Cologne, Germany

Aims: Objectives: The influence of the glymphatic system on ß-amyloid plaques in Alzheimer's disease (AD) through Aquaporin-4 (AQP4) is increasingly discussed. Studies showed that *AQP4* Single Nucleotide Polymorphisms (SNPs) are associated with cognitive decline and brain amyloid, measured by [^{18}F]Florbetapir PET. However, *AQP4* is not among the risk loci identified in GWAS, suggesting potential involvement of *AQP4* variants in endophenotypes related to AD like brain amyloid burden. We have used machine learning as a tool to address *AQP4* SNPs, followed by methods of explainable AI, to define a *AQP4* polymorphism-based risk score with respect to brain amyloid burden.
Methods: Methods: We have used tree ensembles with ADNI data, namely *AQP4* SNPs, age and [^{18}F]Florbetapir uptake (SUVR). SHapley Additive exPlanations (SHAP) were used to explain the models with respect to the effect of single SNPs on SUVR. We have formulated a polymorphism-based risk score for increased SUVR as the number of SNPs with deleterious effects, and evaluated the findings using linear regression on PET SUVR with both ADNI data and data from the screening process of the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study (all cognitively normal).
Results: Results: SHAP shows clear decisions towards protective or deleterious effects for several *AQP4* SNPs in females. The risk score was associated with increased PET SUVR in females (ADNI: $p = 0.014$, A4: $p = 0.013$) but not in males (ADNI: $p = 0.166$, A4: $p = 0.44$).
Conclusions: Conclusions: In women, brain amyloid burden is associated with a polymorphism-based risk score for the *AQP4* gene, which is already significant in cognitively normal women. The results support the hypothesis of an involvement of the glymphatic system, and particularly AQP4, in brain amyloid burden, with a potential gender-dependent susceptibility.

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ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

NEUROPRO: A COMPILATION OF ALL PROTEOMIC DIFFERENCES IN HUMAN ALZHEIMER'S BRAIN TISSUE

Eleanor Drummond[1], Tomas Kavanagh[1], Thomas Wisniewski[2], Beatrix Ueberheide[2], Manor Askenazi[2]
[1]University of Sydney, Faculty Of Medicine And Health, Sydney, Australia, [2]New York University, Grossman School Of Medicine, New York, United States of America

Aims: Proteomic studies of human brain tissue have exceptional potential to identify protein changes that drive disease. The recent increase in human Alzheimer's disease brain tissue proteomic studies provides a potential data gold-mine regarding the pathogenesis of Alzheimer's. Our aim was to combine all proteomic studies of Alzheimer's human brain tissue into a user-friendly, searchable database (NeuroPro).
Methods: Systematic literature searches identified 38 mass spectrometry studies examining human Alzheimer's brain tissue including studies of bulk tissue homogenate, specific tissue fractions, and analysis of neuropathological lesions (plaques, tangles, CAA). Data from these studies were manually standardised to enable direct comparison.
Results: 18,144 significant protein differences between Alzheimer's and control tissue were identified from 38 studies, mapping to 5,312 proteins significantly altered in Alzheimer's. This included protein differences in 12 brain regions and at three stages of disease (preclinical Alzheimer's, mild cognitive impairment, advanced Alzheimer's). Proteomic studies were remarkably consistent despite differences in sample preparation, mass spectrometry methodology, and type of tissue examined. Of the 851 proteins consistently altered in >5 studies; 305 and 444 proteins were consistently reported to be increased and decreased respectively. Excitingly, many of our most consistently identified protein changes are currently understudied in the Alzheimer's field (<10 publications). NeuroPro highlighted distinct protein differences at early and late stages of disease; for example, plaque associated proteins were increased early in disease, while major tangle proteins were predominantly increased at later stages. Synaptic proteins were significantly decreased early in disease, while mitochondrial proteins were decreased later in disease.
Conclusions: NeuroPro is a powerful new resource that provides new insight into human Alzheimer's brain protein changes and highlights novel proteins of particular interest that may mechanistically drive Alzheimer's disease.

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OD054 / #1483

ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

THE ABOUT ME CARE CARD: AN SHARED DECISION-MAKING (SDM)-BASED TOOL TO PROMOTE PURPOSEFUL DEMENTIA CARE

Greg Kotzbauer[1], Mikele Epperly[2], Yee Huey Tan[3], Supriya Yagnik[4], Heather Kang[5], Stuart Grande[6]
[1]Morph Studio, Morph Studio, Denver, United States of America, [2]F. Hoffmann-La Roche Ltd., Product Development Medical Affairs, Basel, Switzerland, [3]Pharma International, Roche Pharmaceuticals, Ad Marketing Chapter, Selangor, Malaysia, [4]Genentech, Inc., Product Development, Global, South San Francisco, United States of America, [5]Roche Korea, Medical Affairs, Seoul, Korea, Republic of, [6]University of Minnesota School of Public Health, Division Of Health Policy And Management, Minneapolis, United States of America

Aims: Neurocognitive disorders like dementia can be characterised by complex decisions and high emotional distress. People experiencing cognitive decline require support to consider treatment and care options based on their personal circumstances and preferences. Current decision-support tools focus care conversations on discrete clinical choices and fail to shape purposeful decisions that result in whole-person care pathways. This abstract presents the development of the About Me Care Card, a shared decision-making (SDM) tool designed to create human-centred dementia care that is aligned with clinical evidence and each patient's preferences, goals, and values.
Methods: A community-based approach guided the co-development of this SDM tool. A transdisciplinary international steering committee, including a patient, caregivers, multidisciplinary physicians, nurses and administrators, and core research team framed initial prototypes based on an environmental scan and iterative design sessions.
Results: Design and testing sessions with stakeholders emphasised the need to define purpose to overcome challenges of living with dementia. The About Me Care Card content focuses on three primary areas: My Life, Living My Best Life, and My Care Plan. These areas reflect theoretical concepts linked with 'Purposeful SDM', which focus the conversation on an examination of patient purpose, exploration of what matters, and prompts to outline next steps.
Conclusions: The application of iterative prototyping with international transdisciplinary stakeholders resulted in content centred on patient confidence, goal-setting, finding purpose and achieving meaning in daily life. An SDM tool designed to create care pathways based on whole-person discussions may drive care conversations in new ways compared with more traditional decision-based tools.

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OD055 / #1646

ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

REMOTE CHARACTERIZATION OF INDIVIDUALS WITH SUBJECTIVE COGNITIVE COMPLAINTS FROM THE INTUITION BRAIN HEALTH STUDY

Sharon Sha[1,2], Monroe Butler[3], Audrey Gabelle[3], Andrew Becker[3], Roland Brown[3], Paramita Saha-Chaudhuri[3], Jessica Ash[3], Matthew Hobbs[3], Sean Kenny[3], Hanson Lenyoun[4], Matt Bianchi[4], Shibeshih Belachew[3]
[1]Stanford University, Neurology And Neurological Sciences, PALO ALTO, United States of America, [2]Intuition Study, Scientific Committee, Cambridge, United States of America, [3]Biogen, Biogen Digital Health, Cambridge, United States of America, [4]Apple Inc., Apple Health, Cupertino, United States of America

Aims: Subjective cognitive complaints (SCC) may signal risk of cognitive decline. This investigation explores the feasibility of enrolling a decentralized, SCC cohort by self-report, describes the risk factor profile for cognitive decline, and assesses objective cognitive performance compared to healthy controls (HC).
Methods: INTUITION (NCT05058950) is an observational two-year virtual brain health study of 23,000 U.S. adult residents. The overarching study aims are to develop real-world high-accuracy classifiers that distinguish cognitive impairment from healthy aging, and to construct a trackable cognitive health score. Participants provide multimodal data with use of a study-app, iPhone, and Apple Watch. SCC is defined by age (50+ years) and concern for cognitive decline based on a *Cognitive Function Instrument* total score of 4 and above. We report on a 2-to-1 demographically matched HC-to-SCC sample with standard statistical summaries of self-report demographic and medical history information, and we compare baseline cognitive and psychological scores (e.g., *E-Cog-12, PHQ-2, GAD-2*) between groups.
Results: Matched analysis from N=2,045 SCC and N=4,090 HC participants (pooled mean age of 64.1 years, SD of 7.4) shows SCC with higher incidence of modifiable and non-modifiable risk factors for cognitive decline. In measures of cognition and psychological health, SCC participants experience greater burden of cognitive and behavioral symptoms. Results from unsupervised cognitive assessments reveal group-level differences in attention, executive function, learning and memory.
Conclusions: We show the feasibility of enrolling population-based SCC cohorts based on self-reported cognitive symptoms, which reliably align with risk factor profiles and objective measurements of cognitive performance from unsupervised testing.

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OD056 / #663

ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

APPLYING MACHINE LEARNING TO ELECTRONIC MEDICAL RECORD DATA TO IDENTIFY ASSOCIATIONS WITH FUTURE DIAGNOSIS OF ALZHEIMER'S DISEASE

Alice Tang[1,2], Tomiko Oskotsky[1], Silvia Miramontes[1], Sarah Woldemariam[1], Yaqiao Li[1], Sergio Baranzini[3], Zachary Miller[3], Isabel Allen[4], Katherine Rankin[1,3], Marina Sirota[1]
[1]University of California, San Francisco, Bakar Computational Health Sciences Institute, San Francisco, United States of America, [2]University of California, San Francisco, Graduate Program In Bioengineering, San Francisco, United States of America, [3]University of California, San Francisco, Neurology, San Francisco, United States of America, [4]University of California, San Francisco, Epidemiology & Biostatistics, San Francisco, United States of America

Aims: Utilize Electronic Medical Records (EMR) to identify clinical predictors and risk of future Alzheimer's Disease (AD) diagnosis.
Methods: AD patients were identified from the UCSF EMR using UCSF's Memory and Aging Center diagnosis, and Controls obtained from the remaining non-demented patients. Clinical data (conditions, drugs, abnormal lab measurements) were extracted before time 0, defined as first diagnosis of any dementia or anti-dementia drug prescription in the AD cohort and 1 year before the last visit for Controls. Random forest (RF) classification models for AD were trained using clinical features taken multiple years prior to time 0, with 1:3 AD:Control matching on demographics and hospital utilization. Models were evaluated based on AUROC on a 30% held-out set. Cox proportional regression analysis was applied to top RF features as exposures on cross-California UC EMR (UCDDP) to obtain unadjusted and adjusted hazard ratios (HR, aHR) with time to AD diagnosis as the outcome.
Results: From the UCSF EMR, 2,996 AD patients and 534,852 total Controls were identified. RF models performed with AUROC of up to 0.80. Top predictive features identified as associated with AD include cognitive concerns, existence of abnormal blood results, vascular risk factors, and diseases of aging. Several features were further validated in the UCDDP data, with HR/aHR[95%CI] of 2.18[2.06-2.30]/2.04[1.92-2.06] for osteoporosis exposure, 3.66[3.44-3.89]/3.18[2.96-3.40] for cerebrovascular disease, and 1.86[1.66-2.09]/1.80[1.56-2.07] for fecal abnormalities.
Conclusions: EMRs provide a great opportunity to identify at-risk patients in clinical practice and predictive features across clinical domains for AD such as non-neurologic disorders of aging. Further analysis is needed to understand whether features arise due to hidden confounders (e.g. increased clinician testing) or biological relevance. Cox regression analysis highlights clinical features that increase AD risk even after adjusting for confounders.

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OD057 / #967

ON-DEMAND SYMPOSIUM: DIGITAL AND CLOUD BASED TOOLS, AI, MACHINE LEARNING
29-03-2023 07:00 - 08:30

EVALUATION OF DIGITAL BIOMARKERS FROM DIFFUSION MRI TO MONITOR ALZHEIMER'S DISEASE IN THE DAILY CLINIC

Vincent Perlbarg, Jean-Baptiste Martini, Etienne Bories, Iyèd Trimèche, Arthur Bezie, Julie Rachline, Didier Cassereau
BRAINTALE, Research & Development, STRASBOURG, France

Aims: White matter alterations have been already described at early stages of Alzheimer's disease (AD), notably using diffusion tensor imaging (DTI), but the translation in the clinic of meaningful white-matter biomarkers has remained a major challenge. brainTale-care, a recently CE-marked digital platform, overcomes this barrier by providing standardized and fit-for-purpose biomarkers, some of which are already clinically validated for several indications, from coma recovery prediction to drug efficacy monitoring. The objective of this study was to test the ability of these biomarkers to discriminate patients diagnosed with AD or mild cognitive impairments (MCI), and age-matched healthy controls (HC).
Methods: Diffusion weighted and 3DT1-weighted MR sequences were obtained from 113 subjects from the ADNI database (adni.loni.usc.edu): 66 HC, 34 MCI and 13 AD subjects. brainTale-care v2.2 was used to extract global standardized DTI parameters from deep white matter. Mann-Whitney tests were used for group comparisons. Complementary ROC analysis was conducted to evaluate diagnosis performance of DTI markers in combination with brain volumetric features of reference.
Results: Group comparison showed significant differences - decrease in Fractional Anisotropy (FA) ; increase in Mean Diffusivity (MD) - between pathological conditions (AD and MCI) and HC groups. Disease specific stratification is significantly ($p<0.05$) improved (AUC from 81% to 90%) when DTI markers are used in combination with brain volumetric analysis.
Conclusions: This study suggests that standardized biomarkers from brainTale-care platform show important interest in AD patient monitoring in the clinic.. The easy implementation of these biomarkers through a CE-marked medical device opens the potential to improve patient diagnostic and management in clinical setting and potentially as surrogate endpoint in clinical trials. White matter monitoring is becoming meaningful and useful for patient management.

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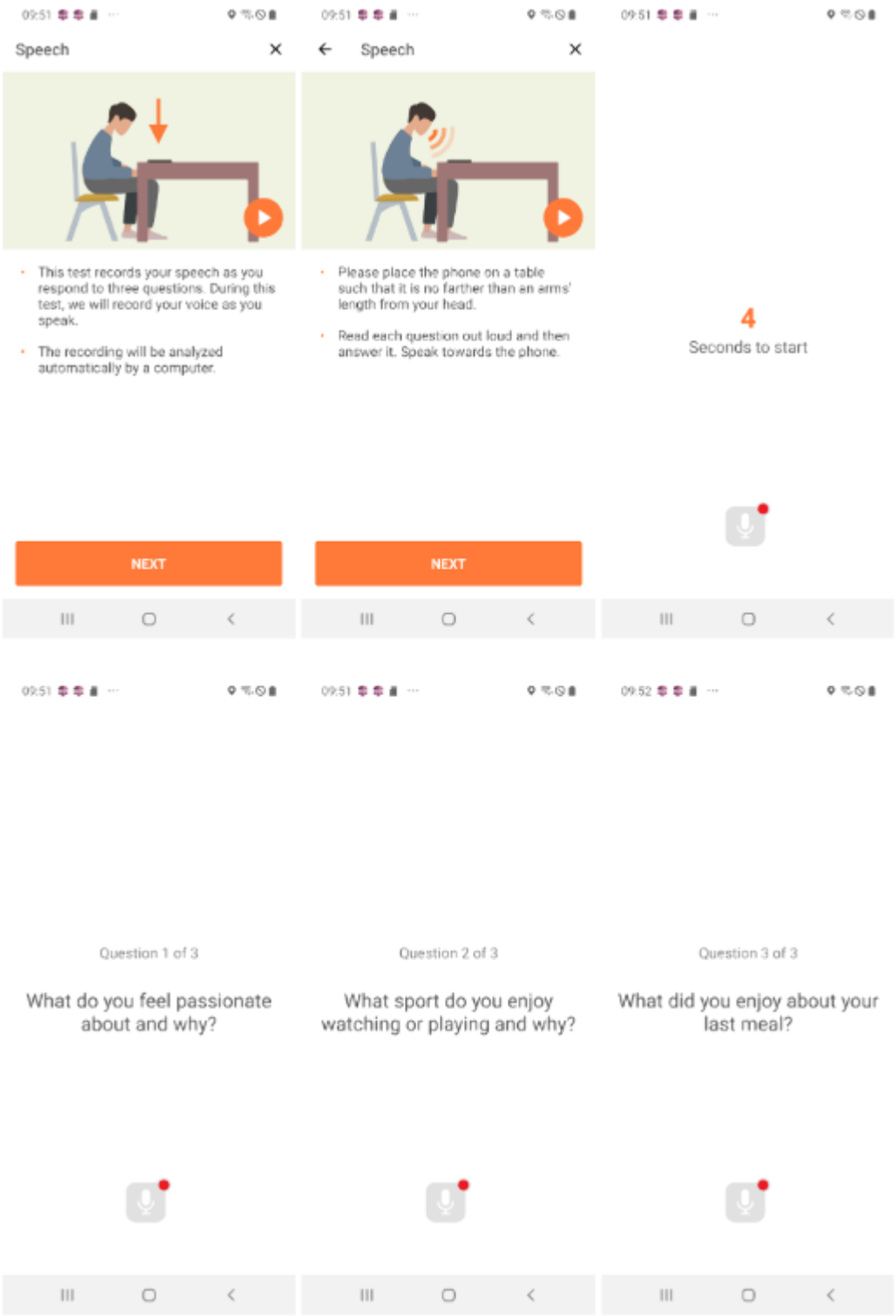
OD058 / #1082

ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

RELIABILITY AND VALIDITY OF DIGITAL SPEECH FEATURES AS BIOMARKERS OF DYSARTHRIA SEVERITY AND PROGRESSION IN INDIVIDUALS WITH EARLY PARKINSON'S DISEASE

Damian Kwasny[1], Jan Rusz[2], Raphael Ullmann[1], Florian Lipsmeier[1], Ekaterina Volkova-Volkmar[1], Bernhard Fehlmann[1], Hanno Svoboda[3], Thomas Kustermann[1], Ron Postuma[4,5], Michael Lindemann[1], Kirsten Taylor[1]
[1]F. Hoffmann-La Roche Ltd., Roche Pharma Research And Early Development, Pred Informatics, Pharmaceutical Sciences, Clinical Pharmacology, And Neuroscience And Rare Diseases Discovery And Translational Area, Roche Innovation Center Basel, Basel, Switzerland, [2]Czech Technical University in Prague, Faculty Of Electrical Engineering, Prague, Czech Republic, [3]F. Hoffmann-La Roche Ltd, Roche Diagnostics Gmbh, Mannheim, Germany, [4]Montreal General Hospital, Neurology, Montreal, Canada, [5]Hôpital du Sacré-Coeur de Montréal, Center For Advanced Research In Sleep Medicine, Montreal, Canada

Aims: To evaluate the reliability and validity of acoustic speech features from remotely collected speech samples as biomarkers of dysarthria severity and progression in individuals with early Parkinson's disease (PD).
Methods: 316 early-stage, drug-naive PD participants of the PASADENA Phase II study (NCT03100149) were remotely monitored with the Roche PD Mobile Application v2, including a speech test every other day (Figure 1). Six acoustic features of speech prosody, phonation, articulation and timing were assessed. For each feature separately, values were aggregated within fortnights until the start of dopaminergic therapy. Robustness was evaluated by intra-class correlations (ICC) and minimal detectable change (MDC) in the first two fortnights. Gender differences (Mann-Whitney U test of baseline clinical and digital data), clinical validity (baseline Spearman correlations with MDS-UPDRS part 2 and 3 bulbar scores) and progression sensitivity (linear mixed effect models fitted to the change from baseline to week 52) were assessed at a significance threshold of $\alpha<.05$. Figure



1

Results: All features evidenced high ICCs (>=75%) and low MDCs (<=25%). At baseline, speech performance was better in females according to the clinical bulbar scores (p<.001) and 5/6 acoustic features (p<.001). 4/6 (p<.001-.02) and 2/6 (p<.05) acoustic features correlated with bulbar scores in males and females, respectively. 4/6 features detected disease progression (p<.001-.002), with one progressing faster in males (p<.05).

Conclusions: Acoustic speech features extracted from remotely collected recordings may serve as reliable and valid biomarkers of dysarthria severity and progression in individuals with early PD.

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OD059 / #1444

ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

DIGITAL HEALTH TECHNOLOGIES CAN REDUCE SAMPLE SIZE AND ENABLE SHORTER PROOF OF CONCEPT CLINICAL TRIAL IN PARKINSON'S DISEASE

Laurent Essioux[1], Daria Rukina[1], Judith Anzures Cabrera[2], Ekaterina Volkova-Volkmar[3], Florian Lipsmeier[3], Michael Lindemann[3,4], Kirsten Taylor[5], Gennaro Pagano[5]
[1]Hoffmann La Roche, Roche Pharma Development Data Science, Basel, Switzerland, [2]Hoffmann La Roche, Roche Pharma Development Data Science, Welwyn garden city, United Kingdom, [3]F. Hoffmann - La Roche AG, Roche Pharma Research And Early Development, Pred Data&analytics, Basel, Switzerland, [4]F. Hoffmann-La Roche Ltd., Roche Pharma Research And Early Development, Pred Informatics, Pharmaceutical Sciences, Clinical Pharmacology, And Neuroscience And Rare Diseases Discovery And Translational Area, Roche Innovation Center Basel, Basel, Switzerland, [5]F. Hoffmann-La Roche Ltd, Roche Pharma Research And Early Development, Basel, Switzerland

Aims: Digital health technologies (DHTTs) allow continuous and objective assessment of Parkinson's disease progression, with expected increased precision. Here, we investigate whether DHTT-based endpoints enable smaller and shorter proof-of-concept (PoC) studies, calculating the sample size required for a hypothetical phase II trial in early-stage Parkinson's disease using a digital multivariate score from the Roche PD Mobile Application v2 tool (Simple Sum Score) as primary endpoint and compare it to sample size obtained using the canonical clinical endpoint, MDS-UPDRS Part III.
Methods: Sample size calculations were made using data from PASADENA study (NCT03100149), assuming a minimal detectable difference (MDD) of 25% decrease progression in the treated population compared to placebo in a two-arm 1:1 24-week PoC study of both the MDS-UPDRS part III and the simple sum score, with a type I error of 0.2. Changes from baseline in MDS-UPDRS Part III and Simple Sum Score were modeled with MMRM and linear mixed effect model, respectively.
Results: Calculated sample sizes at MDD were 550 individuals and 166 individuals for MDS-UPDRS part III and the Simple Sum Score respectively, which represent a 70% reduction in the sample size. Assuming a recruitment rate of 25 individuals per month, a PoC study using MDS-UPDRS Part III as primary endpoint would last approximately 28 months compared to approximately 12 months, using the Simple Sum Score as primary endpoint.
Conclusions: Using a DHTT-based endpoint can enable smaller, shorter and faster PoC studies in Parkinson's disease.

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OD060 / #763

ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

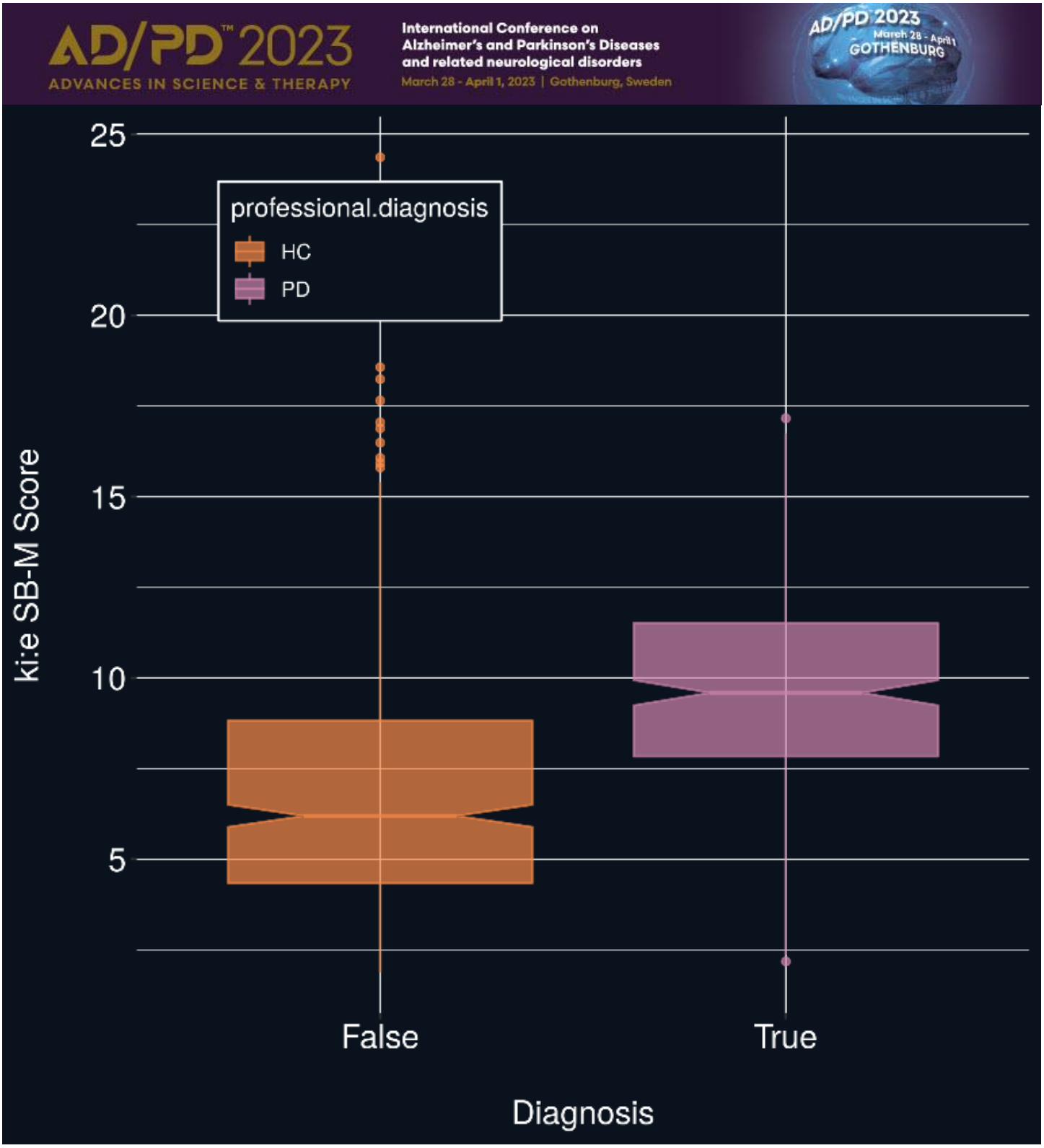
VALIDATING THE REMOTE AUTOMATED KI:E SPEECH BIOMARKER FOR MOTOR FUNCTION IN PARKINSON'S

Mario Mina, Jian Zhao, Nicklas Linz, Johannes Troeger
ki:elements, Science, Saarbrücken, Germany

Aims: The ki:e Speech Biomarker for Motor Function (SB-M) biomarker was developed with the aim of detecting and monitoring abnormal motor function through speech. This abstract describes the clinical validation of the ki:e SB-M.
Methods: We use a set of audio recordings of a sustained phonation task to develop our biomarker from a set of participants as described in figure 1 performed by participants up to three times a day. The same participants were remotely administered corresponding UPDRS assessments on a monthly basis. We split the dataset in a building and a holdout testing set containing all the samples from 25% of the participants.

	Train		Test	
	Healthy Control (HC)	Parkinson's Disease (PD)	Healthy Control (HC)	Parkinson's Disease (PD)
N participants	431	269	148	87
N samples	1617	916	527	318
Age	33.90 (13.99)	60.95 (10.07)	33.94 (4.95)	61.52 (10.21)
UPDRS total	3.31 (2.99)	12.87 (7.23)	4.44 (4.09)	11.59(8.27)

We extract several acoustic features and select features based on validity for measuring motor function as well as descriptive statistics.Multivariate machine learning methods were then used to combine the score. We follow the Digital Medicine Society (DiMe) V3 framework for analytical and clinical validation. We determine analytical validity by examining the SB-M's correlation with UPDRS item 2.10, which specifically measures tremor, and clinical validity by evaluating the SB-M's capacity to discriminate between both groups in terms of statistical significance and machine learning.
Results: We obtain significant score differences between PD and HC groups, along with a moderate significant correlation with UPDRD2.10 (Figure 1b). These results are reflected in the ML scenario, where we achieve an AUC of .69 using only the SB-M.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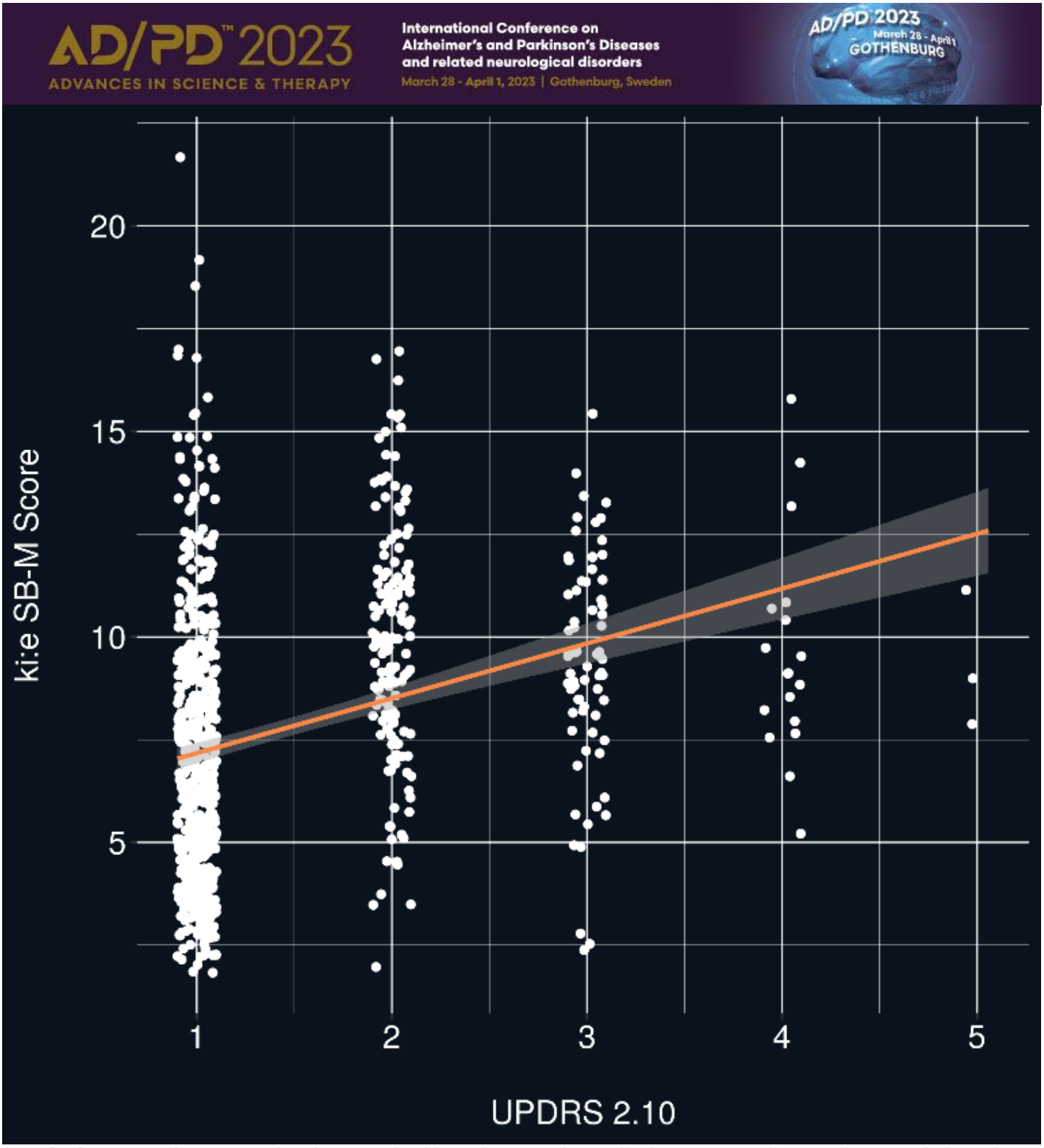

Conclusions: Results suggest that the SB-M is able to detect and quantify the presence of tremor in a vowel phonation task in Parkinson's Disease.

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OD061 / #1864

ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

GAIT ALTERATIONS ARE PROMINENT FEATURE OF DRUG NAÏVE PD: MOBILE HEALTH TECHNOLOGY IDENTIFIES GAIT IMPAIRMENT IN DRUG NAIVE PARKINSON'S DISEASE

Cinzia Zatti[1], Andrea Pilotto[1], Andrea Rizzardi[1], Marcello Catania[1], Giulio Bonzi[1], Clint Hansen[2], Daniela Berg[2], Robbin Romijnders[2], Walter Maetzler[2], Alessandro Padovani[1]
[1]University of Brescia, Neurology Unit, Department Of Clinical And Experimental Sciences, Brescia, Italy, [2]Christian-Albrechts-University of Kiel, Department Of Neurology, Kiel, Germany

Aims: Gait alterations are a common feature of PD patients but their relevance at the onset of the disease is still debated. Aim of the study was to evaluate gait alterations in de novo untreated PD patients using an extensive supervised assessment with mobile health technology (MHT).
Methods: the prospective study included consecutive drug naïve PD patients who underwent a multidimensional assessment including evaluation of motor and non-motor symptoms, cognitive status and comorbidity. All PD patients and age-matched controls underwent gait analyses in supervised normal and dual-task conditions using mobile health technology. PD patients were divided according to standard clinical examination into with (PD-G) and without (PD-nG) clinically-significant gait impairment- independently from gait analyses.
Results: 45 drug-naïve PD patients, including 22 PD-nG and 23 PD-G, and eighty age-matched controls entered the study. PD-G exhibited higher MDS-UPDRS-III but were similar in the clinical characteristics namely age, sex distribution cognitive and autonomic symptoms compared to PD-nG. The application of inertial sensors evidenced that gait alterations were present in all PD patients, specifically in PD with and without gait impairment. Step time and asymmetry index differentiate PD-nG and PD-G from controls only in dual-task gait. Increased step length was the only gait variable able to differentiate PD-G but also PD-nG from controls in normal gait, but its sensitivity increased with dual-task gait.
Conclusions: mobile health technology is able to identify subtle gait alterations in the large majority of de novo PD patients and thus differentiate them from controls independently from clinical evaluation. Further studies are important to evaluate the role of digital technology to evaluate the response to pharmacological and non-pharmacological interventions in early PD patients.

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OD062 / #1559

ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

EVALUATING THE DIAGNOSTIC USABILITY OF DEEP-LEARNING-DERIVED CT-BASED VOLUMETRIC MEASURES IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS.

Meera Srikrishna[1], Woosung Seo[2], Anna Zettergren[3], Silke Kern[3], Lars-Olof Wahlund[4], Eric Westman[4], Johan Virhammar[5], David Fällmar[2], Ingmar Skoog[3], Michael Schöll[6]
[1]Institute of Neuroscience and Physiology, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Wallinsgatan , Mölndal, Sweden, [2]Neuroradiology, Uppsala University, Department Of Surgical Sciences, Uppsala, Sweden, [3]University of Gothenburg,, Department Of Psychiatry And Neurochemistry, Centre For Ageing And Health (agecap), Institute Of Neuroscience And Physiology, Sahlgrenska Academy, Mölndahl, Sweden, [4]Division of Clinical Geriatrics, Department Of Neurobiology, Care Sciences And Society, Center For Alzheimer Research, Karolinska Institutet, Stockholm, Sweden, [5]Neurology, Uppsala University, Department Of Medical Sciences, Uppsala, Sweden, [6]Sahlgrenska University Hospital, Department Of Clinical Physiology,, Gothenburg, Sweden

Aims: Brain computed tomography (CT) is an affordable and widely accessible modality routinely used to assess ventricular enlargement and other neuroimaging signatures of idiopathic normal pressure hydrocephalus (iNPH). In this study, we aim 1) to develop a transfer-learning-based deep learning model trained with automatically derived MR labels and manually derived CT labels to segment ventricular cerebrospinal fluid (VCSF) in brain CTs, 2) to assess the diagnostic accuracy of CT-based volumetric measures to distinguish iNPH patients from healthy controls.
Methods: First, we trained a U-Net to predict VCSF segmentations from input CT scans learning from VCSF labels segmented from paired magnetic resonance images (MRI) using standard automated tools. For this, we included 917 (70.4 ± 2.6 years, 99% cognitively normal) CT scans of which 734 had paired T1-weighted MRI scans from the Gothenburg H70 Birth Cohort. A second U-Net was initialised using the features from the previous U-Net and further trained to segment VCSF from input CT scans by learning from manually segmented CT-VCSF labels. We used 62 CTs and paired manual VCSF labels from iNPH patients (79.3 ± 6.46 years) from Uppsala University Hospital. Post model development, we derived CT-based VCSF volumetric metrics and evaluated their diagnostic usability.
Results: High volumetric correlations were observed between automatically and manually derived CT-VCSF ($\rho = 0.94$) in iNPH datasets, and CT-VCSF and MR-VCSF ($\rho = 0.90$) in the Gothenburg H70 Birth Cohort. The deep-learning-derived CT volumetric measures distinguished iNPH patients from cognitively normal individuals with high accuracy (AUC = 0.96).
Conclusions: Our results demonstrate clear potential of CT-derived volumetric measures to scan and flag clinical CT scans, to support clinical iNPH diagnostics, and to serve as a practical and economic alternative to MRI.

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OD063 / #148

ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

A COMPUTER SIMULATION MODEL TO PREDICT COGNITIVE IMPAIRMENT

Lewis Mehl-Madrona
Wabanaki Public Health and Wellness, Recovery Programs, 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 13 individuals, adjusting parameters to make correct predictions for all people. Then we entered the data from another 17 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 10 successes. We then modeled an additional 17 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. Twelve indicated willingness.
Conclusions: Interaction with computer simulation models can provide tools of persuasion to overcome difficulties inherent in people changing their modifiable risk factors.

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OD064 / #189

ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

CUSTOMIZED VIRTUAL REALITY INTERVENTION IN PEOPLE WITH ALZHEIMER DISEASE : FIRST COMPARATIVE RESULTS IN FRENCH NURSING HOMES AND LONG-TERM CARE UNITS

Anne-Julie Vaillant-Ciszewicz, Cassandra Quin, Olivier Guerin
CHU DE NICE, Pole Rav, NICE, France

Aims: According to the scientific literature, virtual reality (VR) is an innovative medium for reminiscence therapy. Recent studies show several benefits of using VR on anxiety, mood and the recall of episodic memories. Our work aims to describe the impact of customized VR on mood disorders in elderly people with cognitive disorders.
Methods: 30 participants (≥ 65 years) are recruited in 4 centers and randomized in two groups, both with immersive VR conditions (customized versus generic). Material : GoProFusion camera and Oculus Rift 360° headset. Before VR sessions (twice a week during 6 week), the cybersickness was evaluated during a pretest. Anamnesis was explored for each participant and clinical assessments were done pre– and post-intervention (depression, anxiety, apathy, quality of life, MMSE).
Results: Inclusion: 24/30 participants (mean age = 91.5; mean MMSE = 16.3). The Wilcoxon test was performed for statistical analysis. Anxiety decreased significantly in the customized group (n=10), (NPI frequency*gravity p=0.027). In the generic group (n=14): depression (HDRS p=0.012; NPI frequency*gravity p=0.007), anxiety (NPI frequency p=0.041) and apathy (IA p=0.046) scores decreased significantly. These results will be interpreted at the end of the study after adjusting for variables (mood disorders were more severe in the control group). MMSE scores improved 1 point in the customized group, but there was no change in the generic group.
Conclusions: VR is well tolerated by participants with cognitive disorder (no cybersickness effects). Surprisingly significant impacts on anxiety/depression were found in both groups.

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ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

A NEW DIGITAL BIOASSAY FOR SERUM-BASED DIAGNOSIS OF NEURODEGENERATIVE DISEASE

Matthew Cheetham[1], Emre Fertan[1], Zengjie Xia[1], Dorothea Boeken[1], Jeff Lam[1], Henrik Zetterberg[2], David Klenerman[1]
[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]Neuroscience and Physiology, Department Of Psychiatry And Neurochemistry, Mölndal, Gothenburg, Sweden

Aims: To develop a new highly sensitive aggregate-specific assay that is compatible with the SIMOA platform, to detect the presence of amyloid-beta and alpha-synuclein aggregates in samples of patients' serum and other biofluids.
Methods: In the SIMOA platform, beads are coated with capture antibody, incubated with the sample, then with biotinylated detector antibody, and finally with streptavidin conjugated enzyme. The beads are then loaded into a large array of microwells, each of which fits a single bead inside. Resorufin conjugates are then added to this array, and any wells containing an immunocomplex exhibit fluorescence. This way, the analyte concentration is obtained from the fraction of beads in the "on" state. This affords sensitivity down to femto-molar concentrations of the analyte. The standard use of SIMOA is to detect monomers, however we are specifically interested in aggregates as biomarkers of disease. Our assay was developed 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: We could see in-vitro aggregates down to ~10 pM, with low background levels. When accounting for the typical size of aggregates, this takes us to an effective concentration in the femto-molar range. We demonstrated that this is easily sufficient to detect the presence of aggregates in serum, and that monomers are not detected.
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.

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ON-DEMAND SYMPOSIUM: DIGITAL HEALTH TECHNOLOGIES, MACHINE LEARNING
29-03-2023 07:00 - 08:30

AN INTEGRATED MACHINE LEARNING ANALYSIS WORKFLOW FOR HUMAN PROTEOMIC PROFILES IDENTIFIED NETWORKS OF PLASMA BIOMARKERS FOR ALZHEIMER'S DISEASE

Zheng Yin[1], Lin Wang[1], Stephen Wong[2]
[1]Houston Methodist Research Institute, Systems Medicine And Bioengineering, Houston, United States of America, [2]Houston Methodist Hospital, T. T. And W. F. Chao Center For Brain And Houston Methodist Neal Cancer Center, Houston, United States of America

Aims: Alzheimer's disease (AD) has two pathological hallmarks in tau-containing neurofibrillary tangles and amyloid-β protein (Aβ)-containing neuritic plaques.However, levels of these pathological proteins in blood fail to distinguish AD from healthy control subjects. We performed tandem mass tag (TMT)-based quantitative proteomic analysis of proteins from plasma, and aim to discover potential plasma proteins associated with AD pathology using an integrative machine learning workflow.
Methods: With two independent Mass Spec experiments and duplicated plasma samples for each subject in each experiment, there are 72 total protein abundance data points from each experiment. We developed an integrative machine learning workflow to identify plasma markers with significantly different total protein abundances between AD and Control group, and constructed protein networks connecting identified plasma markers to AD related signaling pathways.
Results: Overall, a group of 40 proteomics markers were identified. Three groups of established markers related to different aspects of AD were collected via literature search and database query, these established plasma markers cover 1) association with AD diagnosis and progression; 2) variation of Aβ load in brain and 3) AD specific blood-brain barrier (BBB) dysfunction. PPI networks were constructed to illustrate the interactions between our AD plasma markers and these established markers. Specifically, eight of our 40 markers were previously reported as related to AD diagnosis or progression in meta-analysis; additionally, four of our markers interacted with established BBB markers including CRP (interacting with S100B, NFKBIA, AGER, LRP1), APOA1 (with RELA, LRP1 and MMP9), VTN (with LRP1 and MMP9) and AHSG (with MMP2 and MMP9).
Conclusions: Our results demonstrated the relevance on defects in lipid handling and blood brain barriers during the onset and progression of AD. Those differentially regulated plasma proteins are explored as candidate biomarker.

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OD067 / #2291

ON-DEMAND SYMPOSIUM: MCI, AD & FAD THERAPEUTIC STRATEGIES
29-03-2023 07:00 - 08:30

FORTASYN-PSI STUDY: BENEFIT OF SOUVENAID ON DEPRESSION, ANXIETY, APATHY, AND IRRITABILITY OF PEOPLE WITH MILD COGNITIVE IMPAIRMENT OR MILD DEMENTIA.

Miquel Aguilar Barberá[1], Natalia Rodrigálvarez[2], Eduardo Castro[2], Ana Isabel Tabuenca[3], Laura Prieto[3], Paquita Soler[1]
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Aims: To assess the benefits of Fortasyn Connect (Souvenaid®) in the behavior of people with mild cognitive impairment (MCI) and mild dementia at 3,6 and 12 months of treatment.
Methods: Observational, retrospective, national, unicentric study including 153 patients with MCI and 83 with dementia. Mean age [SD]: 76.1 [6.7]; 58.1% women (Alzheimer: 130; non-Alzheimer: 106). Changes in behavior were assessed with the Neuropsychiatric Inventory (NPI). Treatment effects were determined using the Wilcoxon test (month 3, month 6 and month 12 vs baseline). To analyze the effect of patient characteristics (sex, age, stage, etiology) and concomitant treatment (IACE, antidepressants, ginkgo biloba) a mixed model for repeated measures was used.
Results: A significative decrease ($p<0,001$) in number of items, severity, caregiver impact and NPI total score was observed compared to baseline at 3, 6 and 12 months. Improvement of depression, anxiety, apathy, and irritability was maintained at months 3, 6 and 12 ($p<0.001$). The decreases were more pronounced ($p<0.001$) when NPI baseline score was higher than >20 points. At 12 months, 65.3% of patients improved behavior and 12.2% remained stable. The benefit was independent of gender, age, or the etiology. Concomitant use of IACEs, antidepressants and/or ginkgo biloba did not change the results. Better response is demonstrated in MCI versus dementia ($p<0.0001$)
Conclusions: Fortasyn Connect improved behavior at 3, 6, and 12 months in patients with MCI and mild dementia. The benefit was greater if prescribed early and the basal NPI score was higher. Depression, anxiety, apathy, and irritability were the symptoms that improved the most. The benefits were observed when Fortasyn Connect was used alone or combined with IACE, antidepressants and/or ginkgo biloba. Fortasyn Connect may be useful in Alzheimer's and in other neurodegenerative etiologies.

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OD068 / #221

ON-DEMAND SYMPOSIUM: MCI, AD & FAD THERAPEUTIC STRATEGIES
29-03-2023 07:00 - 08:30

THE CURRENT AND FUTURE LANDSCAPE FOR PHARMACOTHERAPEUTICS IN ALZHEIMER'S DISEASE

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Aims: To our knowledge, there have been no up-to-date overviews of the current progress and potential outlook of Alzheimer's Disease pharmacotherapeutics. In this review, we will discuss the approved drugs used in clinical practice for AD patients, as well as elucidate the priority areas and avenues for drug development to generate future treatment options.
Methods: A literature review of the existing pharmocotherapeutics approved for the treatment of AD was conducted and synthesised, consisting of cholinergic-targetting, glutaminergic-targetting, as well as direct amyloid-beta neuropathology-targetting agents. Following this, a scoping review was conducted to elucidate future potential therapeutics that are currently in development.
Results: Whilst most drugs work to alter chollinergic transmission through anti-cholinesterases, other neurotransmitter systems are involved in cognitive dysfunction hence glutaminergic targetting drugs are used such as memantine. By targeting the neuropathology directly by using the recently approved aducanumab, trials suggested clinical improvents to subjects with mild cognitive impairment or mild dementia stage of disease progression. The future of AD pharmacotherapeutics include targetting other components of cholinergic and glutaminergic signalling pathways, as well as targetting multi-system therapeutics to manipulate noradrenergic, dopaminergic systems. The potential to directly target tau pathology also holds potential.
Conclusions: In this review we have discussed the approved drugs used in clinical practice for AD patients, as well as elucidated the priority areas and avenues for drug development to generate future treatment options. As we approach a new era of precision medicine, we not only must consider the expansion in armamentarium of pharmacological treatment used, we can use biomarker confirmation to act as indications for specific therapies, to stratify for use in the relevant patient subset, targeting an individual's unique neuropathology.

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OD069 / #807

ON-DEMAND SYMPOSIUM: MCI, AD & FAD THERAPEUTIC STRATEGIES
29-03-2023 07:00 - 08:30

PRELIMINARY DATA ON INDUCTION OF GAMMA OSCILLATIONS WITH NOVEL 40 HZ NON-INVASIVE LIGHT THERAPY SYSTEM IN PATIENTS WITH ALZHEIMER'S DISEASE

Maibritt Horning[1,2,3], Marcus Carstensen[2,4], Else Danielsen[5], Anders Baandrup[5], Mai Nguyen[2], Luna Hansen[2], Mark Henney[2,6], Kristoffer Madsen[6,7], Kamilla Miskowiak[8,9], Martin Ballegaard[1,3], Paul Michael Petersen[4], Troels Kjaer[1,3], Peter Høgh[1,3], Mikkel Agger[1,3]
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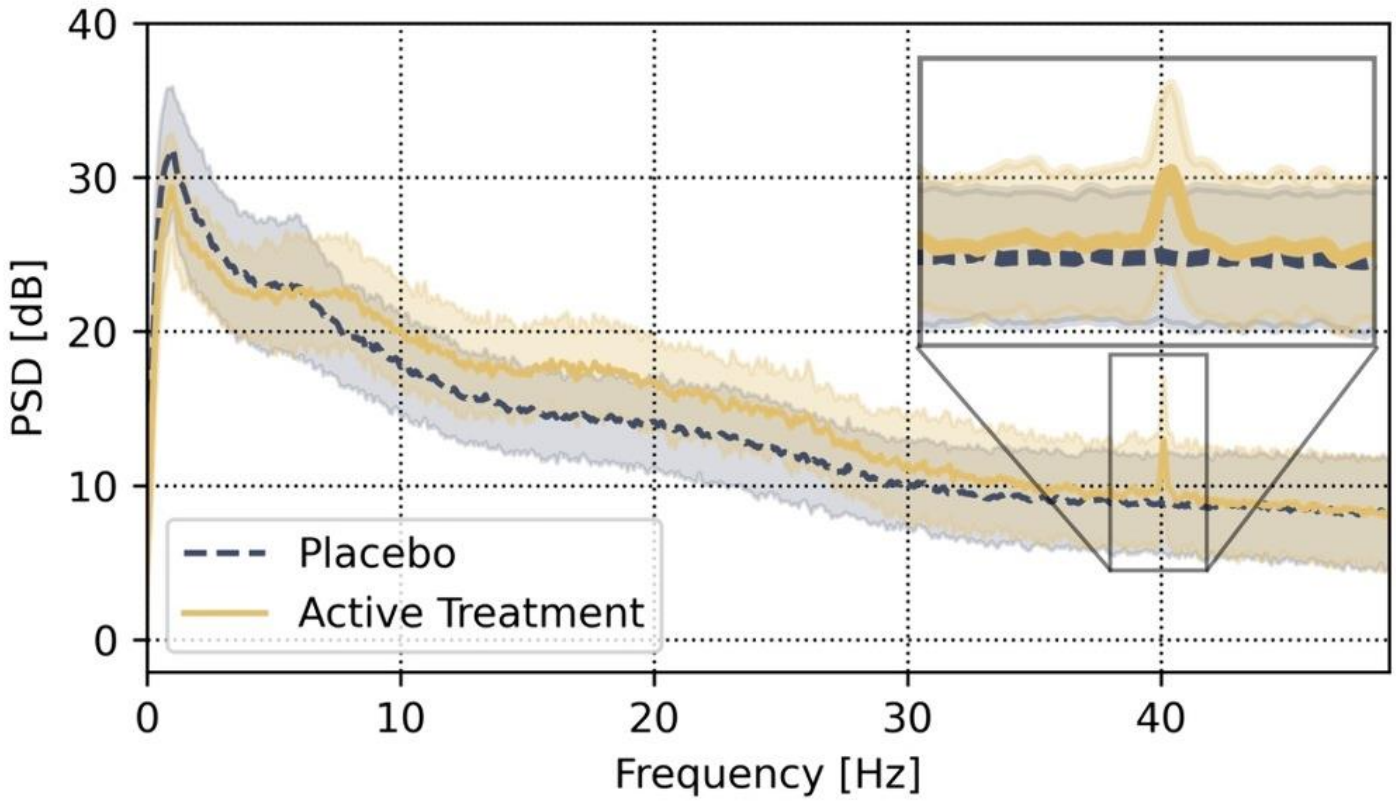
Aims: Growing evidence has shown a beneficial effect of the induction of 40 Hz neural oscillations in Alzheimer's disease (AD). Particularly, exposure to 40 Hz flickering light resulted in decreased brain atrophy, increased cognitive function, and rescue of circadian rhythms. Nevertheless, the side effects induced by flickering stroboscopic light in clinical trials and real-world settings may present a challenge. Therefore, ALZLIGHT Pilot (NCT04574921) investigates an alternative novel 40 Hz non-invasive Light Therapy System (LTS) (Optoceutics ApS, Copenhagen, Denmark) emitting 40 Hz Invisible-Spectral Flicker (ISF) in patients with probable mild to moderate AD for six weeks.
Methods: Within a parallel-group randomized (1:1), double-blinded, placebo-controlled, clinical trial, 11 patients were exposed to one-hour daily LTS stimulation of 40 Hz ISF (active treatment) or placebo ISF with continuous white light matched in color and temperature (placebo). After six weeks, electroencephalogram (EEG) was recorded during active and placebo stimulation, depending on the participant's allocation, to assess secondary endpoints on acute gamma entrainment. The acute gamma response is quantified from the Power Spectral Density (PSD) of the EEG and the signal-to-noise ratio (SNR) of the 40 Hz steady-state visually evoked potential (SSVEP) response.
Results: Preliminary analyses of the secondary endpoint indicate that there is a significant difference in the SSVEP responses of the active treatment group compared to the placebo group (mean difference = 3.11, CI 95% [0.56, 5.65], p = 0.022); Figure
1.



Conclusions: The results indicate the ability of the 40 Hz non-invasive ISF LTS stimulation to elicit acute gamma oscillations in AD patients.

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OD070 / #2398

ON-DEMAND SYMPOSIUM: MCI, AD & FAD THERAPEUTIC STRATEGIES
29-03-2023 07:00 - 08:30

THE EFFECTS OF ACETYLCHOLINESTERASE INHIBITORS ON THE RISK OF FRACTURES AND FALLS IN PATIENTS WITH ALZHEIMER'S DISEASE

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Aims: With an ageing population, the prevalence of Alzheimer's Disease (AD) and osteoporosis is rising, increasing the economic burden on the NHS. AD and osteoporosis are closely associated and patients are at significant risk of falls and fractures. Acetylcholinesterase inhibitors (AChEIs) have been shown to decrease the risk of fracture in some patients. Recent research has provided insight into the significance of cholinergic components in bone tissue. The aim of this project was to analyse whether AChEIs have protective effects against the risk of fracture and falls and also to determine whether AChEIs could be used in the treatment of osteoporosis.
Methods: A systematic review and meta-analysis was performed. A search was carried out on PubMed, Medline, AMED and Embase using pre-determined search terms to obtain studies published between 2000-2021. Additional studies were identified through manual searching of reference lists of selected publications. Publications were screened and selected based on pre-determined inclusion criteria, resulting in a total of 10 eligible publications. The IBM SPSS statistical analysis package was used to individually analyse fractures and falls. We were unable to adjust for confounders in the meta-analysis.
Results: Acetylcholinesterase inhibitors were found to have no significant effect on the risk of falls or fractures in patients with AD. The pooled odds ratio for the effects of acetylcholinesterase inhibitors on the risk of fractures was -0.25 (95% CI = -0.66 - 0.17). The pooled odds ratio for the effects of acetylcholinesterase inhibitors on the risk of falls was 0.12 (95% CI = -0.35 - 0.58).
Conclusions: We found no association between the use of acetylcholinesterase inhibitors and the risk of falls or fractures in patients with AD. There were multiple limitations that warrant further research on this topic.

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OD071 / #1480

ON-DEMAND SYMPOSIUM: MCI, AD & FAD THERAPEUTIC STRATEGIES
29-03-2023 07:00 - 08:30

IMPACT OF THE HIGHLY SELECTIVE D1-LIKE PARTIAL DOPAMINE AGONIST TAVAPADON ON DAYTIME SLEEPINESS: EVIDENCE FROM A PHASE 2 CLINICAL TRIAL

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Cerevel Therapeutics, Clinical Pharmacology And Pharmacometrics, Cambridge, United States of America

Aims: D2-like receptors are expressed in sleep-regulating dopaminergic pathways, and dopamine agonists (DAs) targeting D2-like receptors (eg, pramipexole, ropinirole, rotigotine) can be associated with increased somnolence, excessive daytime sleepiness, and sudden-onset sleep, presenting challenges for daytime activities, including driving (Ondo et al. *Neurology*. 2001;57:1392-1396). For example, in two previous clinical trials in early Parkinson's disease (PD), pramipexole monotherapy was associated with Epworth Sleepiness Scale (ESS) score increases from baseline of 1.2 to 1.8 points compared with -0.6 and 0.3-point changes from baseline for placebo, respectively (Hauser et al. *Mov Disord*. 2010;25:2542-2549; Poewe et al. *Neurology*. 2011;77:759-766). Tavapadon, a new, highly selective partial agonist for D1-like receptors in development for PD, may ameliorate daytime sleepiness effects and sudden-onset sleep by avoiding D2-like receptor agonism. Herein, we report daytime sleepiness data from a phase 2 proof-of-concept trial investigating tavapadon in early-stage PD.
Methods: This randomized, double-blind, placebo-controlled phase 2 trial of tavapadon monotherapy flexible dosing up to 15 mg once daily enrolled participants with early-stage PD (Hoen and Yahr Stage I-III) who were treatment naïve or had received dopaminergic agents for ≤28 days (NCT02847650). The change from baseline in daytime sleepiness was investigated as an exploratory endpoint using the ESS (range, 0-24).
Results: Mean (SD) baseline ESS scores were 5.1 (3.02) and 4.3 (2.95) for tavapadon (flexible dosing up to 15 mg; N=26) and placebo (N=22), respectively. The mean change from baseline (SD) ESS score at Week 15 was -1.1 (3.01) for tavapadon flexible dosing and 0.3 (2.71) for placebo.
Conclusions: Preliminary results indicate that unlike D2-like DAs, the unique mechanism of action of tavapadon may impart avoidance of increase in daytime sleepiness effects. Larger ongoing phase 3 trials will further characterize daytime sleepiness with tavapadon.

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OD072 / #949

ON-DEMAND SYMPOSIUM: MCI, AD & FAD THERAPEUTIC STRATEGIES
29-03-2023 07:00 - 08:30

MELATONIN HAS A THERAPEUTIC EFFECT ON THE ALZHEIMER'S-LIKE PATHOLOGY INDUCED BY REM SLEEP DEPRIVATION

Aysen Cakir[1], Sevda Sehzade[1], Cansu Koc[2], Guldal Gulec Suyen[3], Aylin Bican Demir[4], Nevzat Kahveci[1]
[1]Bursa Uludag University School of Medicine, Depatment Of Physiology, Bursa, Turkey, [2]Bursa Uludag University School of Medicine, Department Of Pharmacology, Bursa, Turkey, [3]Acibadem Mehmet Ali Aydinlar University School of Medicine, Department Of Physiology, Istanbul, Turkey, [4]Bursa Uludag University School of Medicine, Department Of Neurology, Bursa, Turkey

Aims: Sleep deprivation causes a variety of health concerns in many people. The aim of this study was to investigate the effects of REM sleep deprivation (REMSD) on Alzheimer's-like pathology, as well as the potential therapeutic role of melatonin in these processes.
Methods: The study was approved by the Local Ethics Committee on Experimental Animal Research of Bursa Uludag University, Bursa, Turkey (Approval ID: 2020-13/04). Male, 12-week-old Sprague Dawley rats were randomized to 7 groups (n=7 in each group). Rats in the control group were kept in standart lab cages. REMSD was induced by the modified multiple platform method (MMPM). The animals in REMSD were placed on platforms (6.5cm in diameter) inside the tank that was located 2 cm above the water surface for six days. Environmental control group (EC+S) was under the same conditions but placed on a grid within the tank to prevent falling into the water. Rats were randomized to receive either saline (REMSD+S) or Dimethyl sulfoxide (REMSD+DMSO) or 4-Phenylbutyric acid (REMSD+PBA, 100mg/kg) or melatonin (REMSD+MEL, 20mg/kg) intraperitoneally once a day for six days. The rats were decapitated on the 7th day and the hippocampus and cortex tissues were dissected. Amyloid 1-40, Amiloid 1-42, Tau and APP levels were determined by ELISA.
Results: Amyloid 1-40, Amiloid 1-42, Tau and APP levels were higher in the REMSD+S group compared to the control group and melatonin administration decreased these parameters in the hippocampus. The REMSD+S group also had higher levels of amyloid 1-40, tau, and APP than the control group and melatonin alleviated these effects in the cortex.
Conclusions: REMSD induces Alzheimer's-like pathology in the hippocampus and cortex. Melatonin may play a therapeutic role in this pathology. (Supported by TUBITAK, Grand Number: 220S210)

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OD073 / #1989

ON-DEMAND SYMPOSIUM: MCI, AD & FAD THERAPEUTIC STRATEGIES
29-03-2023 07:00 - 08:30

OPTIMAL CONDITIONS FOR ENTRAINING GAMMA RHYTHM USING FLICKERING LIGHT STIMULATION IN THE HUMAN BRAIN

Yeseung Park, Euisuk Yoon, Ji Won Han, Ki Woong Kim
Seoul National University Bundang Hospital, Neuropsychiatry, Seongnam, Korea, Republic of

Aims: Gamma entrainment using flickering light stimulation (FLS), which was found to reduce Alzheimer's disease (AD) pathologies in AD-modeled mice, may be influenced by the microstructural integrity of white matter tracts in humans. To examine the effect of the microstructural integrity of white matter tracts on the entrainment of gamma rhythms in visual cortex and propagation of them to other target brain regions in health older adults.
Methods: We enrolled 31 cognitively normal volunteers aged 65 years or older. We measured the resting state EEG and the steady state visually evoked potential (SSVEP) of gamma rhythms induced by 700cd/m^2 white light flickering at 32Hz . We analyzed the entrainment of gamma rhythms using event-related stimulation (ERS), the propagation of gamma rhythms from visual cortex to other brain regions using the spectral Granger Causality (sGC) and measured the fractional anisotropy (FA) of the white matter tracts of interest.
Results: We included 26 participants after excluding five participants who showed the SSVEP deficit. The lowest quartile group of the FA of left posterior thalamic radiation ($FA_{l\text{-}PTR}$) showed the significantly lower ERS of gamma rhythms at the visual cortex than the second-to-highest quartile group of the $FA_{l\text{-}PTR}$ ($p = 0.045$). In the multiple linear regression analyses, the effects of the FAs of middle longitudinal fasciculus and superior longitudinal fasciculus on the sGCs of the gamma rhythm connectivity from occipital to temporal, central and cortices were statistically significant ($p < 0.05$).
Conclusions: These findings suggest that intact white matter microstructural integrity may be required for proper gamma entrainment using FLS. In future clinical trials on the gamma entrainment using FLS, the white matter microstructural integrity should be considered in selecting study participants.

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OD073a / #2546

ON-DEMAND SYMPOSIUM: MCI, AD & FAD THERAPEUTIC STRATEGIES
29-03-2023 07:00 - 08:30

TARGETING NEUROINFLAMMATION IN NEURODEGENERATIVE DISORDERS: A FIRST IN HUMAN STUDY OF MT1980, A NOVEL FORMULATED ANTI-INFLAMMATORY MEDICINE

Kiri Granger[1], Jennifer Barnett[1], Sheryl Caswell[1], J Mark Treherne[1], Robin Bannister[2], John Brew[2], Dan Gooding[2], Lennaert Hoek[3], Brenda Zoer[3], Jart Oosterhaven[3]
[1]Monument Therapeutics Ltd, Research & Development, Macclesfield, United Kingdom, [2]TRx Biosciences Ltd, Research & Development, Cambridge, United Kingdom, [3]Icon plc, Early Development Services, Groningen, Netherlands

Aims: Neuroinflammation exacerbates the pathogenesis of numerous neurological disorders. Attempts have been made to repurpose non-steroidal anti-inflammatory drugs, particularly for Alzheimer's disease, but with limited success. As most drugs with peripheral anti-inflammatory action have minimal blood-brain-barrier penetration, there is an opportunity for reformulations to improve bioavailability and uptake into the central nervous system. Following positive preclinical data, we tested a formulation of an oral anti-inflammatory molecule (MT1980) in a first-in-human study.
Methods: Healthy volunteers were randomized to receive different doses of MT1980 (n=22) or placebo (n=4), in a parallel study design. Cerebrospinal fluid (CSF) samples were taken for measurement of drug levels to provide a surrogate indication of neural tissue concentrations. Safety and tolerability were assessed by collection of adverse events, vital signs, ECGs and routine clinical laboratory tests. Blood samples were also taken to determine peripheral pharmacokinetic (PK) characteristics.
Results: Measurable levels of drug in the CSF at 7 hours post dose were demonstrated in all subjects at each dose level of MT1980, with a linear relationship between drug level in CSF and dose. Average drug levels of 3.1 ng/mL to 11.0 ng/ml were achieved. MT1980 was well tolerated with no clinically significant adverse events or other safety signal identified.
Conclusions: The first clinical study demonstrated that MT1980 is brain penetrant. Concentrations of drug achieved in the CSF were at levels anticipated to provide meaningful anti-inflammatory effects, suggesting MT1980 has potential utility as a novel treatment of neuroinflammatory conditions. A further clinical study to assess PK and anti-neuroinflammatory effects is now planned.

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OD074 / #2667

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

XENON GAS TREATMENT TO RESTORE MICROGLIAL FUNCTIONS IN ALZHEIMER'S DISEASE

Wesley Brandao[1], Zhuoran Yin[1], Ilya Ilin[2], Howard Weiner[1], Oleg Butovsky[1]
[1]Brigham and Women's Hospital, Harvard Medical School, Ann Romney Center For Neurologic Diseases, Boston, United States of America, [2]General Biophysics, Neurology, Wayland, United States of America

Aims: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder. Emerging evidence shows that homeostatic dysregulation of the brain immune system orchestrated by microglia plays a significant role in the onset and progression of the disease. Our aim is to develop a therapy based on Xenon inhalation that addresses 1) penetration through the blood-brain barrier, 2) microglial modulation, and 3) neuroprotection.
Methods: Through a special chamber that can control the supply of Xenon gas in a closed-circuit system, we evaluated the Xenon effect in microglia biology in models of acute and chronic neurodegeneration and humanized AD mice.
Results: We found that Xenon-treatment can directly modulate the microglia phenotype by increasing their phagocytic response and decreasing their proinflammatory signature. Weekly-based Xenon inhalation decreased Aβ-plaque load and maintained the microglia in an intermediated state associated with IFN and lipid biosynthesis signatures. Moreover, Xenon treatment also affects the peripheral immune response with a decrease in B cell distribution and an increase in the tolerogenic signature in myeloid cells, which was validated by scRNAseq and FACS analysis. Importantly, Xenon treatment directly modulated IPS-derived microglia (iMGL) *in vitro* by suppressing their inflammatory signature and inducing lipid biosynthesis. Finally, treatment of humanized 5xFAD mice transplanted with iMGLs, reduced Aβ plaque load.
Conclusions: Xenon treatment modulates microglia and peripheral immune cells phenotype towards a repair phenotype. This modulation is accompanied by a reduction in Ab pathology in both mouse and humanized models, showing that Xenon inhalation can be used as a possible treatment for AD.

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ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

DYSREGULATION OF MICROGLIAL B-GLUCOCEREBROSIDASE-1 SIGNALLING DRIVES NLRP3 INFLAMMASOME ACTIVATION IN PARKINSON'S DISEASE

Nanthini Jayabalan[1], Madison Young[1], Katerina Hanton[1], Katherine (Kerry) Sakzewski[1], Sara Jose[1], Robert Adam[2], John O' Sullivan[1], Peter Lansbury[3], Richard Gordon[1]
[1]University of Queensland, Faculty Of Medicine, Brisbane, Australia, [2]Department of Neurology, Royal Brisbane And Women's Hospital, Brisbane, Australia, [3]Bial, Biotech, MA, United States of America

Aims: Parkinson's disease (PD) is characterised by the accumulation of α-synuclein aggregates and progressive loss of dopaminergic neurons and that is accompanied by persistent inflammasome activation. Glucocerebrosidase 1 (GBA1), the gene encoding the lysosomal enzyme glucoslyceramidase (GCase), has been identified as one of the most important genetic risks for the development of PD. The loss GCase functional activity is also common in sporadic PD patients, making it an important target for disease modification. In this study, we uncovered that GBA1 is highly expressed in microglial cells which drive neuroinflammation in the CNS. Therefore, we sought to define the role of GBA1 dysregulation in the immune system during PD.
Methods: We tested this novel signalling paradigm in *in vitro utilising* primary mouse microglia and in *in vivo* using the 6-hydroxydopamine (6- OHDA) model of PD in which inflammasome activation occurs at 3 days.
Results: We observed a marked loss of GCase protein expression and activity in primary microglia which correlated with NLRP3 inflammasome activation by synuclein aggregates. Importantly, using a small molecule GCase activator, we found that pharmacological activation of GCase could effectively prevent inflammasome activation *in vitro* triggered by synuclein aggregates. Using the preclinical mouse model of PD, we have shown the pharmacological activation of GCase ameliorates inflammation and rescued the neuropathology in the nigrostriatal system.
Conclusions: Together, our studies demonstrate a novel role of lysosomal GCase signalling in regulating inflammasome activation and neuroinflammation in the CNS, providing a new therapeutic avenue by which to ameliorate chronic NLRP3 pathology in PD.

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OD077 / #1981

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

ROLE OF PRO-INFLAMMATORY S100A9 PROTEIN IN AMYLOID-NEUROINFLAMMATORY CASCADE IN NEURODEGENERATIVE DISEASES.

Ludmilla Morozova-Roche
Umeå University, Medical Biochemistry And Biophysics, Umeå, Sweden

Aims: We studied the interaction and co-aggregation mechanisms between S100A9 and Aβ peptides as main processes leading to amyloid plaques formation, neural cytotoxicity and tissue damage in Alzheimer's disease. The regulation of this process by small molecules is also addressed in the light of their therapeutic potential.
Methods: The kinetic analysis of aggregation by thioflavin-T fluorescence and Rayleigh scattering assays, microfluidic analyses, charge-detection mass-spectroscopy, AFM-microscopy and molecular-dynamic simulation were used.
Results: We found that S1009 protein is intrinsically amyloidogenic and forms amyloids both in vitro and in vivo – in solution, cell models and the brain tissues during Alzheimer's, Parkinson's and traumatic brain injury. By using charge-detection mass-spectrometry in combination with AFM-microscopy, kinetic analysis and microfluidic binding assay we demonstrated that S100A9 co-assembles with Aβ42 fibrils, forming a new type of hetero-amyloid complexes. In these complexes the autocatalytic surfaces of Aβ42 fibrils template S100A9 amyloids, where each component represents a homo-molecular domain in the hetero-molecular Aβ42-S100A9 co-assembly. These change the dynamics of Aβ42 amyloid aggregation and distribution of sizes of co-assembled Aβ42-S100A9 complexes. The formation of larger Aβ42-S100A9 complexes may sequestrate smaller and more toxic species from the environment, which is consistent with our previous finding that co-aggregation of S100A9 with either Aβ42 or A β40 mitigate the overall amyloid cytotoxicity.
Conclusions: These findings contribute to understanding of amyloid co-aggregation processes both from a fundamental perspective and in revealing disease relevant processes.
Small molecules, regulating S100A9 amyloid aggregation and functions, including cell penetrating NCAM1 peptide constructs, oleuropein aglycone, Nb10 and TiNb9 polyoxometalates, cyclin and DOPA derivatives, are viewed in the light of their prospective therapeutic applications and also providing insight into specific sequences in S100A9 structure, which can drive or block its amyloid formation.

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OD078 / #279

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

BAG3 PROMOTES AUTOPHAGY AND SUPPRESSES NLRP3 INFLAMMASOME ACTIVATION IN PARKINSON'S DISEASE

Qian-Kun Lv[1], Xiao-Yu Yao[2], Fen Wang[3], Chun-Feng Liu[2,3]
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Aims: Parkinson's disease (PD) is a neurodegenerative disease characterized by movement disorder. Neuroinflammation mediated by microglia plays a key role in the pathogenesis of PD. In our previous studies, enhanced autophagy has been shown to significantly inhibit neuroinflammation in PD. This suggests that it is feasible to regulate microglial activation through autophagy to control microglia-mediated neurodegeneration and neuroinflammation. Bcl2-associated athanogene (BAG)3 is a pivotal co-chaperone of the autophagy pathway. We have shown that BAG3 can regulate autophagy to clear the PD pathogenic protein α-synuclein. However, the relationship between BAG3 and neuroinflammation is not clear. In this study, we investigated whether BAG3 regulated PD-related neuroinflammation and its underlying mechanism.
Methods: The inflammatory model of PD was established by injecting adeno-associated virus-BAG3 into the bilateral striatum of mice to induce overexpression of BAG3, followed by injection of lipopolysaccharide (LPS). The striatum was extracted at 3 days after injection of LPS for western blotting and reverse transcription quantitative polymerase chain reaction, and immunohistochemical staining was performed at 21 days after LPS injection. At the same time, LPS was used to induce activation of BV2 cells to verify the effect of BAG3 in vitro.
Results: Overexpression of BAG3 reduced LPS-induced pyroptosis, by reducing activation of caspase-1 and the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome and release of interleukin-1β and tumor necrosis factor-α.
Conclusions: The LPS-induced inflammatory environment inhibits autophagy, and overexpression of BAG3 can restore autophagy, which may be the main way for BAG3 to reduce neuronal inflammation in PD.

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OD079 / #1191

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

NPT520-34 SELECTIVELY BLOCKS NLRP3 INFLAMMASOME ACTIVATION INDUCED BY COMPLEX I INHIBITORS OVER TYPICAL CANONICAL OR NONCANONICAL INFLAMMASOME STIMULI

Adrianne Pike[1], Jon Kaisen Bowden-Verhoek[1], Ildiko Szabo[2], Luigi Bubacco[2], Diana Price[3], Douglas Bonhaus[3]
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Aims: NPT520-34 has yielded promising results in animal models of Parkinson's disease (PD) and other neurodegenerative disorders (NDs). However, the underlying molecular mechanisms of NPT520-34 have not been fully elucidated. Since NLRP3 inflammasome-mediated signaling impacts many underlying pathological features of NDs rectified by NPT520-34, we tested whether NPT520-34 could modulate inflammasome signaling. Further, since mitochondrial dysfunction is a core feature of PD and directly impacts the NLRP3 inflammasome, we tested whether NPT520-34 specifically modulates NLRP3 inflammasome activation associated with disruption of mitochondrial function.
Methods: Biochemical techniques including multiplex quantification of cytokine secretion and mitochondrial Complex I activity assays were employed to gain insight into NPT520-34-mediated inhibition of NLRP3 inflammasome activation in iPSC-derived human microglia and the THP-1 model. Established inflammasome activators and Complex I inhibitors were applied to cells after pretreatment with NPT520-34, inflammasome or K^+ channel inhibitors, or the Complex I-bypassing quinone idebenone.
Results: All reference activators tested resulted in IL-1β secretion that was responsive to NLRP3 inflammasome inhibition. Interestingly, NPT520-34 was able to block inflammasome-induced IL-1β secretion in a concentration-dependent manner when the inflammasome was activated by mitochondrial Complex I inhibitors, but not other inflammasome activators not acting primarily through mitochondrial Complex 1. Based on K^+ channel inhibition experiments, the Complex I inhibitors responsive to NPT520-34 demonstrated significant dependence on the Kv1.3 channel, but not necessarily at the plasma membrane.
Conclusions: Because the action of NPT520-34 was selective for Complex I inhibition-induced NLRP3 inflammasome activation, we propose that NPT520-34 likely does not block IL-1β secretion by directly inhibiting inflammasome component proteins. Instead, it may act indirectly by binding to Complex I to prevent recruitment and activation of the NLRP3 inflammasome at the mitochondrial membrane and/or the association of Kv1.3 with Complex I.

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OD080 / #1365

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

NLRP3 INFLAMMASOME MODULATES TAU PATHOLOGY AND NEURODEGENERATION IN VIVO

Ilie Cosmin Stancu[1], Chritica Lodder[1], Pablo Botella Lucena[1], Sarah Vanherle[1], Manuel Gutiérrez De Ravé[1], Dick Terwel[1], Astrid Bottelbergs[2], Ilse Dewachter[1]
[1]Biomedical Research Institute, Hasselt University, Department Of Neurosciences, Diepenbeek, Belgium, [2]Janssen Research and Development, A Division of Janssen Pharmaceutica NV, Neuroscience Department, Beerse, Belgium

Aims: The NLRP3-ASC inflammasome is increasingly identified as an active contributor in Alzheimer's disease and related tauopathies, supporting its role as a potential therapeutic target. Its contribution in tau-associated neurodegeneration, a key-process in tauopathies, remains to be identified in detail. Although tau pathology and neurodegeneration are closely correlated, it must be noted that different tau forms may act as culprits in both characteristics and NLRP3-dependent microglial processes may differently affect both processes. This indicates the need to study the role of NLRP3 in both processes.
Methods: We generated crosses of NLRP3 deficient mice with tauP301S (PS19) transgenic mice, to study the role of NLRP3 on tau pathology, prion-like propagation and tau-associated neurodegeneration.
Results: We show that tau pathology in hippocampus and cortex was significantly decreased in tau.NLRP3-/- compared to tau.NLRP3+/+ mice. Interestingly, hippocampal atrophy was significantly decreased in tau.NLRP3-/- mice, indicating a role of NLRP3 in neurodegeneration. We next assessed the role of NLRP3 on tau propagation and associated hippocampal atrophy, using our well-characterized tau seeding paradigm in tau.NLRP3-/- mice. NLRP3 deficiency significantly decreased prion-like seeding and propagation of tau pathology, i.e. tau pathology was significantly decreased in the ipsi- and contra- lateral hippocampus and cortex in tau.NLRP3-/- following tau seeding. Also hippocampal atrophy was significantly less in tau-seeded tau.NLRP3-/- mice at 8 months.
Conclusions: Our data indicate that NLRP3 activation affects tau-associated neurodegeneration and seeded and non-seeded tau pathology. NLRP3 thereby affects key pathogenic processes of tauopathies. Our data are important in the validation of NLRP3 inflammasome as therapeutic target for AD and related tauopathies.

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OD081 / #1924

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

APOE E4 SUPPRESSOR ON ALZHEIMER'S DISEASE RISK MIGHT ALTER THE TRANSCRIPTOME OF HUMAN MICROGLIA

Yiyi Ma[1], Masashi Fujita[1], Lei Yu[2], Vilas Menon[1], David Bennett[2], Philip De Jager[1]
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Aims: We have identified a potential suppressor of *APOE* ε4 risk on AD, a principal component capturing the greatest variations of the post-mortem human brain DNA methylation levels of the four CpG sites. Based on the human brain bulk RNA sequencing data, we further found that this ε4-suppressor altered the transcriptions of microglia-related genes so we named it as the epigenomic factor of activated microglia (EFAM). We aimed to explore the targeted cell type of this ε4-suppressor using the single-nucleus RNA sequencing (snRNAseq) dataset.
Methods: We included 270 individuals from the Religious Order Study or the Rush Memory and Aging Project who have both measurements of snRNAseq and DNA methylation from the postmortem brain tissues. We conducted a cell type specific transcriptome-wide analysis (TWAS) to identify the genome-wide significant genes associated with our identified *APOE* ε4-suppressor within each estimated cell type of excitatory neurons, inhibitory neurons, endothelial cells, pericytes, oligodendrocytes, astrocytes, and microglia.
Results: The *APOE* ε4-suppressor is significantly associated with the expression of one gene in endothelial and twenty-five genes in microglia. In addition, this ε4-suppressor is significantly associated with the count and proportion of microglia only not the other cell types. Comparing with our reported TWAS results of bulk brain tissues, more than 60% of the genes showing nominal significance ($P<0.05$) in both brain bulk tissue and microglia.
Conclusions: We have more evidence to support our previous finding that the targeted cell type of the *APOE* ε4-suppressor maybe microglia. However, further confirmative evidence is needed.

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OD082 / #1081

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

TREM2 DRIVES MICROGLIA RESPONSES TO AMYLOID B PATHOLOGY VIA PROTEIN TYROSINE KINASE SYK-DEPENDENT AND -INDEPENDENT PATHWAYS

Shoutang Wang[1], Raki Sudan[1], Vincent Peng[1], Yingyue Zhou[1], Siling Du[1], Carla Yuede[2,3], Tingting Lei[1], Jinchao Hou[1], Zhangying Cai[1], Marina Cella[1], Khai Nguyen[1], Pietro Poliani[4], Wandy Beatty[5], Yun Chen[1], Siyan Cao[1], Kent Lin[1], Cecilia Rodrigues[6], Ali Ellebedy[1], Susan Gilfillan[1], Gordon Brown[6], David Holtzman[7,8], Simone Brioschi[1], Marco Colonna[9]
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Aims: Genetic studies have highlighted microglia as pivotal in orchestrating Alzheimer's disease (AD). Microglia that adhere to Aβ plaques acquire a transcriptional signature, "disease associated microglia" (DAM), which largely emanates from the TREM2-DAP12 receptor complex that transmits intracellular signals through the protein tyrosine kinase SYK. The human TREM2R47H variant associated with high AD risk fails to activate microglia via SYK. Based on these observations we hypothesized that SYK signaling may play a central role in microglial responses to Aβ.
Methods: To test this hypothesis, we crossed the 5xFAD mouse model of amyloid pathology with Cx3cr1CreERT2 x Sykfl/fl mice lacking Syk expression in microglia.
Results: Using complementary techniques, we demonstrated that SYK-deficient microglia develop an intermediate activation signature in response to Aβ, but fail to attain a complete DAM phenotype, indicating that microglia require cooperation of both SYK-dependent and -independent pathways to elicit an effective response to Aβ. Furthermore, we demonstrated that immunotherapies boosting SYK through CLEC7A improve microglia activation during Aβ pathology.
Conclusions: The results described above provide a possible therapeutic avenue for AD via Clec7A-Syk mediated signaling pathway.

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OD083 / #2543

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

PORPHYROMONAS GINGIVALIS OUTER MEMBRANE VESICLES AS THE MAJOR CAUSATIVE FACTOR OF NEURO-INFLAMMATION/DEGENERATION LEADING TO COGNITIVE DECLINE, DEMENTIA AND ALZHEIMER'S DISEASE WITHDRAWN BY AUTHOR

Peter Nara[1], Dan Sindelar[2]
[1]Keystone Bio Inc., Bio-therapeutics, St. Louis, United States of America, [2]Keystone Bio Inc., Oral Health, St Louis, United States of America

Aims: Addressing novel mechanisms and effective therapeutic treatments for cognitive decline, Dementia and Alzheimer's Disease is a major public health need. Keystone Bio, have identified that specific virulent strains of Porphyromonas gingivalis (Pg) and the release of specific virulence factors/toxins in the oral cavity as the primary driver/causation of systemic/neuro-vascular inflammation/degenerative diseases i.e. cognitive decline/dementias/Alzheimer's disease (Nara et. al 2021).
Methods: Pg OMVs and systemic system diseases has many well defined examples such as: cardiometabolic diseases- Pg OMVs attenuate insulin induced Akt/GSK-3_ signaling in hepatic HepG2 cells, thereby causing changes in glucose metabolism in the liver and promoting the development of diabetes and increase vascular permeability by cleaving endothelial cell connexins such as PECAM-1, thereby promoting cardiovascular diseases.
Results: Keystone Bio has further developed both a companion diagnostic (CDx) and a clinical, proof-of-concept tested, first generation, safe, efficacious, precision, bio-therapeutic murine monoclonal antibody (KB-001) for the diagnosis, treatment and monitoring against the oral bacteria and major virulent factor/toxin of Pg. The antibody engagement is with the later stages of the complex virulent factor/toxin secretion containing outer membrane vesicles from the bacteria thereby interfering/stopping all necessary metabolic, host defense, energy-producing sources, adherence and biofilm formation and integrity (Nara et. al 2021). The talk will review what now seems like a solid case for causation in the role of virulent/toxin secreting strains of in neuro-inflammation leading to cognitive decline, dementia, Sporadic Alzheimer's disease and possibly Parkinson's.
Conclusions: The talk will review what now seems like a solid case for causation in the role of virulent/toxin secreting strains of in neuro-inflammation leading to cognitive decline, dementia, Sporadic Alzheimer's disease and possibly Parkinson's.

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OD084 / #829

ON-DEMAND SYMPOSIUM: NLRP3 INFLAMMASOME, NEUROINFLAMMATION, TREM2, MICROGLIA DYSFUNCTION
29-03-2023 07:00 - 08:30

SERPINE 1, BRAIN CELL SENESCENCE, AND ALZHEIMER'S DISEASE

Rui-Ming Liu[1], Chunsun Jiang[1], Tapasi Rana[1], Lee-Way Jin[2], Hong Wei Qin[3], Susan Farr[4], John Morley[4], Erik Roberson[3]
[1]University of Alabama at Birmingham, Department Of Medicine, Birmingham, United States of America, [2]University of California at Davis, Pathology And Laboratory Medicine, Sacramento, United States of America, [3]University of Alabama at Birmingham, Dcdib, Birmingham, United States of America, [4]Saint Louis University, Geriatric Medicine, St. Louis, United States of America

Aims: The etiology for late-onset Alzheimer's disease (LOAD) is unknown. Emerging evidence suggests that cellular senescence contributes importantly to AD pathophysiology, although the underlying mechanisms remain largely unknown. In this study, we test a novel hypothesis that aging-related increase in Serpine1, a serine protease inhibitor, contributes importantly to brain cell senescence and thereby neuron degeneration in LOAD.
Methods: The expression of Serpine1 and cell cycle repressors p53/p21/p16 in the hippocampus/cortex and astrocytes of senescence accelerated mouse prone 8 (SAMP8) mice and LOAD patients was assessed by Western and immunofluorescence staining techniques. Serpine1 expression was modulated to further study its role in the senescence of primary mouse/human astrocytes as well as in astrocyte secretome-mediated neuron apoptosis.
Results: We show that Serpine1 expression is increased, in correlation with the increase in p53/p21/p16 expression, in the hippocampus/cortex of SAMP8 mice and LOAD patients compared to the corresponding controls. Double immunostaining show that more astrocytes undergo senescence in the brain of LOAD patients and SAMP8 mice relative to the corresponding controls. In vitro studies further show that overexpression of Serpine1 alone induced, whereas silencing Serpine1 attenuated H_2O_2-induced, senescence in primary mouse/human astrocytes. Treatment with the CM from senescent astrocytes induced neuron apoptosis whereas deletion of astrocyte Serpine1 dramatically reduced the effect of the CM on neurons. Importantly, the CM from astrocytes that overexpress a secretion deficient Serpine1 induced much less neuron apoptosis compared to the CM from astrocytes that overexpressed wild type PAI-1, although both mutant and wild type Serpine1 induced similar astrocyte senescence.
Conclusions: Together, our results suggest that increased Serpine1 may underlie brain cell senescence in LOAD and that senescent astrocytes can promote neuron apoptosis through secreting pathologically active molecules, including Serpine1.

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OD085 / #1231

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

NEURONAL DAMAGE CAUSED BY EXTRACELLULAR TAU OLIGOMERS

George Bloom[1], Merci Best[2], Xuehan Sun[1], Yunu Lim[1], Nina Ferenc[1], Nayoung Kim[1], Dora Wang[1], Kamyar Sharifi[1], Anna Wasserman[1], Subhi Saibaba[1], Karsten Siller[3], James Mandell[4]
[1]University of Virginia, Department Of Biology, Charlottesville, United States of America, [2]University of Virginia, Department Of Pharmacology, Charlottesville, United States of America, [3]University of Virginia, Research Computing, Charlottesville, United States of America, [4]University of Virginia, Department Of Pathology, Charlottesville, United States of America

Aims: Prion-like propagation of toxic tau forms from neuron to neuron is a key factor in the pathogenesis of Alzheimer's disease (AD) and other tauopathies. Substantial evidence indicates that this process involves misfolded and aggregated intracellular tau escaping affected neurons, then being taken up by other neurons whose endogenous "good tau" is provoked by the exogenous "bad tau" to become similarly misfolded, aggregated, and toxic. Despite a growing mechanistic understanding of this inter-neuronal spread of toxic tau , little is known about how neurons respond to its intracellular accumulation.
Methods: Western blotting and immunofluorescence microscopy were used quantitatively to analyze effects of extracellular tau oligomers (xcTauOs) on cultured neurons, and for comparing the same markers in human brains from AD patients and age-matched normal controls, and from AD model and wild type (WT) mice.
Results: In cultured neurons, xcTauOs cause rapid, long-lasting invagination of the neuronal plasma membrane, impaired nucleo-cytoplasmic transport, and partial loss of the axon initial segment (AIS). Remarkably, all these effects require intracellular tau. *In vivo* relevance of these results was established by finding that nuclear invagination and partial loss of AIS structure were markedly elevated in brains of human AD patients, and in the case of invaginated nuclei, in brains of AD model mice as well.
Conclusions: xcTauOs profoundly damage cultured neurons in multiple ways by mechanisms dependent on endogenous tau. xcTauO effects on nuclei likely alter neuronal gene expression patterns, and the AIS effects potentially enable ectopic accumulation of endogenous tau in the somatodendritic compartment and impair action potential generation. The cultured neuron results implicate xcTauOs for causing the partial AIS loss and invaginated nuclei found in human AD brain.

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OD087 / #1557

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

SMALL MOLECULE INDUCERS OF TAU FIBRILLATION: MECHANISM OF ACTION AND INFLUENCE ON POLYMORPHISM

Dmitry Malyshka[1], Jeff Kuret[2]
[1]Ohio State University College of Medicine, Biological Chemistry And Pharmacology, Columbus, United States of America, [2]Ohio State University, Biological Chemistry And Pharmacology, Columbus, United States of America

Aims: Tau filaments exhibit polymorphism, where the microtubule binding repeat region adopts disease-specific folding patterns. Individual conformers also uniquely engage non-covalent binding partners. Here we investigate how interactions between tau and a small-molecule aggregation inducer drives nucleation and influences polymorphism.
Methods: Full-length recombinant human 2N4R tau was fibrillized in the presence of the small-molecule dye Geranine G (GG). Resulting aggregates were subjected to CryoEM analysis to identify GG binding poses and their spatial relationship with nucleation motifs. Function associated with binding sites was investigated using mutagenesis and in vitro aggregation assay.
Results: Sedimentation and spectrophotometric analysis showed that GG remained stably associated with tau aggregates after induction (8.7 ± 0.6 mol/mol stoichiometry). CryoEM analysis revealed the presence of multiple polymorphs, and one species was solved to 3.3 Angstrom resolution. The core region of this tau aggregate was unique but closely resembled the heparin-induced synthetic protofilament and the kernel of three-layer tau aggregates isolated from human brain (e.g., globular glial tauopathy). The density map also captured densities for seven GG molecules in complex with it. Ionic interactions were mediated primarily through Lys residues via solvent-separated ion pairing. Mutagenesis identified the binding pose associated with Lys317/Lys321 as making the greatest contribution to GG induced tau aggregation propensity.
Conclusions: GG drives tau aggregation through at least two mechansims. First, it neutralizes the net positive charge of tau protein via non-specific interactions with Lys sidechains. Second, GG specifically stabilizes the heterosteric zipper formed by the PHF6* nucleating motif through bridging and stabilizing its interacting segment (^{317}KVTSK^{321}). This segment frequently associates with nonproteinaceous densities in tauopathy polymorphs, consistent with its potential role in promoting aggregation and modulating formation of disease conformers.

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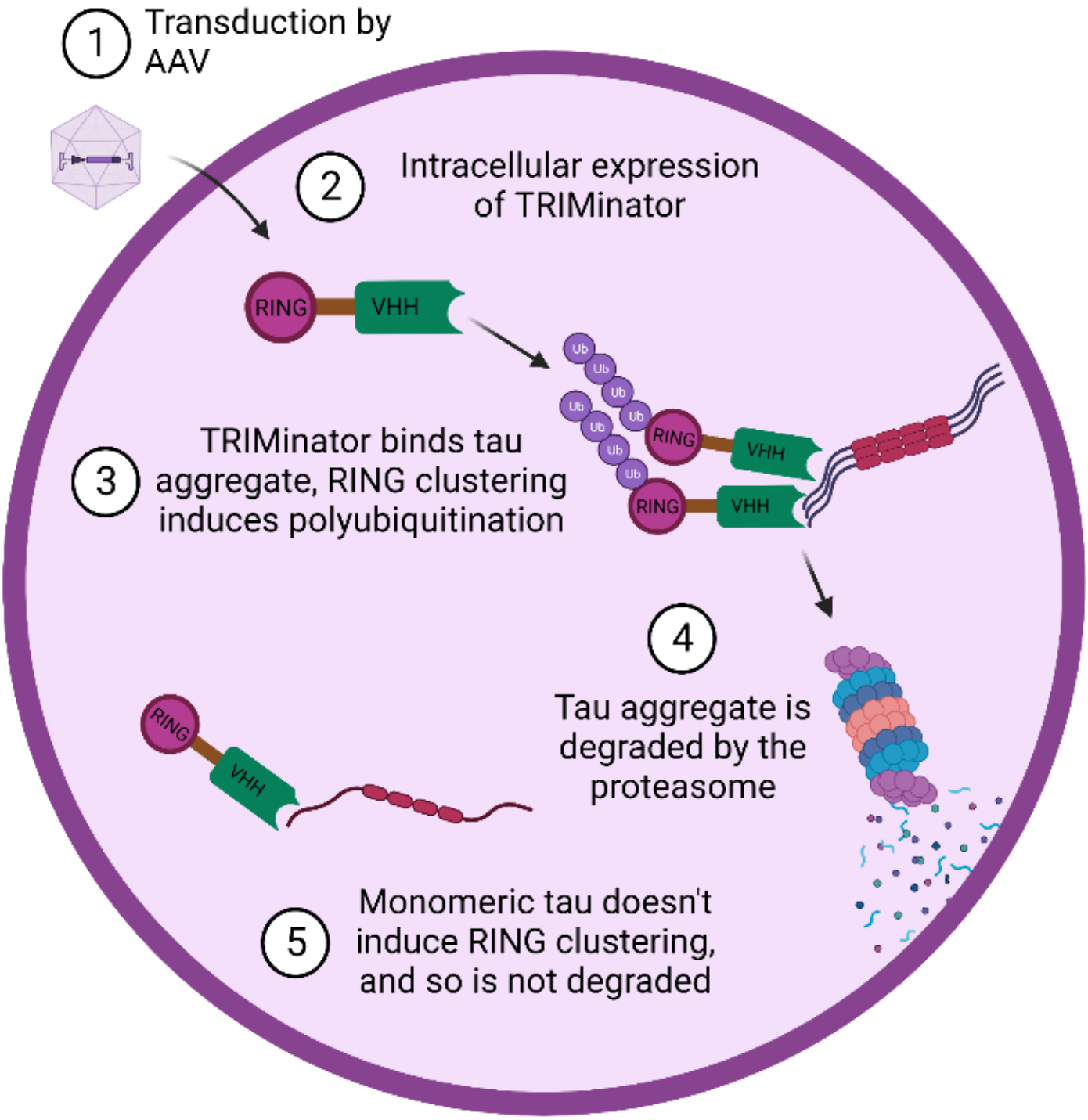
OD089 / #1455

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

SELECTIVE DEGRADATION OF AGGREGATED TAU PROTEIN VIA VECTORED NANOBODY-E3 LIGASE FUSION CONSTRUCTS (TRIMINATORS)

Jonathan Benn[1], Shi Cheng[1], Leo James[2], William Mcewan[1]
[1]UK Dementia Research Institute, Department Of Clinical Neurosciences, University Of Cambridge, Cambridge, United Kingdom, [2]Medical Research Council, Laboratory Of Molecular Biology, Cambridge, United Kingdom

Aims: The accumulation of intraneuronal aggregated tau protein underlies many neurodegenerative diseases and is a key target in therapeutic development. Whilst promising in pre-clinical models, tau targeting antibodies have performed poorly in clinical trials, potentially due to the low efficiency with which they access the CNS and enter the neurons where tau aggregates reside. To directly target aggregated tau for degradation we have developed intracellularly expressed constructs (TRIMinators) consisting of a tau targeting nanobody (VHH) fused to the E3 ubiquitin ligase domain (RING) of TRIM21. This E3 ligase activity is triggered via intermolecular clustering, which we hypothesise will allow for the selective degradation of multivalent aggregated tau:TRIMinator complexes and leave physiological monomeric tau unaffected.



Methods: To evaluate TRIMinator mediated degradation, constructs were expressed in cell lines containing either constitutively aggregated, or monomeric, tau-GFP. To assess the ability of TRIMinators to ameliorate tau pathology in an *ex vivo* model of seeded tau aggregation and in a mouse model of tauopathy, TRIMinators were packaged into adeno associated viral (AAV) vectors for direct addition or intravenous administration respectively.
Results: In cell line models we demonstrate that TRIMinators rapidly degrade pre-formed tau-GFP aggregates whilst leaving monomeric tau-GFP unaffected. AAV delivered TRIMinator ablates seeded tau aggregation in primary neuronal culture and reduces levels of tau pathology in aged transgenic P301S tau mice two weeks after administration.
Conclusions: TRIMinators are capable of not only inhibiting the aggregation of tau protein, but of removing pre-formed aggregates whilst leaving physiological monomeric species unaffected. This system of selective aggregate degradation

has potential as a future therapeutic strategy not only for tauopathies, but for the various other neurodegenerative proteinopathies driven by pathological protein aggregation.

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OD089A / #1126

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

STRUCTURAL DOMAINS DRIVING PRION-LIKE STRAIN EFFECTS IN POPULATIONS OF TAU CONFORMERS IN ALZHEIMER'S DISEASE

Jiri Safar[1], Tracy Haldiman[2], Sang-Gyun Kang[3], Mark Cohen[4], Mohammad Khursheed Siddiqi[4], Janna Kiselar[5], Rohan De Silva[6], Lenka Hromadkova[4], David Westaway[3], Chae Kim[4]
[1]Case Western Reserve University, Department Of Pathology, Neuroscience, And Neurology, Cleveland, United States of America, [2]Case Western Reserve University, Pathology, Cleveland, United States of America, [3]University of Alberta, Center For Prions And Protein Folding Diseases, Edmonton, Canada, [4]Case Western Reserve University, Department Of Pathology, Cleveland, United States of America, [5]Case Western Reserve University, Department Of Nutrition, Cleveland, United States of America, [6]UCL Institute of Neurology, Department Of Molecular Neuroscience, London, United Kingdom

Aims: As AD cases with differing rates of cognitive decline accumulate diverse populations of prion-like 2N4R and 2N3R tau conformers with distinct structural characteristics (Kim et al., Sci Transl Med 2022), our goals were to ascertain their origins and critical structural determinants of prion-like effects — replication, propagation, and toxicity.
Methods: We used photochemical hydroxylation monitored with europium labeled antibodies and synchrotron footprinting mass spectrometry to determine at single amino acid resolution the structural domains driving the seeding potency, replication kinetics, and toxicity of distinct tau conformers.
Results: Rapidly progressing AD cases yielded rapidly replicating, distinctly misfolded tau conformers, composed of ~80% four-repeat (4R) tau and ~20% of three-repeat (3R) tau isoform with the same conformational signatures. We identified major differences in the structural organization of R4 repeats and C-terminus tails of tau in rapidly progressive AD, including in diverse protease sensitive prefibrillar particles. The ensemble of misfolded conformers, comprised of up to three distinct populations of tau with varying structural organization in each AD case demonstrated distinct kinetics in seeding assays, variable cell loss and fluorescent signals at the nuclear margin of transfected cells, and evolved in explant neurons into conformers causing divergent presynaptic and postsynaptic pathology.
Conclusions: These observations indicate that major conformational heterogeneity in populations of misfolded 4R tau conformers is due to the alternatively misfolded R1, R4, and C-terminal domains that drive the rapid decline in AD and suggest that effective therapeutic strategies will need to consider an evolving cloud of alternatively misfolded tau conformers.

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OD090 / #1935

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

CEREBROSPINAL FLUID FROM ALZHEIMER'S DISEASE PATIENTS IMPAIR HUMAN NEURONAL NETWORK ACTIVITY

Julia Izsak[1], Henrik Zetterberg[2,3,4], Stephan Theiss[5], Sebastian Illes[1]
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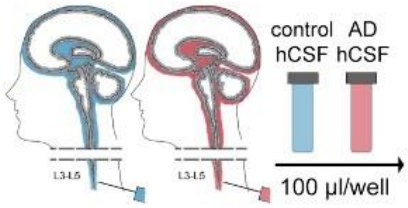
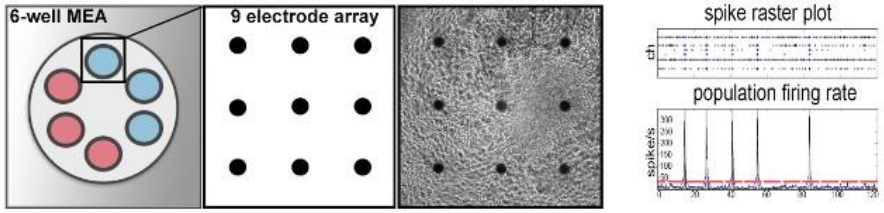
Aims: Alterations of cerebrospinal fluid (CSF) content occur in all neuropsychiatric disorders and neurological diseases, including Alzheimer's disease (AD). CSF molecules diffuse and disperse through the brain parenchyma via the ventricular system and CSF. CSF from AD patients may provide a pathologically extracellular milieu for neurons, leading to neuronal dysfunction. We assessed if CSF samples obtained from Alzheimer's disease patients and age-matched healthy individuals influence human neuronal network activity.
Methods: By combining human iPSC derived-neurons with microelectrode array-technology, we measured neuronal network activity of human iPSC derived-neurons exposed to human CSF samples obtained from Alzheimer's disease patients and age-matched control individuals. CSF samples were obtained via lumbar puncture. Measurement of total-tau, phospho-tau and abeta42 concentration of age-matched CSF and AD-CSF samples were conducted.

CSF sampling from AD-patients and age-matched control individuals*



Multielectrode array recordings of human iPSC-derived neuronal networks exposed to AD-CSF or control CSF samples



* $A\beta_{42}$, t-tau, and p-tau_{181} were quantified with sandwich ELISAs (INNOTEST β-amyloid1-42, hTAU-Ag and Phospho-Tau[181P], respectively).

Results: Human iPSC-derived neurons showed a significant increase in neuronal activity within 15 minutes after the application of age-matched control CSF. In contrast, human iPSC-derived neurons exposed to AD-CSF samples did not show a significant increase in neuronal activity compared to aCSF. Comparison between age-matched control CSF and AD-CSF treated groups shows a significantly lower increase of neuronal activity in human iPSC neurons exposed to AD-CSF. AD-CSF samples showed a significant rise in total-tau and phospho-tau concentration and a significant decrease in abeta42 concentration in comparison to aged-matched control CSF samples.
Conclusions: CSF from Alzheimer's disease patients causes a reduction of electrophysiological activity in human neurons. While changes in total-tau, phospho-tau, and abeta42 CSF concentrations in CSF correlate with AD-CSF effects on human neuronal activity, detailed mechanistic studies are needed. We are interested in collaborations to evaluate the effects of potential disease-modifying modalities on AD-CSF-mediated impairment of human neuronal network function.

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OD091 / #2450

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

A DUAL ROLE OF DAP12 IN BRAIN TAU INCLUSIONS AND TAU-INDUCED CHANGES IN OLIGODENDROCYTES IN TAUOPATHY MICE

Wenjie Luo, Hao Chen, Li Fan, Bangyan Liu, Gillian Carling, Man Ying Wong, Fangmin Yu, Nessa Foxe, Li Gan
Weill Cornell Medicine, Helen And Robert Appel Alzheimer's Disease Institute, Brain And Mind Research Institute, New York, United States of America

Aims: The progress of Alzheimer's disease (AD) is accompanied by accumulation of pathogenetic tau, microglial activation, and white matter abnormality, in addition to grey matter degeneration. Clinical studies demonstrate that tau pathology is associated with white matter degeneration in AD brains. The biological mechanism underlying the abnormal white matter integrity in AD remains unclear.
Methods: Brain tissues from wild-type, Dap12+/+ tau+, or Dap12-/- tau+ mice were analyzed by snRNAseq, immunohistochemistry or western blotting.
Results: We found that tau induces a unique cluster in both microglia and oligodendrocytes. The gene signature of tau-induced oligodendrocyte resembles previously identified intermediate oligodendrocytes (iOli). Strikingly, inactivation of Dap12, an adaptor protein important for microglial immune activities, completely suppressed the formation of tau-induced OL cluster and rescued the expression of myelin genes. Meanwhile, Dap12 deletion in tau mouse brains significantly restored homeostatic microglial population, profoundly decreased disease associated microglial population and repressed inflammatory signaling. Moreover, phosphor-proteomics showed an increase of phosphorylation of myelin-based protein in tau mouse brain with Dap12 deficiency, suggesting an impact on myelination signaling in oligodendrocytes. On the other hand, deficiency of Dap12 exaggerated tau pathology in tauopathy mouse brain. In primary cultured microglia, Dap12 deletion caused more tau retention in cells exposed to tau fibrils, without affecting tau uptake, suggesting Dap12 signaling is required for microglia-dependent tau metabolism.
Conclusions: Taken together, our results demonstrated a dual role of Dap12 in regulating pathogenic events in tauopathy mouse brains. Dap12 is required for microglia-dependent tau metabolism in brain as well as serves in a checkpoint governing tau-induced toxicities in oligodendrocytes via modulating microglia activation status. Our study strongly suggests that a functional regulation of activated microglia on oligodendrocytes during tau pathogenesis could contribute to white matter abnormality in AD.

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OD092 / #2227

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

ALTERED DIRECTED FUNCTIONAL CONNECTIVITY IS ASSOCIATED WITH AMYLOID AND TAU PATHOLOGY ACROSS THE ALZHEIMER'S DISEASE CONTINUUM

Mite Mijalkov[1], Dániel Veréb[1], Anna Canal-Garcia[1], Giovanni Volpe[2], Joana Pereira[1,3]
[1]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, Huddinge, Sweden, [2]Göteborgs universitet, Department Of Physics, Göteborg, Sweden, [3]Lund University, Clinical Sciences Malmö, Lund, Sweden

Aims: Alzheimer's disease (AD) is characterized by abnormal deposition of amyloid beta (Aβ) and tau proteins, resulting in progressive loss of memory and other cognitive functions. Previous studies found alterations in the topological organization of functional networks in AD using methods that assume that brain activation is a static process that does not change over time. Here, our aim was to assess whether our newly developed method that assesses directed and dynamic activity patterns through *anti-symmetric correlations* is sensitive to AD progression and is associated with brain pathology.
Methods: The anti-symmetric correlation network was computed as the anti-symmetric part of a lagged correlation matrix, which was built by calculating pairwise correlations between all brain regions after introducing a temporal delay (Figure 1). We evaluated this method in 166 participants with functional MRI scans, amyloid-β (Aβ) and tau PET from the Alzheimer's Disease Neuroimaging Initiative: 81 Aβ- and 36 Aβ+ controls, 31 Aβ+ participants with mild cognitive impairment (MCI) and 18 Aβ+ AD
patients.

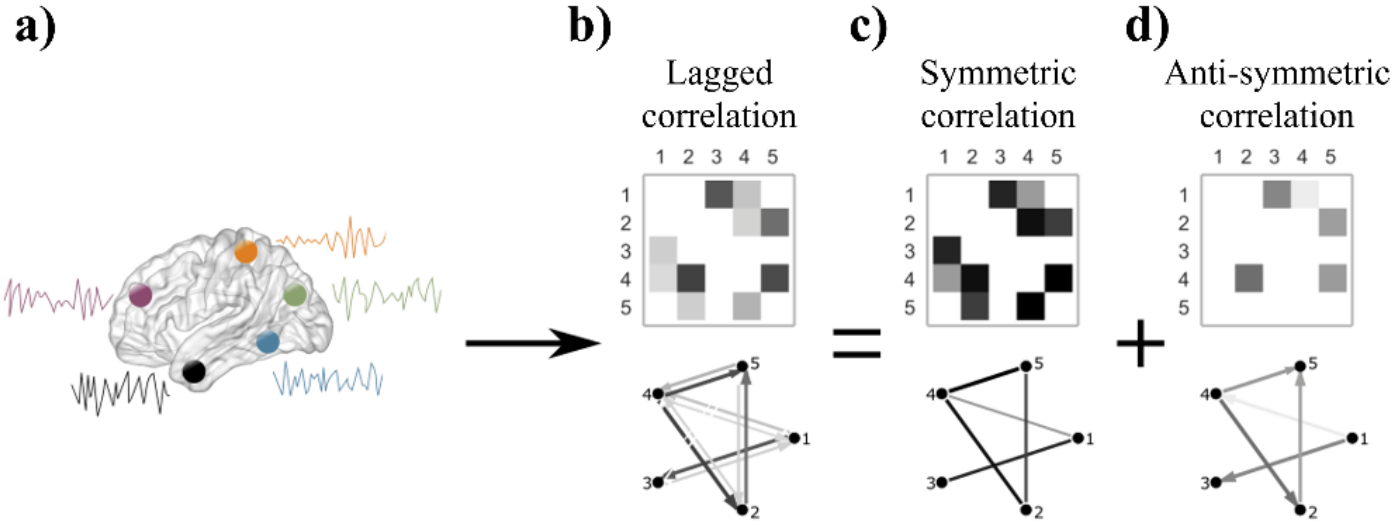

Figure 1: Calculation of whole-brain directed functional connectivity network using anti-symmetric correlations. a) As an example, we show this method by using the time activation series of only five nodes. b) Lagged correlation functional networks can be estimated by calculating the pairwise lagged Pearson's correlation coefficient, at different temporal lags. As a square matrix, the lagged connectivity matrix can be uniquely expressed as a sum of c) symmetric and d) anti-symmetric correlation matrix. Here, we use this anti-symmetric matrix to model the whole-brain directed functional connectivity.

Results: AD patients had lower clustering coefficient and global efficiency when compared to all other groups. Similar decreases were found in Aβ+ controls group when compared to Aβ- controls. However, the MCI group had higher clustering and global efficiency than Aβ- controls, indicating non-linear functional changes across AD continuum. Partial least squares analysis showed that both measures were associated with tau PET burden across Braak stages, global Aβ PET burden and cognition using mPACC scores.
Conclusions: Directed networks revealed nonlinear functional connectivity changes throughout the AD continuum. These

measures were associated with tau and Aβ pathology as well as cognitive abilities, suggesting they are sensitive to clinical impairment in AD and could be used as an indicator of AD-related neuronal alterations.

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OD094 / #806

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

JOINT COMPUTATIONAL/CELL-BASED PROTOCOL FOR SCREENING INHIBITORS OF TAU OLIGOMERIZATION

Viet Man[1], Da Lin[2,3], Xibing He[1], Jie Gao[3], Junmei Wang[1]
[1]University of Pittsburgh School of Pharmacy, Department Of Pharmaceutical Sciences And Computational Chemical Genomics Screening Center, Pittsburgh, United States of America, [2]The Ohio State University Wexner Medical Center, Neuroscience, Ohio, United States of America, [3]The Ohio State University Wexner Medical Center, Department Of Neuroscience, Columbus, United States of America

Aims: The aim of this study is to develop a joint computational/cell-based protocol for screening inhibitors of Tau oligomerization.
Methods: Docking is used to examine the binding affinity of ligands to tau aggregates. Virtual oligomerization inhibition (VOI) experiment using molecular dynamics simulations are performed to screen potential inhibitors of Tau PHF6 oligomerization. Tau seeding assay, which is directly related to the outcome of therapeutic intervention, is then carried out to confirm a ligand's ability in inhibiting Tau assembly formation.
Results: Our developed protocol was tested on two known compounds, EGCG and Blarcamesine. EGCG inhibited both the aggregation of PHF6 peptide in VOI and Tau assembly in Tau seeding assay, while Blarcamesine was not a good inhibitor at the two tasks. We also pointed out that good binding affinity to Tau aggregates is needed, but not sufficient for a ligand to become a good inhibitor of Tau oligomerizaion.
Conclusions: VOI goes beyond traditional computational inhibitor screening of amyloid aggregation by directly examining the inhibitory ability of a ligand to Tau oligomerization. Comparing with the traditional biochemical assays, Tau seeding activities in cells is a better indicator for the outcome of a therapeutic intervention. Our hybrid protocol has been successfully validated. It can effectively and efficiently identify the inhibitors of amyloid oligomerization/aggregation processes, thus, benefit to the drug development of Tau-related neurodegenerative diseases.

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OD095 / #1630

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

STRUCTURAL MODELING OF NOVEL TAU INTERACTION PARTNER, SERPINA5, REVEALS METASTABLE CONFORMATION OF DISEASE RELEVANT N-TERMINUS

Tiffany Sirmans, Oleksandr Savytskyi, Matt Coban, Kelly Hinkle, Caleb Weber, Evette Radisky, Thomas Caulfield, Melissa Murray
Mayo Clinic, Neuroscience, Jacksonville, United States of America

Aims: Objectives: Recently, our lab discovered a novel tau interaction partner, SERPINA5, to be upregulated in Alzheimer's disease (AD) cases (Crist 2021). Immunohistochemical evaluation of numerous SERPINA5 antibodies in postmortem AD cases revealed differential staining patterns. We hypothesized that the epitope of these antibodies would inform molecular interactions between SERPINA5 and tau. Thus, we aimed to structurally characterize SERPINA5 and its antibodies to understand the disease relevance of different SERPINA5 protein regions.
Methods: Methods: Peptide microarrays from JPT: Innovative Peptide Solutions were used to determine the antibody epitopes of SERPINA5. We next created a homology model of SERPINA5 to include the N-terminus using the Schrodinger Suite. Following this, exascale molecular dynamics simulations were performed by Desmond using OPLS4 forcefield.
Results: Results: Epitope mapping revealed binding sites for two (R&D-MAB1266; Abcam-ab172060) antibodies we tested. The other antibodies were likely not detected due to conformational epitopes. R&D-MAB1266 antibody displayed immunohistochemical staining of neurofibrillary tangles in AD while Abcam-ab172060 does not. R&D-MAB1266's epitope was present at the N-terminus (residues 6-12) while Abcam-ab172060's epitope was near the middle of the protein (residues 202-208) **(Figure 1)**. To understand the N-terminus' role in neuropathology, we modeled the full-length SERPINA5 (included previously unstructured N-terminus) using PDB 3B9F as a structural template. Molecular dynamics studies revealed the N-terminal region of SERPINA5 adopting a metastable anti-parallel beta sheet. Interestingly, this conformation interacts with Abcam-ab172060's binding site **(Figure 2)**.

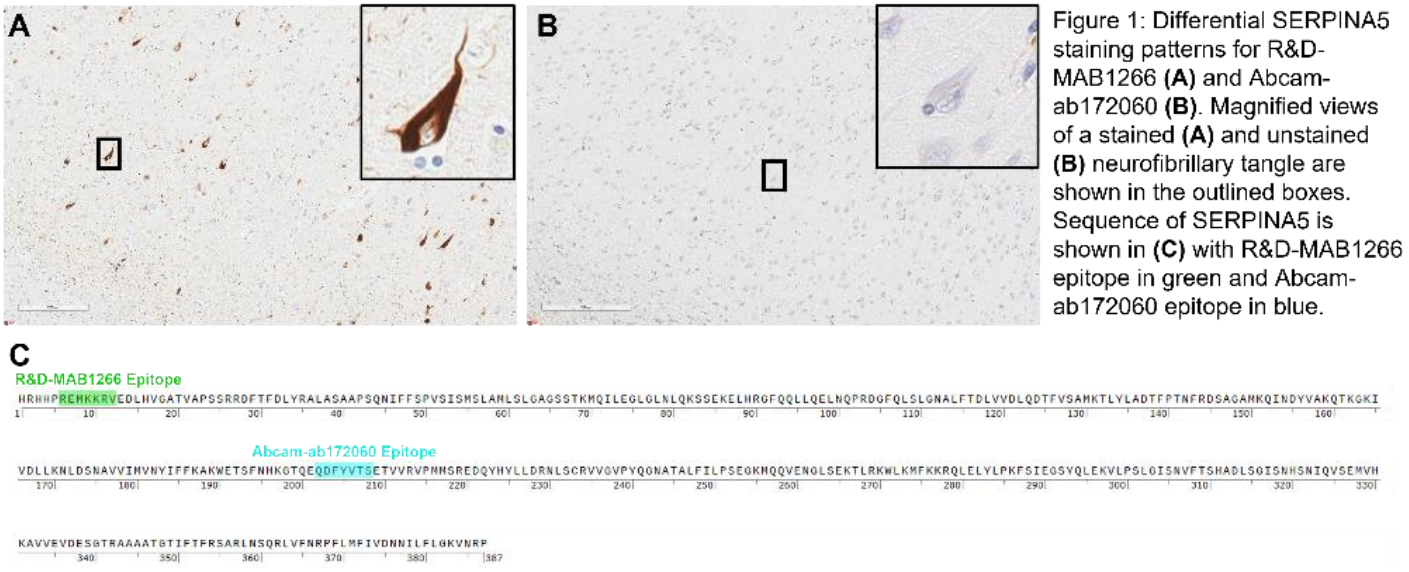

Figure 1: Differential SERPINA5 staining patterns for R&D-MAB1266 **(A)** and Abcam-ab172060 **(B)**. Magnified views of a stained **(A)** and unstained **(B)** neurofibrillary tangle are shown in the outlined boxes. Sequence of SERPINA5 is shown in **(C)** with R&D-MAB1266 epitope in green and Abcam-ab172060 epitope in blue.

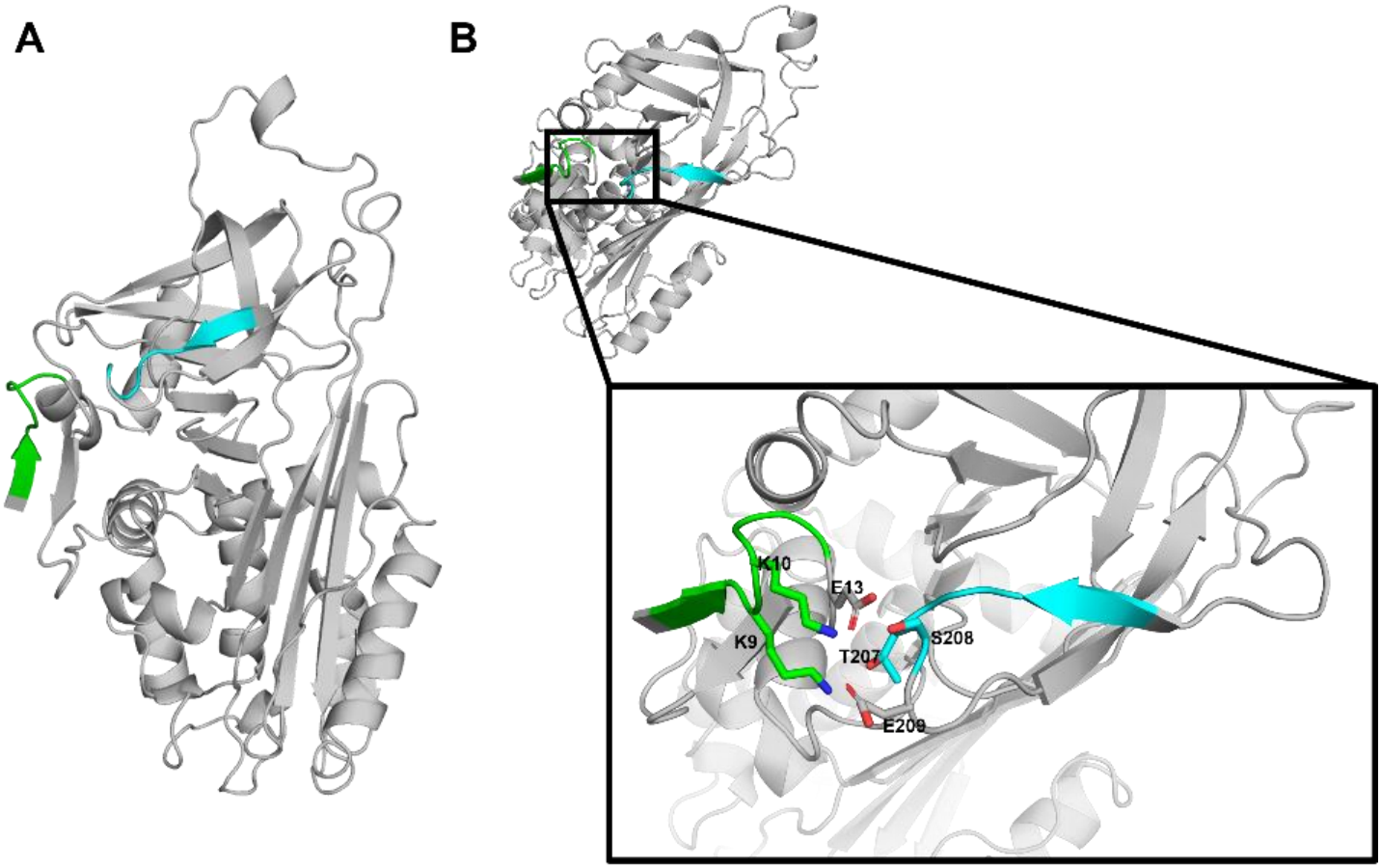

Figure 2: SERPINA5 homology model in the metastable conformation shown as a global view **(A)** and a magnified view to display specific interactions **(B)**. R&D-MAB1266 antibody epitope site colored green, and Abcam-ab172060 antibody epitope colored blue. Shown in **B**, glutamic acid 13 (E13) forms a hydrogen bond with serine 208 (S208) at a distance of 2.8Å. A second hydrogen bond is found between lysine 9 (K9) and threonine 207 (T207) at a distance of 2.8Å. Finally, lysine 10 (K10) and glutamic acid 209 (E209) are 2.9Å apart and have the potential to form a salt bridge if at the correct pH.

Conclusions: Conclusions: Our data suggest that regions of SERPINA5 are disease relevant while others are not. Epitope mapping studies will be performed to further characterize other SERPINA5 antibodies. Computational studies, such as docking tau with SERPINA5, will be run to understand whether the affinity for tau is higher or lower in the metastable conformation.

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OD096 / #1518

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

INVOLVEMENT OF THE GAP JUNCTION PROTEIN CONNEXIN-32 IN THE UPTAKE AND PROPAGATION OF HALLMARK PATHOLOGY ASSOCIATED WITH ALZHEIMER'S DISEASE

Juan F Reyes[1], Alexander Sandberg[1], Robert Vassar[2], Per Nilsson[3], Nicholas Kanaan[4], Michel Goedert[5], Martin Ingelsson[6], Martin Hallbeck[1]
[1]Linköping University, Biomedical And Clinical Sciences, Linköping, Sweden, [2]Northwestern University, Neurology, Chicago, United States of America, [3]Karolinska Institutet, Neurobiology, Care Science, And Society., stockholm, Sweden, [4]Michigan State University College of Human Medicine, Translational Neuroscience, Grand Rapids, United States of America, [5]MRC Laboratory of Molecular Biology, Neurobiology, Cambridge, United Kingdom, [6]University Health Network, Krembil Brain Institute, Toronto, Canada

Aims: The intercellular transfer of amyloidogenic proteins has been implicated in the progression of multiple neurodegenerative conditions including Alzheimer's (AD) and Parkinson's disease (PD). We previously demonstrated that the gap junction protein connexin-32 (Cx32) is centrally involved in the uptake and propagation of oligomeric alpha-synuclein assemblies associated with PD. In this study, we asked whether Cx32 is also involved in the uptake and propagation of oligomeric tau and amyloid beta (Aß) protein assemblies, hallmark pathology associated with Alzheimer's disease (AD).
Methods: We overexpressed Cx32 in human SH-SY5Y cells and analyzed pathological protein uptake in differentiated human SH-SY5Y cells. To confirm Cx32 involvement, we applied multiple pharmacological strategies targeting Cx32 activity to prevent protein uptake and propagation. To validate our findings, we analyzed Cx32 levels in cellular and animal models of AD as well as human AD brains using biochemical and imaging techniques.
Results: Our preliminary results demonstrate Cx32 involvement in the cellular uptake and propagation of Aß and tau protein assemblies in differentiated human SH-SY5Y cells. Consistent with these results, pharmacological strategies targeting Cx32 activity successfully blocked pathological protein uptake. Finally, we demonstrate an differential dysregulation of Cx32 protein levels in cellular and animal models of AD as well as human AD and non-AD tauopathy brains.
Conclusions: Our preliminary observations indicate that increased levels Cx32 promote the uptake and propagation of AD-associated pathology. In cellular and animal models of AD, we observe a differential dysregulation of Cx32 protein levels which depend on the protein expressed. In human AD and non-AD tauopathy cases, we observed an upregulation of Cx32 relative to age-matched controls. Taken together, our data suggests that Cx32 is partially involved in the propagation of hallmark pathology associated AD and non-AD tauopathies.

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OD097 / #1338

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

TAU-ASSOCIATED GENES OF GSKB, CAPN1 AND CDK5R1 ARE EXPRESSED IN CORTICAL AREA OF THE BRAIN OF AGED CYNOMOLGUS MONKEYS WITH COGNITIVE IMPAIRMENT

Huda Darusman[1], Jann Hau[2], Uus Saepuloh[1], Steven Schapiro[3], Lis Rosmanah[1]
[1]Institute of Research and Community Services, Primate Research Center, Ipb University, Bogor, Indonesia, [2]University of Copenhagen, Experimental Medicine, Copenhagen, Denmark, [3]University of Texas, Md Anderson Cancer Center, Bastrop, United States of America

Aims: We have studied the genes associated with the Tau-protein in our histopathology brain-slides collection using Reverse-Transcriptase Polymerase Chain Reaction techniques.
Methods: Our study use Reverse-Transcriptase Polymerase Chain Reaction techniques. The Tau-protein associated genes are APHIA, GSKβ, CAPN1 and CDK5R1 that are measured from the area of cortex and hippocampus of the brain.
Results: The Tau-protein associated genes are APHIA, GSKβ, CAPN1 and CDK5R1 that are measured from the area of cortex and hippocampus of the brain. The slides are originated from nine cynomolgus monkeys which divided into two groups of Adults (up to 10 years old) and Aged monkeys (more than 20 years old). We have found that the genes of GSKβ, CAPN1 and CDK5R1 are increased up to 5 folds in the cortical area of the aged subjects compared to the adults' conspecific. The findings suggest a hyper-phosphorylation of the Tau-protein in the cortical area which furthermore promote the Tau-protein reaction to Phosporylated-Tau (pTau) protein. Since the p-Tau itself is known as the major biomarkers of the NFT pathology.
Conclusions: Our current study has added informations about the mollecular mechanism of possible-pTau pathology in aged cynomolgus monkeys and decribe more the potential of non-human primate model for both amyloid and pTau protein studies of AD.

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OD098 / #1094

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

TAU DEFICIENCY PROTECTS HUMAN NEURONS FROM ABETA-INDUCED REDUCTION OF NETWORK ACTIVITY

Sarah Buchholz, Mhd Aghyad Al Kabbani, Michael Bell-Simons, Lena Kluge, Jennifer Klimek, Hans Zempel
University Hospital Cologne, Institute Of Human Genetics, Cologne, Germany

Aims: The microtubule-associated protein Tau is a key driver of the neurodegeneration observed in Alzheimer's disease (AD). Besides its role in disease pathogenesis, Tau stabilizes microtubules and thereby promotes essential functions, such as axonal transport, synapse formation, and neuronal activity. Alternative splicing results in the expression of six isoforms in the human brain. Most models of AD and TAU pathology are based on rodents, which express a different set of isoforms. Focusing on human cellular and neuronal models is crucial for understanding the mechanisms behind disease pathology and validating that the proposed functions of Tau are not limited to the model system used. Therefore, in this project, we aim to establish a suitable human neuronal model to study functions of Tau, characterize isoform-specific properties of TAU in the model system, investigate TAU-mediated toxicity in AD, and identify therapeutic targets, which will significantly advance the development of treatments for AD.
Methods: Using CRISPR/Cas9 and *Ngn2*-induced neuronal differentiation, we successfully established Tau KO hiPSC-derived neurons. To further investigate the role of Tau and its isoforms, live-cell imaging methods, immunofluorescence staining techniques, in vitro models of AD, as well as multi-omics approaches, microfluidic culture devices, high throughput imaging, and MEA recordings are used.
Results: Initial results suggest putative novel roles of Tau in axonal growth and AIS formation. Interestingly, Tau KO neurons are resistant to an Abeta-induced reduction of network activity. Multi-omic screens identified promising candidates protecting Tau KO neurons from Abeta's detrimental effects.
Conclusions: Our results suggest novel functions of Tau in human neurons and validate the protective effects of Tau KO onto AD pathology. Identification of novel modifiers of disease will help identifying potential therapeutic targets for the treatment of AD.

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OD099 / #277

ON-DEMAND SYMPOSIUM: TAU PATHOLOGY 03
30-03-2023 07:00 - 08:30

INTRANEURONAL TAU AGGREGATION INDUCES THE INTEGRATED STRESS RESPONSE IN ASTROCYTES

Kevin Batenburg[1], Nael Nadif Kasri[2], Vivi Heine[3,4], Wiep Scheper[1,5]
[1]Vrije Universiteit Amsterdam, Functional Genome Analysis, Amsterdam, Netherlands, [2]Radboud UMC, Donders Institute For Brain, Cognition And Behaviour, Nijmegen, Netherlands, [3]Vrije Universiteit Amsterdam, Complex Trait Genetics, Amsterdam, Netherlands, [4]Amsterdam UMC location VUmc, Child And Adolescent Psychiatry, Amsterdam, Netherlands, [5]Amsterdam UMC location VUmc, Human Genetics, Amsterdam, Netherlands

Aims: Progressive aggregation of tau protein in neurons is associated with neurodegeneration in tauopathies. Cell non-autonomous responses in astrocytes may be important drivers of the disease process but remain largely elusive.
Methods: We developed a fully human co-culture model of seed-independent intraneuronal tau pathology. High-content microscopy was used to identify cell type-specific responses to intraneuronal tau pathology prior to neurodegeneration. Treatment with tau-directed antisense oligonucleotides was employed to target tau aggregation.
Results: We developed a fully human co-culture model of seed-independent intraneuronal tau pathology, which shows no neuron- and synapse loss. Using high-content microscopy we show that intraneuronal tau aggregation induces oxidative stress accompanied by activation of the integrated stress response specifically in astrocytes. This requires the direct co-culture with neurons and is not related to neurodegeneration or extracellular tau levels. Tau-directed antisense therapy reduced intraneuronal tau levels and aggregation and prevented the cell non-autonomous responses in astrocytes. These data identify the astrocytic integrated stress response as a novel disease mechanism activated by intraneuronal tau aggregation. In addition, our data provide the first evidence for the efficacy of tau-directed antisense therapy to target cell autonomous and cell non-autonomous disease pathways in a fully human model of tau pathology.
Conclusions: This novel human model will provide new opportunities to further investigate disease mechanisms in neurons and astrocytes, and evaluate tau-directed therapeutics in a translationally relevant *in vitro* context.

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OD100 / #804

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

DEVELOPMENT AND VALIDATION OF A NOVEL PANEL OF CSF BIOMARKERS FOR ALZHEIMER'S DISEASE

Yanaika S. Hok-A-Hin[1], Katharina Bolsewig[1], Daimy Ruiters[1], Lynn Boonkamp[1], Daniel Alcolea[2], Alberto Lleó[2], Afina W. Lemstra[3], Yolande Pijnenburg[3], Wiesje Van Der Flier[3], Charlotte E. Teunissen[1], Marta Del Campo[1,4,5]
[1]VU University Medical Centers, Amsterdam UMC, Neurochemistry Laboratory, Clinical Chemistry Department, Amsterdam Neuroscience, Amsterdam, Netherlands, [2]Institut d'Investigacions Biomèdiques Sant Pau - Hospital de Sant Pau, Universitat Autònoma de Barcelona, Hospital de la Santa Creu i Sant Pau, Department Of Neurology, Barcelona, Spain, [3]Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Alzheimer Center Amsterdam, Amsterdam, Netherlands, [4]San Pablo CEU University, Departamento De Ciencias Farmacéuticas Y De La Salud, Madrid, Spain, [5]Fundación Pasqual Maragall, Barcelonabeta Brain Research Center, Barcelona, Spain

Aims: Using antibody-based proteomic arrays, we previously identified a novel panel of cerebrospinal fluid (CSF) proteins (n=9) that discriminates Alzheimer's Disease (AD) from non-AD dementias. Here, we aimed to translate this biomarker panel into immunoassays that can be easily implemented in routine diagnostics using two immuno-based technologies: custom multiplex proximity extension assays (custom-PEA) and the microfluidics Ella platform.
Methods: The developed custom-PEA was able to measure seven out of nine CSF proteins simultaneously (THOP1, DDC, NSE, ITGB2, MMP7, ABL1, VEGFR; Olink proteomics). Immunoassays were developed for four proteins (THOP1, DDC, NSE, ITGB2) on Ella. One assay (MMP7) was commercially available. Not all proteins were translated into immunoassays due to technical limitations. Custom-PEA was validated in a multicenter CSF cohort of AD patients (n=81), non-AD dementias (104 DLB and 105 FTD patients) and controls (n=86). THOP1 and DDC levels were measured in the same cohort (excluding FTD) on Ella and their associations with custom-PEA was tested by Spearman correlations. ROC analysis was performed to determine the accuracy of the custom-PEA panel (7 proteins).
Results: We translated our discovery findings to a custom-PEA, which showed good accuracy to discriminate AD from non-AD dementias (AUC=0.80, 95%CI=0.75-0.85). We developed and analytically validated Ella immunoassays for five biomarker candidates (THOP1, DDC, NSE, ITGB2, MMP7), all showing optimal parallelism between 85-115%. Protein levels strongly correlated between technologies (THOP1: *Rho*=0.801, p<0.001; DDC: *Rho*=0.732, p<0.001).
Conclusions: Biomarker candidates analyzed with either custom-PEA or Ella showed similar trends to those detected in the discovery study. This highlights the value of using antibody-based technologies in both discovery and validation phases, possibly accelerating the development of novel fluid biomarkers. Current studies are ongoing to validate the biomarker panel on Ella with an independent CSF cohort.

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OD101 / #916

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

AFRICAN ANCESTRY APOE E4 NON-CARRIERS WITH HIGHER EDUCATIONAL ATTAINMENT ARE MORE RESILIENT TO ALZHEIMER DISEASE PATHOLOGY-SPECIFIC BLOOD BIOMARKER PTAU181.

Farid Rajabli[1], Bilcag Akgun[1], Azizi Seixas[2], Larry Adams[1], Jovita Inciute[1], Takiyah Starks[3], Renee Laux[4], Michael Cuccaro[1], Jeffery Vance[1], Goldie Byrd[3], Jonathan Haines[4], Margaret Pericak-Vance[1]
[1]Univerity of Miami, John P. Hussman Institute For Human Genetics, Miami, United States of America, [2]University of Miami, Department Of Psychiatry And Behavioral Sciences, Miller School Of Medicine, Miami, United States of America, [3]Wake Forest University, Maya Angelou Center For Health Equity, Winston-Salem, United States of America, [4]Case Western Reserve University, Department Of Population And Quantitative Health Sciences, Cleveland, United States of America

Aims: Studies suggest that higher educational attainment (EA) protects individuals with Alzheimer Disease-related pathology (ADP) from cognitive decline. However, little is known about the protective effect of higher EA on functional decline in the presence of the *APOE-e4* AD risk allele, particularly in individuals of African ancestry (AA). We investigated in 410 AA individuals with advanced levels of pTau181 (ADP-specific biomarker used as a proxy for ADP), whether EA promotes functional resilience differently between *APOE-e4* carriers and non-carriers.
Methods: Using the four non-memory components of the CDR, we formulated a composite score of 12 (0=no impairment, 12=severe). Education levels were stratified into low (≤ 8 years), and high (>8 years) EA. High ADP individuals had $\log_{10}$(pTau181) levels > one standard deviation (SD) above the mean. The dataset was 73.9% female (mean age of exam of 72.9(SD=8.9) years) and mean $\log_{10}$(pTau181) of -0.01(SD=0.42). Seventy-four individuals were in the range of high ADP (mean+1SD); 43 individuals were *APOE-e4* carriers and 31 non-*e4*.To test, we used the non-parametric Kruskal-Wallis test.
Results: showed a significant increase in functional decline in individuals with low EA compared to high EA in both *APOE e4* carriers (pv=0.02) and non-carriers (pv=0.01) (Kruskal-Wallis). Among the individuals with high EA, the increase of functional decline in *e4* carriers was significantly higher compared to non-carriers (pv=0.02).
Conclusions: Thus, we showed that higher EA protects individuals with advanced ADP from exhibiting functional decline and that among individuals with high EA, e4 non-carriers were more resilient to ADP than e4 carriers. These results support EA as a measure of cognitive reserve (CR) in AA, extending the role of CR and EA to functional performance, and those multiple variables, including the social determinants, genetic risk factors, and AD biomarkers, need to be considered for predicting AD risk.

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OD102 / #1000

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

CSF AND PLASMA MEASUREMENT OF TAU PHOSPHORYLATED AT BOTH T181 AND T231 SITES

Anna Wojdala[1], Dandan Shan[2], Giovanni Bellomo[1], Silvia Paciotti[1], Lorenzo Gaetani[1], Davide Chiasserini[1], Lucilla Parnetti[1]
[1]University of Perugia, Department Of Medicine And Surgery, Perugia, Italy, [2]Quanterix Corporation, Assay Development, Billerica, United States of America

Aims: Different isoforms of phosphorylated tau (p-tau) have shown potential as Alzheimer's Disease (AD) biomarkers, hence we hypothesized that targeting two phosphorylation sites may provide an increased diagnostic value. We developed and validated a new Simoa® immunoassay detecting tau simultaneously phosphorylated at T181 and T231 (CapT231DetT181) in cerebrospinal fluid (CSF) and plasma.
Methods: Technical validation of the assay included standard curve development, assessment of LLOQ, dilutional linearity, spike-recovery, and inter- and intra-assay precision. For clinical validation, we measured CSF CapT231DetT181, p-tau181, and p-tau231 in a cohort (n=180), composed of preclinical AD (pre-AD; positive CSF AD biomarker profile without cognitive impairment), mild cognitive impairment due to AD (MCI-AD), AD-dementia (AD-dem), frontotemporal dementia (FTD) patients, and a cognitively healthy subjects with other neurological diseases and negative CSF AD biomarker profile (CTRL). Additionally, we measured plasma CapT231DetT181 in a subcohort of 60 patients (MCI-AD, AD-dem, CTRL) and plasma p-tau181 and p-tau231 in the 180 patients' cohort.
Results: Implementation of a synthetic peptide concurrently phosphorylated at T181 and T231 confirmed the assay specificity, while a mix of single-site phosphorylated (T181, T231) peptides excluded antibodies cross-reactivity. CSF CapT231DetT181, p-tau181, and p-tau231 levels were significantly elevated in all AD groups vs. CTRL (AUC pre-AD/MCI-AD/AD-dem vs. CTRL approx. 1.00). Plasma p-tau231 levels were increased at all AD stages (AUC range pre-AD/MCI-AD/AD-dem 0.85-0.87) and p-tau181 at MCI-AD and AD-dem stages (AUC range MCI-AD/AD-dem vs. CTRL 0.77-0.85). Plasma CapT231DetT181 did not change among clinical groups.

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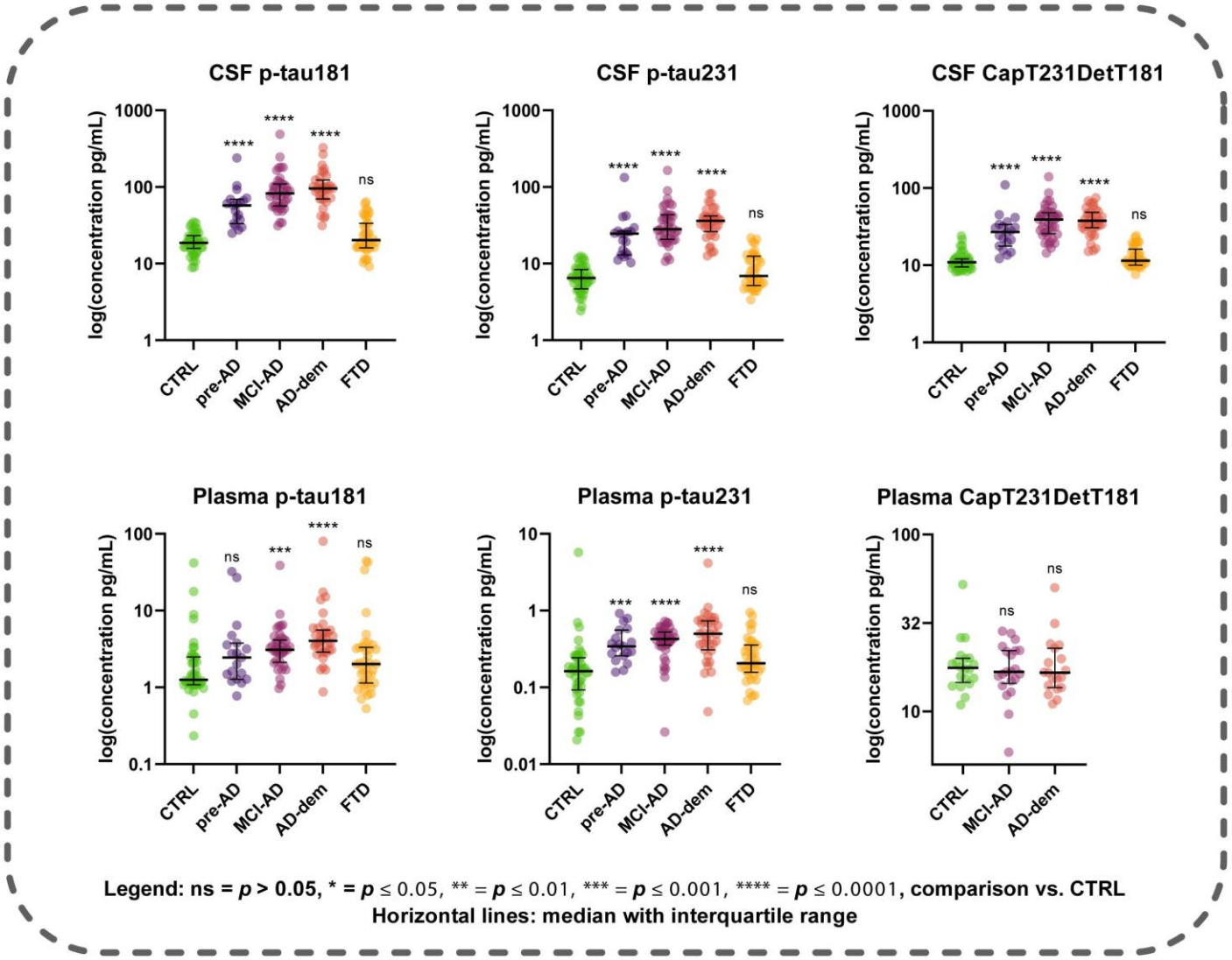

Conclusions: A new ultrasensitive immunoassay detecting tau simultaneously phosphorylated at T181 and T231 was developed and validated. This tau species is significantly elevated across the AD continuum in CSF, while it shows a limited diagnostic value in plasma. The differences between CSF and plasma warrant further investigation.

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OD103 / #1028

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

A PLASMA MARKER OF COGNITIVE DECLINE, AZ284 IS CORRELATED WITH PTAU181 IN THE AUSTRALIAN IMAGING BIOMARKERS AND LIFESTYLE STUDY

James Doecke[1], Pratishtha Chatterjee[2], Steve Pedrini[3], Simona Piccirella[4], Christopher Fowler[5], Stephanie Rainey-Smith[6], Kevin Taddei[3], Vincent Dore[7], Brett Trounsen[5], Rebecca Rumble[5], Colin Masters[5], Paul Maruff[8], Larry Ward[5], Ralph Martins[9], Aibl Research Group Aibl Research Group[10], Paul Kinnon[4]
[1]1Australian E-Health Research Centre, Csiro, Herston, Australia, [2]Macquarie University, Biomedical Sciences, Sidney, Australia, [3]Edith Cowan University, School Of Medical Sciences, Joondalup, Australia, [4]Diadem SpA, Diagnostics, Brescia, Italy, [5]The Florey Institute of Neuroscience and Mental Health, The Florey Institute Of Neuroscience And Mental Health, Melbourne, Australia, [6]Murdoch University, Centre For Healthy Ageing, Health Futures Institute, Murdoch, Australia, [7]Australian E-Health Research Centre, Csiro, Heidelberg, Australia, [8]Cogstate Ltd, Cogstate Ltd, Melbourne, Australia, [9]University of Western Australia, School Of Psychiatry And Clinical Neurosciences, Crawley, Australia, [10]The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), Aibl Research Group, Melbourne, Australia

Aims: New therapeutics for Alzheimer's disease (AD) are being submitted to the FDA for accelerated approval. Given the increasing number of disease-modifying therapies under development, the urgency for validated markers of cognitive change due to AD is becoming apparent. In this study we investigate the correlation between the validated AZ284 marker of AD onset and a marker of underlying AD pathology, tau phosphorylated at threonine-181 (pTau181).
Methods: Samples from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing were chosen whereby data from AZ284 (AlzoSure® Predict; Diadem) and pTau181 (Quanterix), along with clinical classification and PET Beta Amyloid (PET-Ab) were available. In total 60 samples (CN:17, MCI:20, AD:23) were assayed. Measures of the Preclinical Alzheimer Cognitive Composite (PACC) were also assessed. Correlations between AZ284 and pTau181 and the AIBL PACC were measured using Spearman's Rho. Plotted thresholds for each biomarker were derived using the Youden's Index from the ROC assessment of biomarker vs PET-Ab (Centiloid<20:PET-Ab-). Agreement statistics (positive percentage agreement [PPA], negative percentage agreement [NPA]) were calculated for the binary pTau181 and AZ284.
Results: AIBL PACC scores inversely correlated with AZ284 (r=-0.67; p<0.0001, Figure 1A) and pTau181 positively correlated with AZ284 (r=0.63; p<0.0001, Figure 1B). Across the two markers, the NPA was high at 95%, whilst PPA was lower at
66%.

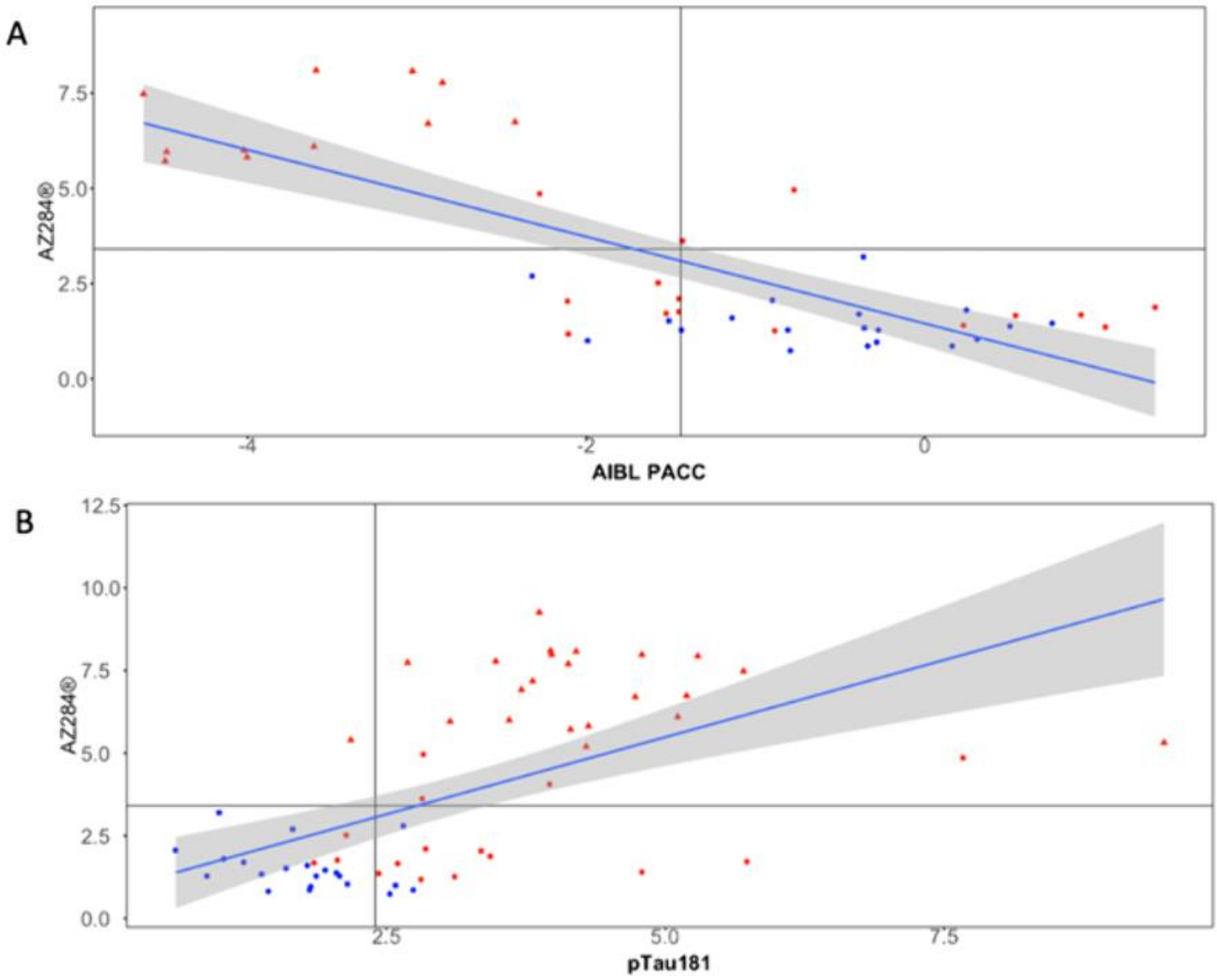

Figure 1: Scatter plot of A) AZ284® vs AIBL PACC and B) AZ284® vs pTau181. Red points represent PET-Aβ+, blue points represent PET-Aβ-. Circles represent cognitively unimpaired, squares represent Mild Cognitive Impairment, and triangle represent AD.

Conclusions: Comparison of the AZ284 marker with the putative blood-based marker for AD, pTau181, showed promising results across a small subset of data from AIBL. Given these results, a larger study is underway to validate these findings.

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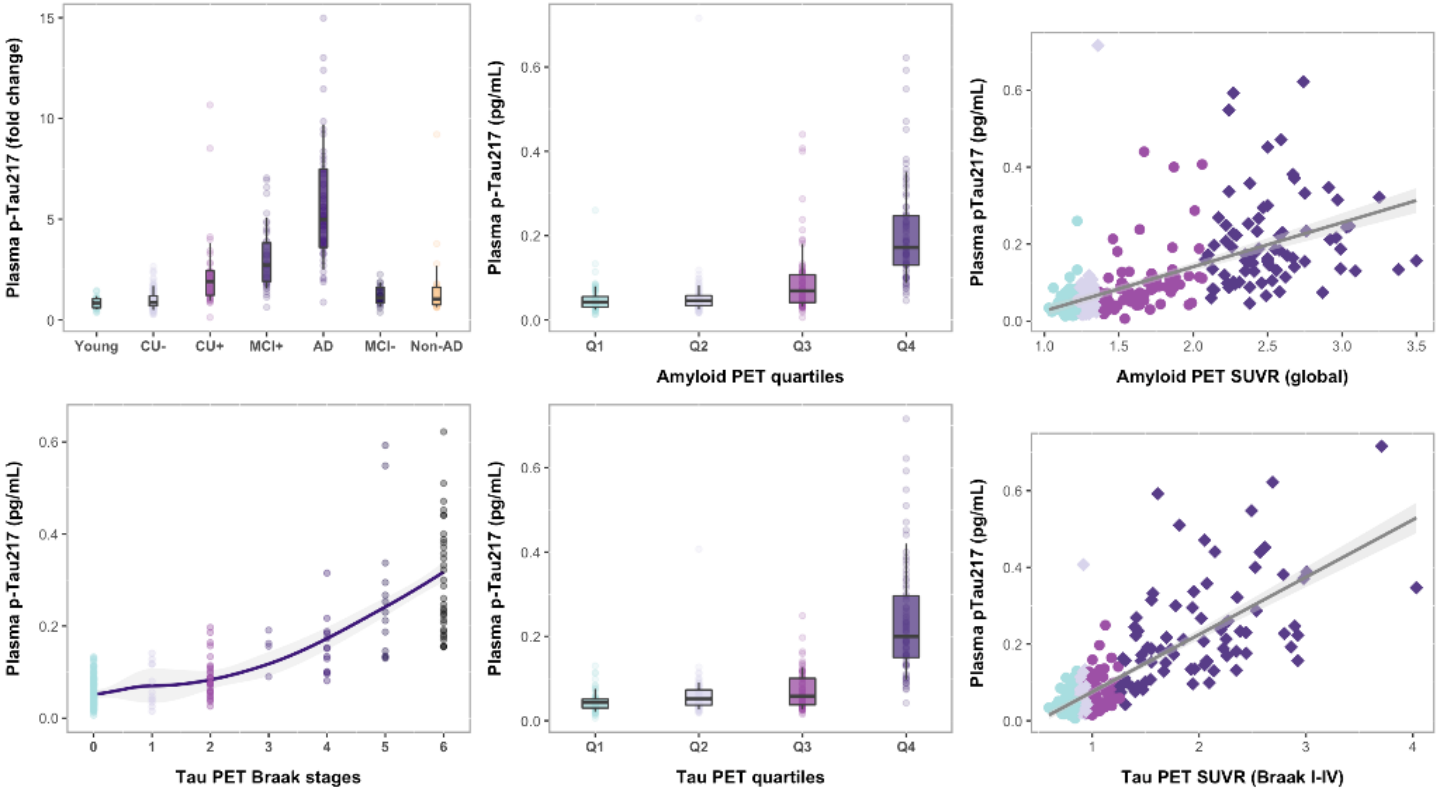
OD104 / #1879

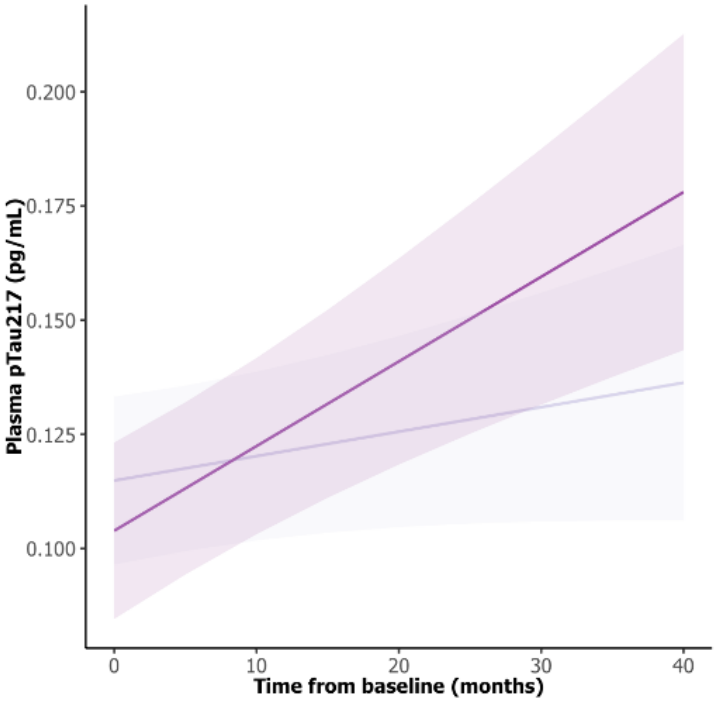
ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

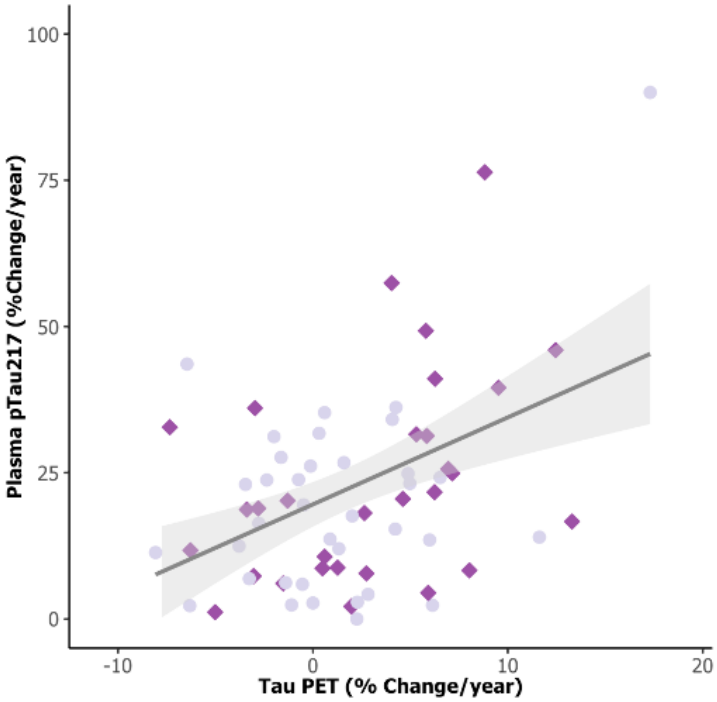
LONGITUDINAL ASSOCIATIONS BETWEEN PLASMA PTAU217 AND IMAGING BIOMARKERS OF ALZHEIMER'S DISEASE

Andrea L. Benedet[1], Nicholas Ashton[2], Gallen Triana-Baltzer[3], Joseph Therriault[4], Firoza Lussier[5], Cécile Tissot[4], Tharick Pascoal[5], Hartmuth C Kolb[3], Henrik Zetterberg[1], Kaj Blennow[2], Pedro Rosa-Neto[6]
[1]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [2]Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [3]Neuroscience Biomarkers Janssen Research & Development, -, La Jolla, United States of America, [4]McGill University Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada, [5]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America, [6]McGill Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada

Aims: Blood biomarkers have been showing their high ability to indicate amyloid and tau pathologies in the Alzheimer's disease (AD) continuum. Amongst the biomarkers studied, plasma tau phosphorylated at Thr217 (pTau217) is being considered, at the moment, the most promising candidate for use in clinical trials. However, it is still to be evaluated how this biomarker progresses in relation to longitudinal changes in amyloid and tau pathologies.
Methods: Plasma pTau217 (Janssen) was assessed in 310 participants from the TRIAD cohort who had also available amyloid and tau PET scans (indexed by [^{18}F]AZD469 and [^{18}F]MK6240, respectively). Longitudinal plasma and PET quantification was available for 111 of those participants. Linear models and linear mixed effect models tested the association between biomarkers cross-sectionally and over time, adjusting for covariates.
Results: As expected, plasma pTau217 shows stepwise increases across the AD spectrum and is highest in participants with high amyloid (ρ=0.68; P<0.001) and tau PET (ρ=0.64; P<0.001) uptake cross-sectionally. Preliminary analysis shows that plasma pTau217 rate of change is higher in amyloid positive participants (P=0.01). In addition, plasma pTau217 rate of change correlates with tau PET rate of change (ρ=0.33; P<0.001) over ~15-18 months.







Conclusions: Findings suggest that plasma pTau217 has the potential to track changes in tau accumulation in the brain, further supporting the use of this blood biomarker in clinical and research trials, not only as a screening tool but also to evaluate drug efficiency.

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OD105 / #1683

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

A TWO-STEP WORKFLOW BASED ON PLASMA P-TAU217 TO SCREEN FOR AB PATHOLOGY WITH FURTHER CONFIRMATORY TESTING ONLY IN UNCERTAIN CASES

Wagner S. Brum[1], Nicholas Cullen[2], Shorena Janelidze[3], Nicholas Ashton[4], Sebastian Palmqvist[5], Erik Stomrud[3], Kaj Blennow[4], Oskar Hansson[6]
[1]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [2]Lund University, Clinical Memory Research Unit, Malmö, Sweden, [3]Lund University, Department Of Clinical Sciences, Clinical Memory Research Unit, Malmö, Sweden, [4]Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [5]Lund University, Dep Of Clinical Sciences, Malmö, Sweden, [6]Lund University, Clinical Sciences Malmö, Lund, Sweden

Aims: Time-and cost-effective means to identify Alzheimer's disease (AD) pathology in patients with cognitive complaints are much needed. While novel blood-based AD biomarkers, especially phospho-tau (p-tau), can detect AD pathology, it remains unclear whether their incorporation into a full diagnostic workflow may lead to an accurate diagnostic work-up while reducing costly confirmatory CSF or PET tests.
Methods: We included patients with mild cognitive impairment (MCI) from two independent cohorts, the Swedish BioFINDER-1 (n=136, NCT01208675) and BioFINDER-2 (n=212, NCT03174938). A logistic regression model, predicting Aβ-positivity using plasma p-tau217, age and *APOEε4*-status, was developed in BioFINDER-1 and cross-validated in BioFINDER-2. Model-derived probabilities were used to stratify patients into low, intermediate and high risk of Aβ-positivity according to three thresholding strategies based on paired 90, 95 and 97·5% sensitivities and specificities. A two-step workflow was tested, assuming a blood biomarker-based diagnostic work-up for low and high-risk participants, while referring intermediate-risk individuals to confirmatory testing with CSF Aβ42/40. We evaluated the accuracy of the overall workflow for detection of Aβ-PET-positivity and the proportion of avoided confirmatory-tests.
Results: The plasma p-tau217-based model presented high discrimination in BioFINDER-1, AUC=88·7% (95% CI, 87·1-89·1%), and BioFINDER-2, AUC=93·8% (89·7-94·9%). The lenient risk stratification strategy (Se/Sp 90%) presented an overall workflow accuracy for Aβ-status of 87·6% (95% CI, 85·3-89·4%), reducing confirmatory CSF-testing by 87·1% [79·9-92·0%]. With the Se/Sp 95% strategy, the two-step workflow accuracy increased to 89·9% [87·4-91·7%], reducing CSF-tests by 74·1% [61·8-83·1%]. The more stringent strategy (Se/Sp 97·5%) led to the highest workflow accuracy, 91·7% [89·9-93·1%], while reducing unnecessary CSF-tests by 59·5% [40·2-72·1%].
Conclusions: Risk stratification of MCI patients with plasma p-tau217 can substantially reduce unnecessary CSF-tests, while maintaining high accuracy for detecting Aβ-status. This workflow may be a cost-effective way to detect AD pathology.

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OD106 / #1206

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

QUANTITATIVE X-RAY CHARACTERIZATION OF AMYLOID MODELS IN LARGE OBJECTS

Karthika Suresh, Eshan Dahal, Sabri Amer, Bahaa Ghammraoui, Aldo Badano
U.S. Food and Drug Administration, Division Of Imaging, Diagnostics, And Software Reliability (didsr), Silver Spring, United States of America

Aims: We investigate the use of a label-free, x-ray-CT method to scan up to 16-cm thick objects to detect and quantify amyloid plaque associated with Alzheimer's disease. Previously, we have demonstrated the potential of 2D-SAXS to estimate brain amyloid in mice without using the contrast agent. However, the method has not been tested for large objects and for spatial mapping of amyloids in whole size brain.
Methods: The prototype system comprised of a high energy polychromatic x-ray source, 2mm collimated beam and a 2D spectroscopic photon-counting. Scattered photons were collected in angle- and energy-dispersive mode. Studies were carried out using 4 to 16 cm polymethyl methacrylate slabs with caffeine powder and an amyloid model as targets. We also applied wavelet transforms to scattering signals from thicker objects with less exposure time and X-ray flux to accurately extract the target peaks.
Results: We show background-subtracted data for 4-, 10-, and 16-cm objects with the known Bragg peaks of caffeine at 8.4 and 18.6 nm^{-1} . Our results indicate recovery of the scattering signature of embedded targets in up to 16-cm objects. Our amyloid burden estimation correlated well with the mass fraction of the target amount embedded within the phantom.

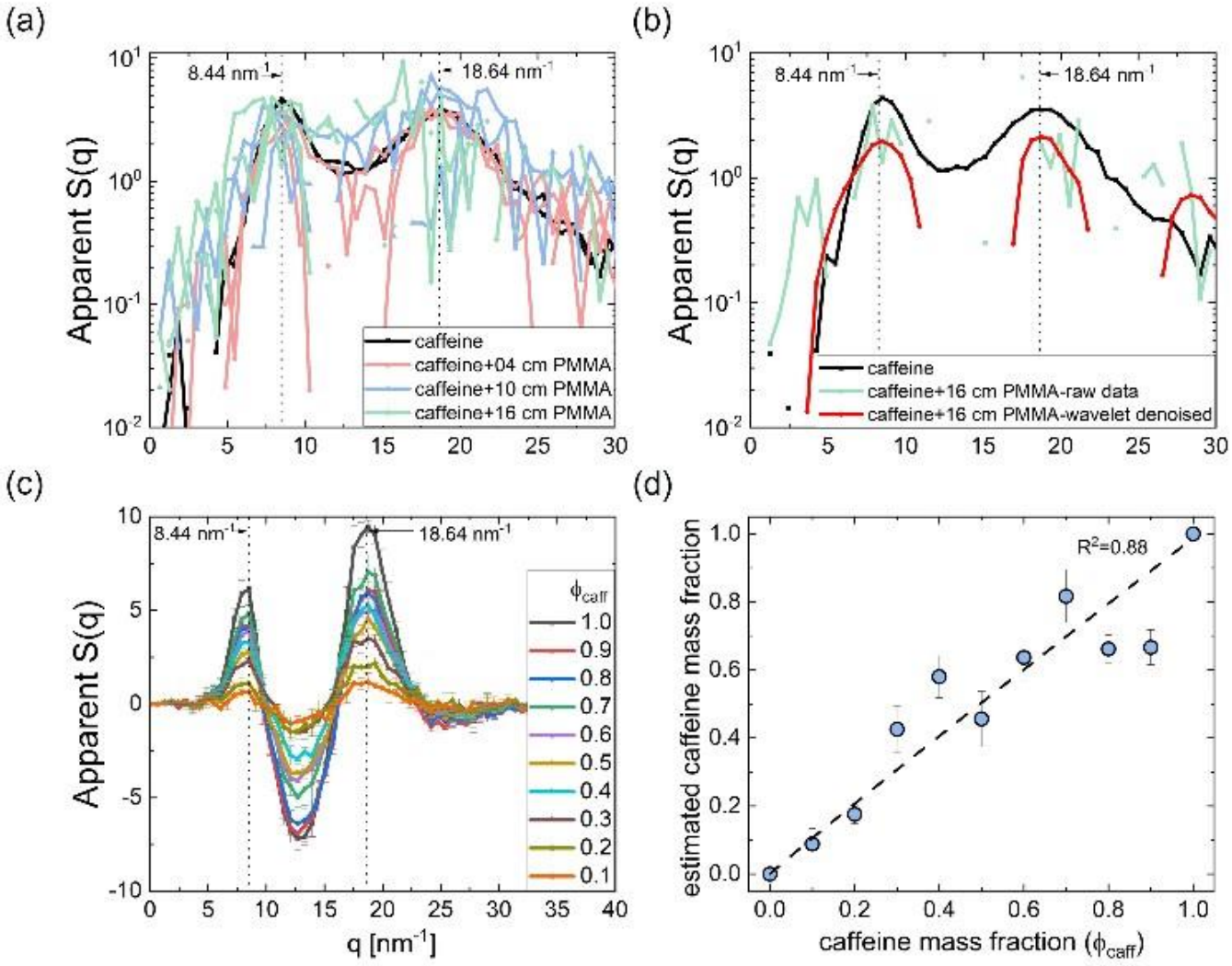

Figure 1. (A) Apparent scattering cross-section as a function of momentum transfer q, S(q), of caffeine target with 4, 10, and 16 cm PMMA. (B) Comparison of original background subtracted S(q) data with the denoised signal. (C) Recovered Bragg peaks of the caffeine when the mass fraction of target alone is varied from 0 to 1. (D) Linear correlation between the actual mass fraction of caffeine target versus the estimated mass fraction using our x-ray-based estimation metric.

Conclusions: Our findings suggest preliminary feasibility of using the proposed label-free x-ray method to detect and quantify beta-amyloid plaque in samples as large as a human head.

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OD108 / #713

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

COMPLEX INTERACTION OF 20 CLINICAL VARIABLES CAN PROVIDE PROGNOSTIC BIOMARKER FOR PD SUBTYPES IN PPMI COHORT

Anant Dadu[1], Brian Avants[2], Roger Gunn[2], Alexandra Reardon[2], Taylor Gosselin[2], Jacob Hesterman[2], Hirotaka Iwaki[1], Michael Nalls[1], Faraz Faghri[1]
[1]Data Tecnica International, Data Science, Glen Echo, United States of America, [2]Invicro, Image Analysis, needham, United States of America

Aims: Parkinson's disease (PD) is a complex, age-related condition with heterogeneous patterns of clinical progression. We propose a machine learning-based prognostic biomarker for multi-modality subtyping of PD. Of the diverse modalities that we integrate, serum neurofilament light (Nfl) is the strongest indicator of fast disease progression.
Methods: We assembled longitudinal clinical data from the Parkinson's Progression Markers Initiative (PPMI) with subjects having five-year longitudinal data. Only participants from the Control (n=154) or PD (n=254) diagnostic groups are included in this study. Overall, 122 clinical features across six visits went through data imputation, vectorization, and min-max normalization. Curated data were exposed to non-negative matrix factorization and Gaussian mixture models to delineate coherent PD subtypes. Baseline data were used in a machine learning framework to classify patients into subtypes accurately.
Results: We identified three data-driven clusters, the fastest progressing group showed significantly higher rates of cognitive and motor decline than the other, more moderate groups (Fig. 1). Using five-fold cross-validation, our proposed machine learning model shows 0.91 ± 0.02 (95% CI) area under the receiver operating characteristic curve (with 20 out of 122 baseline measures) in segregating the PD subtypes. Model interpretation identifies Hoehn and Yahr stage, Global Spontaneity of movement and Facial expression as top predictors. Nfl values show significantly different regression slopes across time after adjusting for age at baseline and sex. (Non-PD: 0.37±0.2, PDvec1: 1.09±0.4, PDvec2: 1.17±0.4, PDvec3:
2.35±0.83)

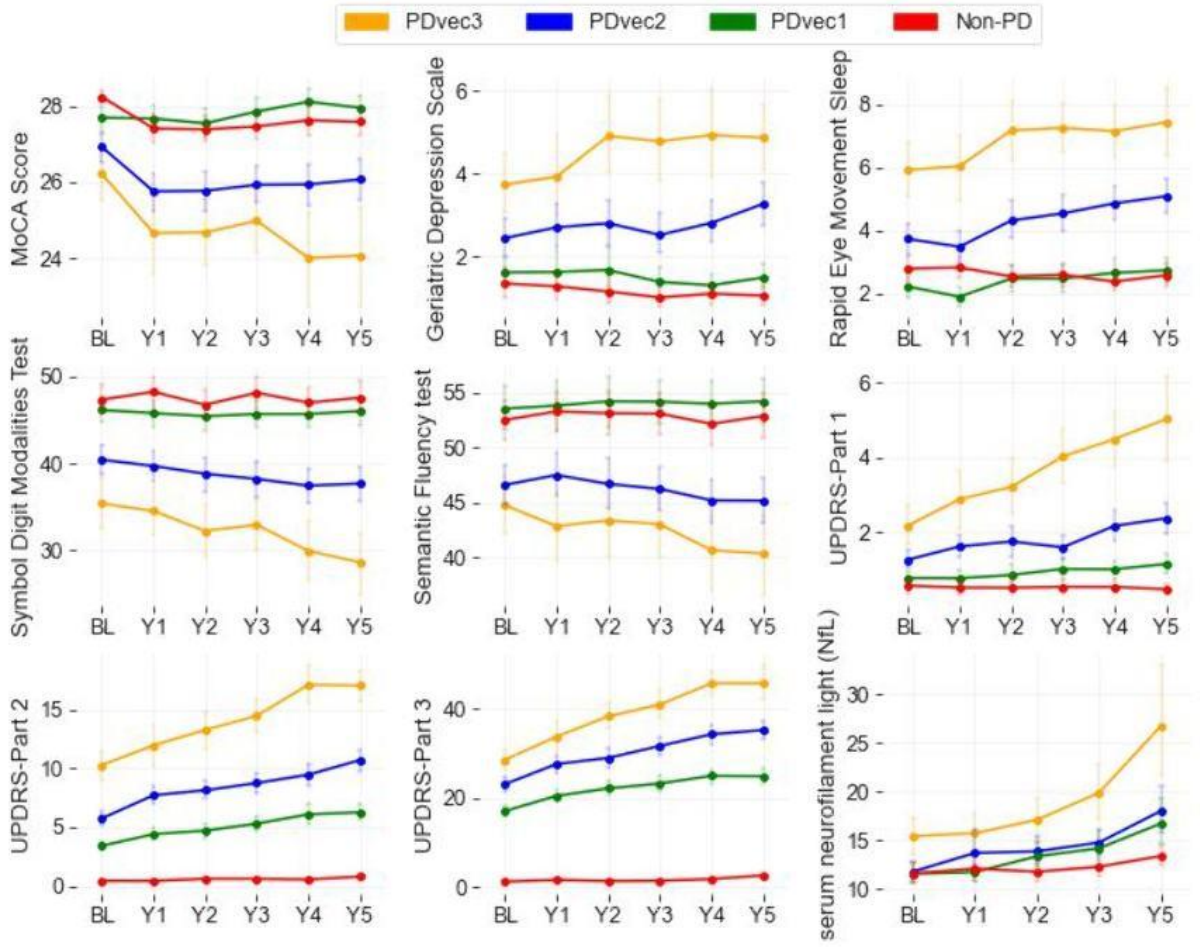

Fig 1. Shows the progression of PD subtypes over time on multiple clinical tests (including movement, cognitive skills and serum neurofilament light levels).

Conclusions: A complex interaction of 20 baseline clinical measures yields a prognostic biomarker stratifying PD population with varying progression rates. Further, Nfl may be informative as a disease monitoring biomarker for PD subjects. We anticipate these results will improve clinical trial design, allocation of healthcare resources, and ultimately individualized patient care.

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ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

ALZHEIMER'S DISEASE BIOMARKER PROFILING IN A MEMORY CLINIC COHORT WITHOUT COMMON COMORBIDITIES

Makrina Daniilidou[1], Francesca Eroli[1], Vilma Alanko[1], Julen Goikolea[1], Maria Latorre Leal[1], Patricia Rodriguez-Rodriguez[1], William Griffiths[2], Yuqin Wang[2], Manuela Pacciarini[2], Ann Brinkmalm[3], Henrik Zetterberg[3], Kaj Blennow[3], Anna Rosenberg[4], Nenad Bogdanovic[5], Bengt Winblad[1], Miia Kivipelto[1], Delphine Ibghi[6], Angel Cedazo-Minguez[1], Silvia Maioli[1], Anna Sandebring-Matton[1]
[1]Karolinska Institutet, Neurobiology, Care Sciences And Society, Solna, Sweden, [2]Swansea University, Medical School, Wales, United Kingdom, [3]Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [4]University of Eastern Finland, Department Of Neurology, Institute Of Clinical Medicine, Kuopio, Finland, [5]Karolinska University Hospital, Theme Inflammation And Aging, Stockholm, Sweden, [6]Sanofi R&D, Neurodegeneration Cluster, Rare And Neurologic Disease Research, Paris, France

Aims: Alzheimer's disease (AD) is a multifactorial disorder with large heterogeneity. Comorbidities such as hypertension, hypercholesterolemia and diabetes are known contributors to the disease progression. However, their mechanistic contribution to AD pathology and neurodegeneration has not been clarified. The aim of this study was to investigate CSF levels of markers reflecting brain changes in synaptic integrity, inflammation, oxidative stress, glucose homeostasis and cholesterol metabolism in memory clinic patients without known AD comorbidities.
Methods: CSF samples from 90 memory clinic patients without diagnosed hypertension, hypercholesterolemia, or diabetes nor other neurodegenerative disorder, were used to investigate 13 molecular markers representing key mechanisms underlying AD pathogenesis. Associations were analyzed by linear regression. Two-step cluster analysis was used to determine patient clusters. Two key markers were analyzed by immunofluorescence staining in hippocampus from control and AD individuals.
Results: CSF angiotensinogen, thioredoxin-1, and interleukin-15 had the most prominent associations with AD pathology, synaptic and axonal damage. SNAP-25 and NFL were increased in MCI and AD cases. Grouping biomarkers by biological function, showed that inflammatory and survival components were associated with AD pathology, synaptic dysfunction and axonal damage. Moreover, a vascular/metabolic component was associated with synaptic dysfunction. In data-driven analysis, two patient clusters were identified; cluster 1 had increased CSF markers of oxidative stress, vascular pathology and neuroinflammation and was characterized by elevated synaptic and axonal damage, compared to cluster 2. Clinical groups were evenly distributed between the clusters. Analysis of post-mortem hippocampal tissue, showed that, compared to non-demented controls, angiotensinogen staining was higher in AD and co-localized with phosphorylated-tau.
Conclusions: The identification of biomarker-driven endophenotypes of cognitive disorder patients further highlights the biological heterogeneity of AD and the importance of tailored prevention and treatment strategies.

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OD110 / #1639

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

THE ATYPICAL CEREBROSPINAL FLUID A-/T+ ALZHEIMER'S DISEASE BIOMARKER PROFILE: PREVALENCE AND CLINICAL RELEVANCE

Pontus Erickson[1], Joel Simrén[1], Wagner Brum[1,2], Gilda Ennis[3], Gwendlyn Kollmorgen[4,5], Margherita Carboni[6,7], Rebecca Langhough Koscik[3,8,9], Erin Jonaitis[3,8,9], Carol Van Hulle[9], Cynthia Carlsson[8,10], Sanjay Asthana[8,10,11], Sterling Johnson[3,8], Leslie Shaw[12], Kaj Blennow[1], Ulf Andreasson[1], Barbara Bendlin[9,13,14], Henrik Zetterberg[15], Alzheimer'S Disease Neuroimaging Initiative (Adni)[16,17]
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Aims: The atypical cerebrospinal fluid (CSF) A-/T+ biomarker profile, as defined by normal amyloid β 42 to 40 (Aβ42/40) ratio and increased phosphorylated tau (P-tau), is occasionally seen in daily clinical laboratory practice. However, knowledge is lacking on its exact prevalence and whether patients with this profile are on a clinically relevant neurodegenerative trajectory.
Methods: The prevalence of the A-/T+ profile was determined using LifeCare (the clinical laboratory database at Sahlgrenska University Hospital) data (Lumipulse-generated CSF AD biomarker results from 7679 unselected CSF samples for AD biomarker analysis in clinical laboratory practice). The clinical progression rate according to AD biomarker profiles (Roche Diagnostics NeuroToolKit-generated data) was determined using linear mixed effects models on clinical and neuroimaging disease progression markers measured in the Alzheimer's Disease Neuroimaging Initiative (ADNI), Wisconsin Registry for Alzheimer's Prevention (WRAP) and Wisconsin ADRC cohorts, on individuals without dementia.
Results: The prevalence of the A-/T+ profile in the LifeCare database was 4.1 %. The progression rate analysis made on the ADNI and WRAP cohorts suggested that the A-/T+ trajectory concorded with the one of A-/T-, which was not associated with cognitive deterioration or neuroimaging evidence of neurodegenerative disease over time.
Conclusions: The trajectory of the A-/T+ profile is a benign pattern; individuals with this profile do not have a higher rate of progression to AD compared with biomarker-negative individuals, and do not display other signs of progressive neurodegeneration. Although mechanistic studies are needed, the pattern might be explained by a CSF dynamics disturbance leading to increased concentration of CSF AD biomarkers, which is compensated for by the Aβ42/40 ratio.

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OD113 / #549

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

NEUROPSYCHOLOGICAL TESTS AND CSF PHOSPHORYLATED TAU PREDICT DEMENTIA WITH OR WITHOUT ALZHEIMER PATHOLOGY – A FOUR-YEAR FOLLOW-UP OF MILD COGNITIVE SYMPTOMS

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Aims: Can a neuropsychological test-battery alone or combined with CSF hyperphosphorylated tau (CSF p-tau) predict Major Neurocognitive Disorder (MND) after four years in patients with mild cognitive symptoms (MCS)?
Methods: 410 patients (females n=210, 52.4 %), age 70.8 ± 5.5 years with MCS, no dementia from the BioFINDER study were included. Composite scores, based on performances on two tests in each domain of Memory, Verbal, Spatial and Executive functions, were predictors as were CSF p-tau, controlling for sex and education, in multinomial logistic regression analyses. Primary outcome was diagnosis after four years: Alzheimer's Disease (AD) (n=114), other dementia (n=65), and no dementia (n=231; reference category).
Results: The Composite scores classify 70.7 % of the patients correct (R^2 0.478, $p<0.001$, with covariates included): no dementia=87 %, AD=64.9 %, other dementia=23.1 %. CSF p-tau classify 63.9 % correct (R^2 0.355, $p<0.001$, with covariates included); no dementia=84 %, AD=54.4 %, other dementia=9.2 %. Combining Composite scores and CSF p-tau classify 75.4 % correct (R^2 0.611, $p<0.001$); no dementia=85.3%, AD=70.2 %, other dementia=49.2%. Memory, Executive function, and CSF p-tau were the significant predictors.
Conclusions: Both neuropsychological assessment and CSF p-tau can separately predict outcome after four years in non-demented patients with MCS. In combination, they strengthen the prediction of progression to MND, particularly the prediction of other dementia, that is without AD pathology.

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OD114 / #1052

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

MACULAR VESSEL DENSITY IS NOT ASSOCIATED TO CEREBROSPINAL FLUID CORE BIOMARKERS FOR ALZHEIMER´S DISEASE IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT: THE NORFACE COHORT

Marta Marquié[1,2], Ainhoa García-Sánchez[1], Sergi Valero[1,2], Itziar De Rojas[1,2], Emilio Alarcón-Martín[1], Adelina Orellana[1,2], Laura Montrreal[1], Pablo García-González[1], Raquel Puerta[1], Amanda Cano[1,2], Joan Martínez[1], Miguel Castilla-Martí[3], Luis Castilla-Martí[4], Isabel Hernández[1], Maitee Rosende-Roca[1], Liliana Vargas[1], Juan Pablo Tartari[1], Ester Esteban-De Antonio[1], Urszula Bojaryn[1], Vanesa Pytel[1], Mario Ricciardi[1], Diana Ariton[1], Montserrat Alegret[1,2], Gemma Ortega[1,2], Ana Espinosa[1,2], Alba Pérez-Cordón[1], Ángela Sanabria[1,2], Nathalia Muñoz[1], Núria Lleonart[1], Núria Aguilera[1], Lluís Tárraga[1,2], Agustín Ruiz[1,2], Mercè Boada[1,2]
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Aims: Optical Coherence Tomography angiography (OCT-A) is a novel biomarker in the dementia field that allows the detection of retinal vascular changes. The comparison of OCT-A measures with established Alzheimer´s disease (AD)-related biomarkers is essential to validate the former as a marker of cerebrovascular impairment in the AD continuum. We aimed to investigate the association of macular vessel density (VD) in the superficial plexus with the AT(N) classification based on cerebrospinal fluid (CSF) Aβ1-42, p181-tau and t-tau measurements in individuals with Mild Cognitive Impairment (MCI).
Methods: Clinical, demographical, ophthalmological, OCT-A and CSF core biomarker for AD data from the Neuro-ophthalmology Research at Fundació ACE (NORFACE) project were analyzed. Differences of macular VD in four quadrants (superior, nasal, inferior and temporal) among three AT(N) groups (Normal, Alzheimer and Suspected non-Alzheimer pathology (SNAP)) were assessed in a multivariate regression model, adjusted by age and using the Normal AT(N) group as the reference category.
Results: The study cohort comprised 147 MCI participants: 67 Normal AT(N), 45 Alzheimer AT(N) and 35 SNAP AT(N). Regression analysis showed no significant association of the AT(N) groups with any of the regional macular VD measures (all $p>0.05$). Age demonstrated a significant inverse association with VD in the superior quadrant ($p=0.02$). The interaction of sex and AT(N) groups had no effect in differentiating VD. Lastly, CSF Aβ1-42, p181-tau and t-tau measures were not correlated to VD (all $r<0.08$; $p>0.12$).
Conclusions: Our study showed that macular VD measures are not associated with the AT(N) classification based on CSF biomarkers in patients with MCI, and do not differ between AD and other underlying causes of cognitive decline in our cohort.

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OD115 / #2722

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

EVALUATION OF PARKINSON'S DISEASE F-DOPA DIAGNOSIS USING SINGLE-CHANNEL EEG FEATURES AND AUDITORY COGNITIVE ASSESSMENT, A PILOT STUDY

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Aims: F-DOPA PET imaging provides a reliable measure of dopaminergic function often used to accurately diagnose Parkinson's disease (PD). We aimed to evaluate the ability to predict F-DOPA results and to separate positive F-DOPA patients and healthy populations using machine-learning (ML) based features extracted from a single-channel EEG during an auditory assessment.
Methods: 32 participants with F-DOPA PET results (abnormal n = 26, normal n = 6) and 20 aged-matched healthy participants performed a 15-minute auditory cognitive assessment (including detection and resting state tasks), while being recorded with a recently FDA-approved single-channel EEG device by Neurosteer. Results of 12 patients' F-DOPA PET scans were not initially revealed and were analyzed using a 2-fold correlational predictive model. Further data analysis included linear-mixed models (LMM) on all participants' EEG frequency-bands and previously extracted ML-based EEG features: A0, correlator of cognitive decline, and L1, correlator of cognitive load.
Results: The correlation model accurately predicted that results of the 12 unrevealed F-DOPA should be labeled as abnormal. Additionally, LMM results showed that Delta and A0 activity were significantly higher for healthy controls and normal F-DOPA patients compared to abnormal F-DOPA patients (p=0.01 and p=0.003, respectively). L1 activity significantly dropped in the resting state condition in the control group (p_{adj}=0.022), but not in the positive F-DOPA group (p_{adj}=1).
Conclusions: This pilot study successfully demonstrated the ability of features extracted from a single-channel EEG to separate between patients with normal F-DOPA PET and healthy controls vs. abnormal results. The Delta band and A0 activity, as well as L1 activity during resting state differentiated between the groups. Future studies should explore the potential usefulness of this accessible tool for characterizing EEG patterns in early PD patients.

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OD116 / #2568

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

PLASMA PHOSPO-TAU IN RELATION TO PART, AD AND OTHER KEY BRAIN PATHOLOGIES IN OLDER ADULTS

Lei Yu[1], Patricia Boyle[1], Shorena Janelidze[2], Tianhao Wang[1], David Bennett[1], Oskar Hansson[2,3], Julie Schneider[1]
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Aims: We investigated the extent to which plasma p-tau biomarkers are implicated in pathologically confirmed AD and mixed neuropathologies. Separately, we examined the utility of plasma p-tau biomarkers in classifying primary age-related tauopathy (PART) and AD.
Methods: Data came from 269 older adults who participated in the Religious Orders Study or Rush Memory and Aging Project. Blood samples were collected during annual clinical evaluations. Participants died and underwent brain autopsy. Two p-tau biomarkers, i.e., p-tau181 and p-tau217, were quantified in the plasma samples proximate to death using Lilly-developed MSD assays. Uniform systematic neuropathologic evaluations assessed common neurodegenerative and cerebrovascular conditions. For PART and AD comparison, the analysis was restricted to individuals with Braak stages of 3 or 4 but different Thal stages (N=160).
Results: Participants died at a mean age of 91. P-tau181 and p-tau217 were highly correlated (Pearson r = 0.92), and their correlations with brain β-amyloid and PHF tau tangles were moderate (Pearson r between 0.4 and 0.6). Both biomarkers were associated with greater odds of AD, but p-tau217 had higher accuracy (area under the ROC curve (AUC): 0.84) than p-tau181 (AUC: 0.77). The plasma p-tau biomarkers were almost exclusively associated with AD pathologic indices. For either biomarkers, we did not observe a level difference between individuals with AD alone and those with mixed AD pathologies. Further, comparing with p-tau181, p-tau217 showed a higher AUC (0.85 versus 0.78) in differentiating AD from PART.
Conclusions: The plasma biomarkers of p-tau181 and p-tau217 were specifically associated with AD pathological changes, but not other non-AD pathologies. Importantly, our data provide initial evidence that p-tau217 may be able to differentiate between individuals with PART and AD who have a similar degree of tau tangle pathology.

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OD116a / #3128

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS AND IMAGING IN AD, PD AND LBD
30-03-2023 07:00 - 08:30

ACCELERATING DRUG DISCOVERY IN ALZHEIMER'S AND PARKINSON'S DISEASE THROUGH INNOVATIVE AND STRATEGIC PUBLIC-PRIVATE PARTNERSHIPS

Alessio Travaglia, Stacey Adams, Wesley Horton, Erin Rosenbaugh, Loni Ajagbe, Sri Ramulu Pullagura, Steve Hoffmann
Foundation for the National Institutes of Health, , North Bethesda, United States of America

Aims: Objectives: The total cost of Alzheimer's Disease (AD) related drug development was estimated to be $5.6 billion, and the timeline was predicted to be approximately 13 years from a pre-clinical study to the approval by regulatory agencies. No cures exist for Parkinson's Disease (PD) due to a limited access to well characterized patient samples, absence of well-defined targets and biomarkers. No single organization can allocate resources to successfully conquer these drug development challenges.

Methods: Method: To overcome these problems, the Foundation for the National Institute of Health (FNIH) has created cross-discipline consortia including clinical researchers at NIH, other government agencies, industry, academia and not for profit organizations with a goal to find potential drug targets and biomarkers for AD and PD, thereby reducing the time and cost of drug development.

Results: Results: This talk will focus on lesson learned, main achievements, past and ongoing work in large and high-profile projects including the Alzheimer's Disease Neuroimaging Initiative (ADNI), Accelerating Medicines Partnership® (AMP®) Program for AD, AMP®-PD, and leading projects in the Biomarkers Consortium focused on the evaluation of the top-performing plasma Aβeta, phospho-Tau and Neurofilament light assays.

Conclusions: Conclusion: These consortia and public-private partnerships are contributing to discovery and validation of new therapeutic targets and biomarkers for disease progression and treatment response, which will lead to increased clinical trial success and new drugs for patients with Alzheimer's disease and Parkinson's disease.

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ON-DEMAND SYMPOSIUM: CLINICAL AND NEUROPATHOLOGICAL FEATURES ACROSS MULTIPLE NEURODEGENERATIVE DISEASES
30-03-2023 07:00 - 08:30

EVIDENCE OF FILAMIN A LOSS OF SOLUBILITY AT THE PRODROMAL STAGE OF ALZHEIMER'S DISEASE IN THE POST-MORTEM BRAIN

Étienne Aumont[1,2,3,4], Cyntia Tremblay[5], Stéphanie Levert[1], David Bennett[6], Frédéric Calon[5], Nicole Leclerc[1]
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Aims: In Alzheimer's disease (AD) Amyloid β (Aβ) peptide and tau protein interact with other proteins that contribute to disease progression. Filamin A (FLNA) is such a protein, and was found to co-localize with tau fibrils and to be involved in the induction of neuroinflammation and tau hyperphosphorylation by Aβ. We aimed to investigate the association between insoluble FLNA (iFLNA) and the stages of AD.
Methods: From 57 parietal cortex samples from the Religious Order Study, we quantified total tau, phosphorylated tau (pTau) and iFLNA by Western blot. Aβ42 and neuritic plaques (NP) were quantified by ELISA and Bielschowsky silver impregnation, respectively. AD staging was determined using the ABC method combining Thal, Braak and the CERAD staging. From this, clinicopathological stages of AD were established by subdividing subjects with neuropathological AD between preclinical AD, prodromal AD and AD dementia (ADD). We used receiver-operating characteristics for the detection of AD by FLNA.
Results: We found significant positive linear correlations between iFLNA levels and clinicopathological, ABC and Thal stages as well as with iAβ42 and NP ($p<.05$ False discovery rate-corrected). No significant correlation between iFLNA and iTau, ipTau and Braak and CERAD stages was noted. The prodromal AD and ADD groups displayed significantly higher iFLNA levels than the non-AD subjects. iFLNA was an excellent predictor of prodromal AD among subjects with MCI (AUC: .830).
Conclusions: We observed increased iFLNA levels in AD-wrought post-mortem brains at an intermediate stage that coincides with the appearance of cognitive symptoms. As such, it may be a key event in the transition from preclinical to prodromal AD. Insoluble FLNA could be useful to identify prodromal AD among subjects with an MCI, indicating that it might be a hallmark of prodromal AD.

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OD118 / #1743

ON-DEMAND SYMPOSIUM: CLINICAL AND NEUROPATHOLOGICAL FEATURES ACROSS MULTIPLE NEURODEGENERATIVE DISEASES
30-03-2023 07:00 - 08:30

CLINICAL AND NEUROPATHOLOGICAL FEATURES OF LATE ARE AFFECTED BY CO-EXISTING LEWY BODY PATHOLOGY

Shih-Hsiu Wang[1], Yuanyuan Guo[2], John Ervin[3], Jay Lusk[3], Sheng Luo[2]
[1]Duke University Medical Center, Pathology, Durham, United States of America, [2]Duke University Medical Center, Biostatistics And Bioinformatics, Durham, United States of America, [3]Duke University Medical Center, Neurology, Durham, United States of America

Aims: Limbic predominant age-related TDP-43 encephalopathy (LATE) neuropathological change is a common brain pathology of aging characterized by the accumulation of TDP-43 inclusions in the limbic system. Previously, we have shown that LATE is strongly associated with arteriolosclerosis across the entire aging spectrum, but other co-existing brain pathologies are more commonly seen in the younger old[1,2]. In this study, we examined in more detail how co-existing Lewy body (LB) pathology affects the clinical and neuropathological characteristics of LATE.
Methods: Participants of the Duke-UNC ADRC autopsy cohort 60 years and older were included in this study. Neuropathological analysis was performed according to published guidelines. Clinical, genetic, and neuropathological associations were examined using the Fisher's exact test or the Mann-Whitney test as appropriate.
Results: We identified 53 participants with LATE neuropathological change in our cohort, 18 of which had co-existing LB pathology. Participants with LB pathology were significantly younger (82.7 +/- 10.9 vs. 90.5 +/- 7.2, p=0.014) and less likely to have moderate to severe arteriolosclerosis (50% vs. 77.1%, p=0.014). Interestingly, participants with co-existing LB pathology had less severe LATE neuropathologic change (27.8% stage 1 vs. 17.1% stage 1). There was no significant difference in other clinical or neuropathological features.
Conclusions: While LATE is most prevalent in the oldest-old, co-existing LB pathology significantly lowers the age at death. Other neuropathological features also appear different in these two groups. Transcriptomic studies are underway to examine underlying differences between brains with pure LATE and those with other co-existing neurodegenerative pathologies. **References**: Harrison WT, Lusk JB, Liu B, Ervin JF, Johnson KG, Green CL, Wang SJ. Acta Neuropathol. 2021 Nov;142(5):917-919 Wang SJ, Guo Y, Ervin JF, Lusk JB, Luo S. Acta Neuropathol. 2022 Jul;144(1):45-57.

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OD119 / #1041

ON-DEMAND SYMPOSIUM: CLINICAL AND NEUROPATHOLOGICAL FEATURES ACROSS MULTIPLE NEURODEGENERATIVE DISEASES
30-03-2023 07:00 - 08:30

MIXED NEUROPATHOLOGY AND NEUROPSYCHIATRIC SYMPTOMS CONTRIBUTE TO CLINICAL UNDER-RECOGNITION OF NEOCORTICAL LEWY BODY DISEASE

Anna Lawson[1], Daniel Erskine[1], Calum Hamilton[1], Kirsty Mcaleese[1], Fiona Matthews[2], Alan Thomas[1]
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Aims: Dementia with Lewy bodies is under-recognised in clinical practice, compared with its observed prevalence in pathological studies. As many as two-thirds of autopsy-confirmed DLB cases may be missed clinically. This disparity may be due to an obscuring effect of widespread concomitant Alzheimer's pathology, or due to DLB cases not appearing to match the expected clinical phenotype (e.g., presenting without cardinal symptoms of DLB or with features more commonly associated with other forms of dementia, such as frontotemporal symptoms). We therefore aimed to examine whether mixed neuropathology and ante-mortem neuropsychiatric symptoms contributed to missed diagnosis of DLB.
Methods: Clinical and neuropathological assessments for 494 donors with dementia prior to death from the Brains for Dementia Research programme were examined as predictors of misdiagnosis and missed diagnosis of DLB. Neuropathological and neuropsychiatric features were assessed as predictors of accuracy of clinical diagnosis.
Results: Neocortical Lewy body cases with co-occurring Alzheimer's type neuropathological change were considerably more likely to have a missed diagnosis of DLB (odds ratio = 21.95, 95% CI [4.52 – 135.62]), with 88% of neocortical Lewy body cases accompanied by widespread Alzheimer-type pathology being missed clinically. Individuals with hallucinations were significantly less likely to have a missed diagnosis of DLB (OR = 0.12 [0.02–0.47]). Neocortical Lewy body disease was significantly under-recognised in those with reported apathy (OR = 5.24 [1.6 – 19.4]) and/or disinhibition (OR = 4.82 [1.2 – 23.3]).
Conclusions: Widespread Alzheimer-type pathology strongly impedes clinical recognition of neocortical Lewy body disease. Cases of Lewy body disease with hallucinations are more likely to be recognised clinically, while symptoms of apathy and disinhibition contribute to missed diagnosis.

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ON-DEMAND SYMPOSIUM: CLINICAL AND NEUROPATHOLOGICAL FEATURES ACROSS MULTIPLE NEURODEGENERATIVE DISEASES
30-03-2023 07:00 - 08:30

PROTEIN SIGNATURES ACROSS MULTIPLE NEURODEGENERATIVE DISEASES

Anna Månberg, Sofia Bergström, Sára Mravinacová, Jennie Olofsson, Julia Remnestål, Peter Nilsson
KTH Royal Institute of Technology, SciLifeLab, Protein Science, Stockholm, Sweden

Aims: The identification of disease-associated protein signatures could contribute to an increased understanding of neurodegenerative disorders. Some key features have been identified, but much remains unknown about the disease pathogenesis. We hypothesize that there are complex patterns and associations to be discovered, specific to and similar between different diseases. To reveal such patterns, it is crucial to investigate many proteins in several independent cohorts.
Methods: Our in-house developed affinity proteomics method allows for measurement of hundreds of proteins in hundreds of samples in the same assay. This is enabled by biotinylation of samples and a single binder setup with antibodies immobilized onto magnetic color-coded beads. We primarily use antibodies produced within the Human Protein Atlas project (proteinatlas.org) and the selection of proteins to be analyzed is tailored for each project, allowing for a high flexibility and adaptability.
Results: Over the years, we have analyzed more than 3000 CSF samples and almost 5000 plasma samples from cohorts including patients with Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis. Additionally, we have analyzed samples from neurologically healthy and cognitively impaired controls. In total, we have utilized over 1500 antibodies to profile almost 1000 proteins and assessed their association to diagnosis and other clinically relevant parameters.
Conclusions: To identify disease-relevant protein signatures, it is crucial to analyze large and independent cohorts including different neurodegenerative diseases. These complex signatures could potentially aid in understanding the underlying mechanisms and identify relevant patient subgroups.

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OD121 / #2205

ON-DEMAND SYMPOSIUM: CLINICAL AND NEUROPATHOLOGICAL FEATURES ACROSS MULTIPLE NEURODEGENERATIVE DISEASES
30-03-2023 07:00 - 08:30

LOW SENSITIVITY OF CLINICAL DEMENTIA WITH LEWY BODIES EVEN IN A PROSPECTIVE LONGITUDINAL COHORT DESIGNED FOR DETECTION OF CORE FEATURES

Ragnhild Skogseth[1,2], Tibor Hortobagyi[3,4,5], Arvid Rongve[1,6], Hogne Soennesyn[5], Audun Vik-Mo[1], Dag Aarsland[4,5]
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Aims: Objectives: We have previously found that clinical dementia with Lewy bodies diagnoses (DLB) are specific, but not sensitive enough – and that core features of DLB might develop after the initial dementia diagnosis. The prospective longitudinal cohort DemVest was designed for optimal clinical detection of DLB and is now completed, 70 participants have come to autopsy. We wanted to explore whether our previous findings are replicated in the whole cohort.
Methods: Methods: Participants with newly diagnosed dementia were subject to annual follow-ups until death. Core DLB features were assessed with standardized instruments as recommended by the International DLB Consortium. Clinical DLB diagnosis were made by expert consensus according to the 2005 McKeith criteria. Initial diagnoses were re-evaluated at several time points. Neuropathological work-ups were performed according to standardized protocols and criteria. Neuropathological findings associated with an intermediate or high likelihood of the clinical DLB syndrome according to McKeith 2005 were defined as DLB.
Results: Results: The sensitivity, specificity and accuracy of a clinical probable DLB diagnosis vs neuropathological diagnosis were 74%, 92% and 96% respectively.
Conclusions: Conclusions: Few studies have like the DemWest cohort both longitudinal information, with core DLB features rated annually and neuropathology. Thus, even when we optimized conditions for clinical detection, one fourth of DLB patients were not recognized as having DLB. Overlap between AD and DLB clinical syndromes and pathology is a likely explanation, highlighting the need for biomarkers for etiological dementia diagnosis and for further refinement of clinical diagnostic criteria.

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ON-DEMAND SYMPOSIUM: CLINICAL AND NEUROPATHOLOGICAL FEATURES ACROSS MULTIPLE NEURODEGENERATIVE DISEASES
30-03-2023 07:00 - 08:30

NMDA RECEPTORS AND TAU DEPOSITION IN MEN AND WOMEN: POSTMORTEM QUANTITATIVE AUTORADIOGRAPHY

Anat Biegon[1], Vanessa Carter[1], Jasbeer Dhawan[1], Aviram Nessim[1], Geidy Serrano[2], Thomas Beach[2], Erin Sundermann[3]
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Aims: 1. Characterize glutamate NMDA receptor (NMDAR) density and tau deposition in hippocampus and adjacent cortex in Alzhemier's disease (AD) and mild cognitive impairement (MCI) 2. Determine whether there are sex differences in NMDAR density along the AD trajectory.
Methods: Sections of hippocampus obtained postmortem were acquired from the Banner Sun Health Research Institute brain repository. Consecutive sections of freshly frozen hippocampi from 36 donors (18 men, 18 women, 6 controls, mild cogntiive impairement or AD per sex) were incubated with [3H]MK801 or [18F]T807 to assess NMDAR and tau deposit density repectively; using published incubation and wash conditions. Dried sections were apposed to radiation sensitive film alongside calibrated standards containing knowm amounts of radioactivity and stained for histology after film development. Binding density in sub regions of the hippocampus (CA1, dentate and subiculum) and the entorhinal cortex were measured using FIJI software. Effects of diagnosis, region and sex were analyzed using SPSS statistical software.
Results: Diagnosis of AD was associated with increased tau and decreased NMDAR density in the hippocampus and entorhinal cortex, although the size of the effect was modulated by sex and sub-region. Sex differences were driven by women demonstrating a steeper decline in NMDAR density, such that female controls had higher densities than males but this was reversed in MCI (no sex difference) and even further in the AD group, where women had lower density than men. The dentate gyrus was resistant to the effects of AD, with smaller increases in tau and decreases in NMDAR density relative to the other regions in both men and women.
Conclusions: NMDAR density is decreased in AD hippocampus and entorhinal cortex, though the effects are modulated by sex and hippocampal subregion.

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OD123 / #2289

ON-DEMAND SYMPOSIUM: CLINICAL AND NEUROPATHOLOGICAL FEATURES ACROSS MULTIPLE NEURODEGENERATIVE DISEASES
30-03-2023 07:00 - 08:30

BIMODALITY COEFFICIENT DIFFERENCE: A ROBUST METRIC FOR REVEALING DISEASE SUBTYPES

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Aims: Objectives: Precision medicine is advancing patient care for many complex human diseases, but little progress has been made for Alzheimer's and Parkinson's diseases. Discovery of biomarkers to diagnose specific subtypes within a heterogeneous diseased population is a key step towards realizing the benefits of precision medicine. However, popular statistical methods for evaluating candidate biomarkers – fold change (FC) and area under the receiver operating characteristic curve (AUC) – were designed for homogeneous data. We present an alternative approach, Bimodality Coefficient Difference (BCD), and evaluate the performance of all three metrics for heterogeneous populations.
Methods: We conducted a series of *in silico* trials to synthesize biomarkers for a range of subtype sizes. These simulation trials included 1000 repetitions of the experiments, each comprised of 1000 cases and 1000 controls and nearly 'ideal' subtype biomarkers representing each subtype percentage.
Results:

Trial	log2FC	AUC	BCD
Sim_0%	0.016 [5.47E-06, 0.080]	0.508 [0.491, 0.542]	0.016 [8.68E-06, 0.076]
Sim_5%	0.0276 [2.25E-06, 0.107]	0.525 [0.483, 0.563]	0.145 [0.066, 0.214]
Sim_10%	0.0544 [2.79E-04, 0.143]	0.548 [0.509, 0.605]	0.282 [0.214, 0.350]
Sim_20%	0.124 [0.037, 0.210]	0.598 [0.563, 0.630]	0.395 [0.325, 0.458]
Sim_30%	0.206 [0.071, 0.320]	0.646 [0.617, 0.675]	0.441 [0.372, 0.514]
Sim_40%	0.337 [0.134, 0.452]	0.695 [0.669, 0.723]	0.464 [0.389, 0.525]
Sim_50%	0.608 [0.221, 0.821]	0.743 [0.719, 0.768]	0.438 [0.383, 0.504]

Results: Table 1 shows the median values for the trials (with minimum and maximum values in brackets). Even when 50% of the cases were associated with the subtype biomarker, the median log2FC value for FC was only 0.608. Also, AUC values are insignificant for all scenarios up to subset size of 50%. The threshold of 0.209 provides a p-value ≤ 0.05 for BCD and *every* one of the 1000 trials for subsets of 10% or more are shown as significant.
Conclusions: Precision medicine is based upon the assumption that different subtypes exist for the given disease. We show here that popular statistics used for assessing biomarkers, FC and AUC, generally perform suboptimally when heterogeneity exists. We also provide a new metric, BCD, which appears to hold promise in this domain.

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OD124 / #1896

ON-DEMAND SYMPOSIUM: MRI 02
30-03-2023 07:00 - 08:30

DEEP SUPER-RESOLUTION IMPROVES ASYMMETRY MEASUREMENTS FROM DIFFUSION TENSOR IMAGING IN PARKINSON'S DISEASE

Brian Avants[1], Alexandra Reardon[2], Taylor Gosselin[2], Roger Gunn[3]
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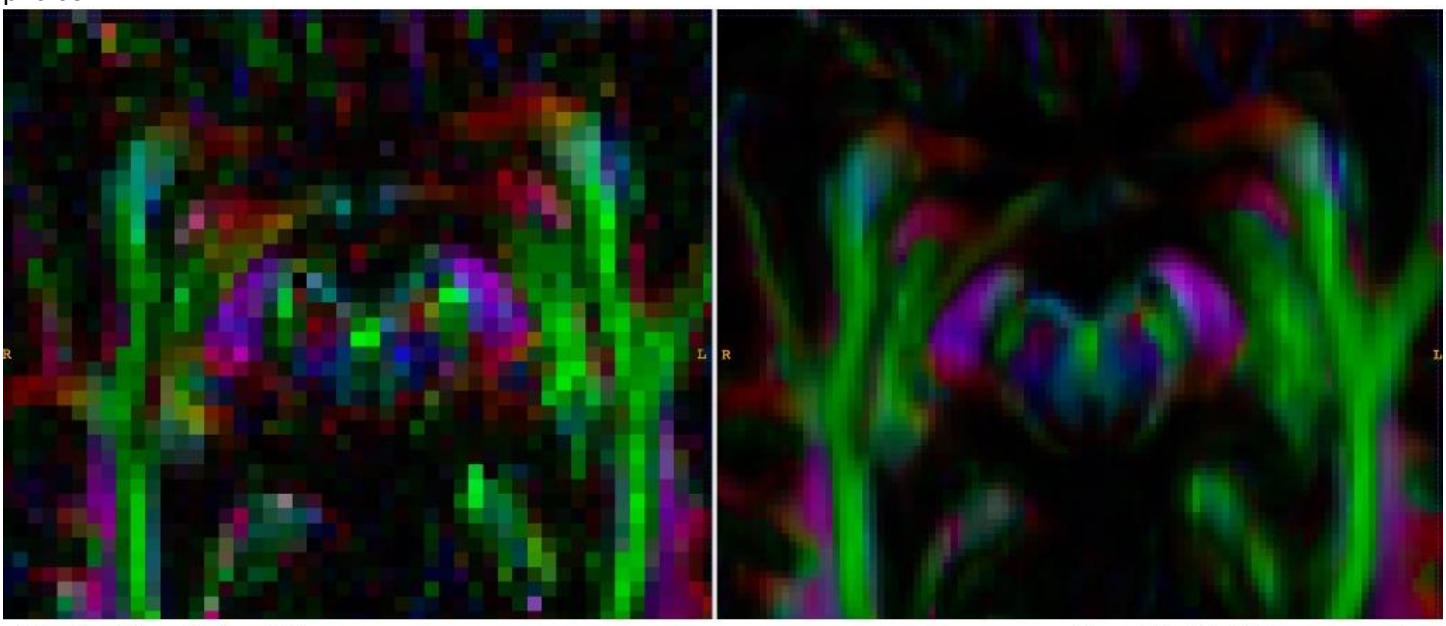
Aims: Motor symptom laterality early in Parkinson's disease (PD) suggests that asymmetry in brain measurements may be an important marker of disease [1]. Deep super-resolution (DSR) techniques in diffusion-weighted magnetic resonance imaging (DWMRI) can improve anatomical detail and, consequently, detection of Parkinson's disease (PD) related asymmetries in white matter that may be uniquely informative. We demonstrate preliminary results showing that DSR enhances asymmetry measures derived from DWMRI by improving test-retest reliability and detection of population effects in a PD cohort.
Methods: We processed DWMRI from the Parkinson's Progression Markers Initiative (PPMI). All DWMRI underwent the identical ANTsPyMM pipeline for both native and perceptual super-resolution (doubling resolution). The cohort included 243 subjects with consensus diagnoses of n=104 controls and n=139 sporadic PD with at least one followup image. We summarized asymmetry in fractional anisotropy (FA) and mean diffusivity (MD) using regions defined by the John Hopkins University white matter atlas.
Results: Reliability for asymmetry measurements overall was assessed by intraclass correlation (ICC): SR = 0.56, OR= 0.48, $p<0.001$; ICC > 0.5 indicates moderate reproducibility. Cross-sectional effect sizes for diagnosis were aggregated across regions with SR showing improvement: mean SR Cohen's d = 0.25; mean OR Cohen's d = 0.14, paired t-test $p<0.05$. Similarly, longitudinal effect sizes for significant changes in asymmetry related to diagnosis groups were also aggregated: mean SR Cohen's d = 0.19, mean OR Cohen's d = 0.13, paired t-test $p<0.05$.



PD subject SN original resolution — Same PD subject SN super resolution

Conclusions: Deep SR improves asymmetry metrics in PD in both cross-sectional and longitudinal designs. The value of DSR is highlighted particularly in longitudinal studies of asymmetry which involves measuring the change of a difference. Future work will investigate the value of such measures in earlier stage PD or prodromal subjects. [1] 10.1002/hbm.25558

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OD125 / #2399

ON-DEMAND SYMPOSIUM: MRI 02
30-03-2023 07:00 - 08:30

DISEASE PROGRESSION MODELLING ON MRI DATA IDENTIFIES SUBTYPES WITH COGNITIVE HETEROGENEITY IN A4 STUDY PRECLINICAL TRIAL COHORT

Cameron Shand[1], Michael Donohue[2], Daniel Alexander[1], Frederik Barkhof[3], Neil Oxtoby[1]
[1]University College London, Centre For Medical Image Computing, Computer Science, London, United Kingdom, [2]University of Southern California, Keck School Of Medicine, San Diego, United States of America, [3]University College London, Queen Square Institute Of Neurology And Centre For Medical Image Computing, London, United Kingdom

Aims: To identify and characterize MRI-based heterogeneity (subtypes) in a large preclinical cohort from the A4 Study. To look for subtype-cognition associations at baseline. To generate hypothetical forecasts for A4 by analyzing cognitive decline in a matched ADNI subset.
Methods: We fed MRI data into the Subtype and Stage Inference (SuStaIn) algorithm to estimate neurodegeneration subtypes in the A4 Study pre-randomization data (N=1240 Aβ+ individuals; N=407 Aβ− controls for covariate adjustment and z-scoring). We then compared demographic variables and cognitive scores across subtypes. Finally, we selected a subset of ADNI that matched the A4 Study inclusion criteria and investigated longitudinal cognitive decline in each subtype using a mixed effects model.
Results: Under cross-validation, SuStaIn identified three subtypes: *Typical*, *Cortical*, and *Subcortical*, named for regions showing early atrophy (z-score>2). 523 (42.2%) individuals belonged to these subtypes, with the remaining 717 (57.8%) having no abnormality (*Subtype Zero*; z-score<1). These MRI-based subtypes displayed significant differences in cognition: PACC and CFI. The *Cortical* subtype had the worst median cognitive scores, worse PACC scores than both *Subtype Zero* (P<0.0001) and the *Subcortical* subtype (P=0.0006), and worse CFI scores than *Subtype Zero* (P=0.0003). In ADNI, the *Cortical* subtype displayed greater cognitive decline in mPACC (P=0.09). Both the *Cortical* (P<0.0001) and *Subcortical* (P<0.0001) subtypes displayed greater cognitive decline on CDR-SB relative to *Subtype Zero*.
Conclusions: We used MRI data and a data-driven disease progression model to identify clinically-relevant baseline heterogeneity in the A4 Study. Different neurodegeneration signatures (subtypes) were associated with different cognitive profiles at baseline (in A4) and longitudinally (in ADNI). These findings have important ramifications for design of secondary prevention trials in Alzheimer's disease, which could leverage disease progression modelling for screening, stratification, or covariate adjustment short of stratification.

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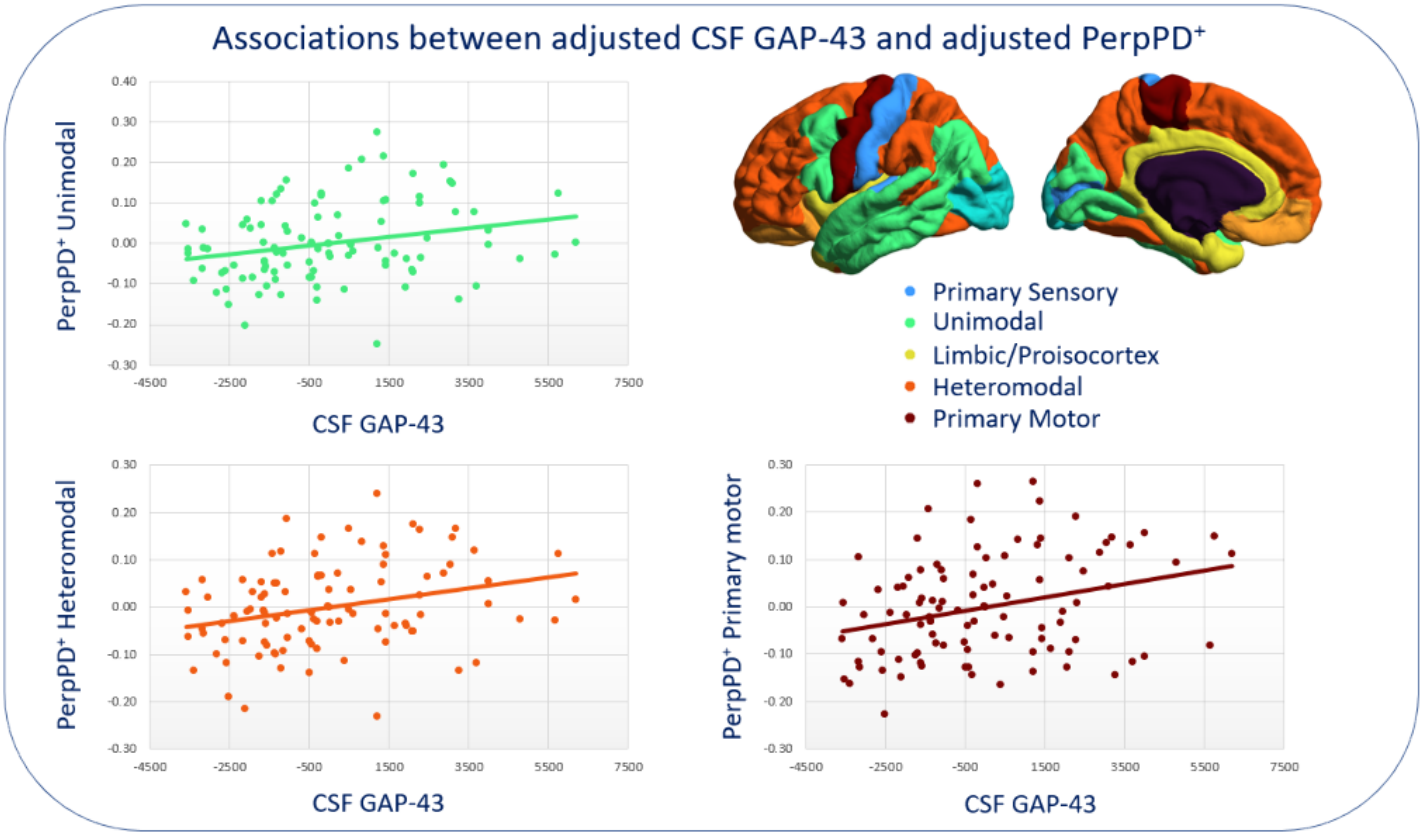
OD126 / #2191

ON-DEMAND SYMPOSIUM: MRI 02
30-03-2023 07:00 - 08:30

SYNAPTIC BIOMARKER CSF GAP-43 IS ASSOCIATED WITH CORTICAL MICROSTRUCTURE ASSESSED USING DIFFUSION MRI

Mario Torso, Gerard Ridgway, Michele Valotti, Ian Hardingham, Steven Chance, A. D.N.I. Alzheimer'S Disease Neuroimaging Initiative
Oxford Brain Diagnostics Ltd, Obd, Oxford, United Kingdom

Aims: To investigate the association of MRI measures of cortical microstructure and macrostructure with CSF GAP-43 (Growth-associated protein 43) - a presynaptic protein, reduced in Alzheimer's brain tissue and increased in CSF.
Methods: 102 participants [30=cognitively normal, 43=Mild cognitive Impairment, 29=Alzheimer's Disease (AD)] from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with CSF GAP-43 were included. T1 structural and diffusion MRI (dMRI) were used to calculate three novel cortical diffusivity measures [1]: the angle between the radial minicolumnar direction and the principal diffusion direction (AngleR); the principal diffusion component parallel with the minicolumns (ParlPD), and the diffusion components perpendicular to the minicolumns (PerpPD$^+$). Cortical mean diffusivity (MD) and standard macrostructual measures (cortical grey matter volume fraction and cortical thickness) were also assessed. Associations between the CSF GAP-43 levels and the cortical measures were evaluated with Pearson's partial correlation analysis, adjusting for age, sex, white matter hyperintensities volume fraction, scanner model, number of diffusion directions and dMRI voxel volume. For whole-brain measures significantly associated with GAP-43, regional correlation analysis was performed.
Results: At the whole brain level, PerpPD$^+$ was the only cortical measure significantly associated with CSF GAP-43 levels (r=0.260; p=0.012). At the regional level, significant associations between PerpPD$^+$ values and CSF GAP-43 concentrations were found in unimodal (r=0.252; p=0.015), heteromodal (r=0.283; p=0.006) and primary motor (r=0.296; p=0.004) regions (Figure 1).



Conclusions: These findings suggest that PerpPD$^+$ is sensitive to synaptic changes in the microstructure of cortical grey matter across the stages of AD. The diversity of brain regions associated with CSF GAP-43 suggests potential contributions from both neurodegeneration in AD vulnerable regions and compensatory plasticity in other regions.

References: McKavanagh et al (2019) "Relating diffusion tensor imaging measurements to microstructural quantities in the cerebral cortex in multiple sclerosis" 40(15):4417-4431 PMID:31355989

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OD127 / #2283

ON-DEMAND SYMPOSIUM: MRI 02
30-03-2023 07:00 - 08:30

EMPIRICALLY DERIVED STRUCTURAL BRAIN NETWORK HUBS ENHANCE PROGNOSTIC PREDICTION OF PROGRESSION IN AMYLOID POSITIVE SUBJECTS WITH MILD COGNITIVE IMPAIRMENT

Viswanath Devanarayan[1], Yuanqing Ye[1], Arnaud Charil[1], Akihiko Koyama[1], Larisa Reyderman[1], Chad Swanson[2], Harald Hampel[1], Michael Irizarry[1], Shobha Dhadda[1], Lynn Kramer[1]
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Aims: Purpose of this research is to determine whether structural brain network (SBN) hubs, when combined with baseline cognitive assessments, enhance the prediction of cognitive decline (CD) in amyloid positive (A+) mild cognitively impaired (MCI) patients.
Methods: Training cohort (TC) included 334 A+ MCI placebo subjects from two clinical trials. Two validation cohorts included 130 and 158 A+ MCI subjects respectively from another clinical trial (VC-1; placebo) and ADNI (VC-2). TC and VC-1 included 18-month follow-up, and VC-2 included 3 to 10-year follow-up. CD was defined by 1 point change or greater in CDR-SB. SBN hubs with strongest correlation to neighboring regions were derived using 207 regional volumetric MRI measures in TC via an algorithm from genomics called "multiscale embedded gene co-expression network analysis" (MEGENA). Signatures for predicting CD were constructed within TC via Bayesian elastic-net algorithm, and tested in VC-1 and VC-2. Added value of SBN hubs to baseline cognitive function was evaluated within this framework.
Results: A+ MCI subjects predicted to be at risk for CD in VC-1 and VC-2 using only baseline cognitive function were more likely to achieve CD, with hazard ratio (HR) of 2.7 and 3.7 respectively. Adding two of the nine SBN hubs generated via MEGENA, inferior parietal cortex and entorhinal cortex, to baseline cognitive function increased HR significantly to 3.8 and 4.8 respectively in VC-1 and VC-2 ($p<0.001$). HR for clinical conversion to Alzheimer's disease also significantly improved from 6.2 to 7.1 ($p=0.038$) in VC-2. Notably, adding all regional volumetric MRI measures instead of SBN hubs did not improve the prediction of CD.
Conclusions: SBN hubs, when combined with baseline cognitive function, significantly enhance the prognostic prediction of early CD in A+ MCI subjects.

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OD128 / #1515

ON-DEMAND SYMPOSIUM: MRI 02
30-03-2023 07:00 - 08:30

CORTICO-CORTICAL SIGNAL TRANSMISSION AND BRAIN CONNECTIVITY IN HEALTHY INDIVIDUALS AS A MODEL FOR STUDYING ALZHEIMER'S DISEASE: A MULTIMODAL APPROACH OF TMS-EEG AND ADVANCED MRI

Elisa Canu[1], Giacomo Bertazzoli[2,3], Antonio Malvaso[1], Veronica Castelnovo[1], Chiara Bagattini[2], Davide Calderaro[1], Claudia Fracassi[2], Moira Marizzoni[4], Valentina Nicolosi[2], Federica Agosta[1,5,6], Marta Bortoletto[2], Massimo Filippi[1,5,6,7,8]
[1]IRCCS San Raffaele Scientific Institute, Neuroimaging Research Unit, Division Of Neuroscience, Milan, Italy, [2]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Neurophysiology Lab, Brescia, Italy, [3]University of Trento, Center For Mind/brain Sciences Cimec, Rovereto, Italy, [4]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Laboratory Alzheimer's Neuroimaging & Epidemiology, Brescia, Italy, [5]IRCCS San Raffaele Scientific Institute, Neurology Unit, Milan, Italy, [6]Vita-Salute San Raffaele, University, Milan, Italy, [7]IRCCS San Raffaele Scientific Institute, Neurophysiology Service, Milan, Italy, [8]IRCCS San Raffaele Scientific Institute, Neurorehabilitation Unit, Milan, Italy

Aims: Signal following a transcranial magnetic stimulation (TMS) pulse can be tracked by electroencephalography (EEG). We wish to establish how contralateral time of signal transmission (STT), specifically the TMS-evoked potential (TEP)'s P20 latency, following a TMS pulse of specific brain nodes is related to the integrity of interhemispheric white matter (WM) fibers.
Methods: 28 healthy controls underwent an MRI and a TMS-EEG session. Resting-state fMRI maps were used to define default mode-DMN and executive control-ECN network nodes to be stimulated: left and right inferior parietal (IPL;DMN) and dorsolateral prefrontal (DLPFC;ECN). Fiber tracking of the main intra- and interhemispheric WM tracts was performed (probtrackx, FSL). TEP's P20 latency for each contralateral area of the stimulated node and DTI indices from each tract were obtained. The ability of WM measures to predict TEP's P20 latency were explored using multiple linear regression models.
Results: We observed that lower WM integrity of the splenium predicts lower TEP's P20 latency after left IPL stimulation. These findings were neither observed for intra-hemispheric connections nor within the ECN.
Conclusions: In healthy controls, we demonstrated that the WM integrity of the splenium predicts the interhemispheric P20 latency within the DMN following a TMS pulse of the left IP nodes. These findings reflect interhemispheric and network specificity. P20 latency is a promising measure of brain interhemispheric connectivity. After our initial validation, this approach could provide a novel single-subject marker of brain connectivity in early cases of Alzheimer's disease. **Funding:** Italian Ministry of Health (GR-2016-02364132). Foundation Research on Alzheimer Disease.

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OD129 / #2070

ON-DEMAND SYMPOSIUM: MRI 02
30-03-2023 07:00 - 08:30

ANTE-MORTEM MAGNETIC RESONANCE IMAGING GREY-WHITE MATTER CONTRAST REGIONAL SIGNATURES OF ALZHEIMER'S DISEASE NEUROPATHOLOGY

Francisco Almeida[1], Ana Coelho[1], Miguel Quintas-Neves[1], Merilee A. Teylan[2], Charles N. Mock[2], Walter Kukull[2], John F. Crary[3], Tiago Gil Oliveira[1]
[1]University of Minho, Life And Health Sciences Research Institute (icvs), School Of Medicine, Braga, Portugal, [2]National Alzheimer's Coordinating Center, University of Washington, Department Of Epidemiology, Washington, Seattle, United States of America, [3]Friedman Brain Institute, Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai, Neuropathology Brain Bank & Research Core, Department Of Pathology, Nash Family Department Of Neuroscience, Department Of Artificial Intelligence & Human Health, New York, United States of America

Aims: Grey matter (GM), white matter (WM) contrast (GWC) in T1-weighted MRI has been shown to decrease with age in healthy populations and cognitive impairment in clinical Alzheimer's Disease (AD). However, the neuropathological determinants of this signal remain unknown. Here, we aimed to study whether GWC is associated with AD neuropathology and longitudinal hippocampal atrophy.
Methods: 157 patients with neuropathological, clinical data and ante-mortem MRI were selected from the National Alzheimer's Coordinating Center database. Cortical volume and GWC (WM/GM intensity) in T1/MRI were obtained with Freesurfer 6.0. Hippocampal volume was divided into anterior, intermediate and posterior regions using a lab-based algorithm. Correlational analysis was conducted for GWC with age, and GWC residuals after linear regression with age for volume, BRAAK stage (neurofibrillary tangles), CERAD score (neuritic plaque density) and Cognitive Dementia Rating Sum-of-Boxes (CDR-SB). APOE genotypes were compared using one-way-ANOVA.
Results: GWC was negatively correlated with age in widespread brain areas ($p < 0.05$, FDR), but only the entorhinal cortex showed a positive correlation between volume and GWC. There were no significant correlations between GWC and BRAAK stage, CERAD score, CDR-SB or differences according to APOE genotype. Entorhinal GWC correlated positively only with the posterior hippocampal volume in BRAAK III-IV ($p = 0.031$; $R = 0.34$).
Conclusions: GWC is highly modulated by age, but not by classical AD neuropathology, APOE genotype or dementia severity in this cohort. Entorhinal GWC correlates with entorhinal and posterior hippocampal volume, suggesting it might reflect an early pathophysiological process distinct from classical AD neuropathology.

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OD130 / #1187

ON-DEMAND SYMPOSIUM: MRI 02
30-03-2023 07:00 - 08:30

WHITE MATTER HYPERINTENSITIES ARE ASSOCIATED WITH REDUCED GRAY MATTER AEROBIC GLYCOLYSIS

Andrei Vlassenko[1,2], Maryam Rahmani[1], Jeremy Strain[1], Tyler Blazey[1], Nickolas Metcalf[1], Tammie Benzinger[1,2], John Morris[2,3], Marcus Raichle[1,2], Manu Goyal[1,2,3]
[1]Washington University School of Medicine, Radiology, St. Louis, United States of America, [2]Washington University, Knight Alzheimer's Disease Research Center, St. Louis, United States of America, [3]Washington University School of Medicine, Neurology, St. Louis, United States of America

Aims: White matter hyperintensities (WMH), a hallmark of small vessel disease, are common associate of brain aging in cognitive health and disease, including Alzheimer disease. Higher WMH burden increases the risk of cognitive decline. Here we evaluated the relationship between WMH burden and aerobic glycolysis in aging brain gray matter.
Methods: We acquired one mm^3 isotropic FLAIR sequences in 142 cognitively unimpaired older adults. WMH were then segmented using intensity thresholding, manual selection of lesions, re-thresholding, and quality control. ^{18}F-FDG, ^{15}O-O_2, ^{15}O-HO_2, and ^{15}O-CO PET scans were performed on participants in the awake, eyes closed state, and processed to yield cerebral blood flow (CBF), cerebral oxygen consumption ($CMRO_2$), total cerebral glucose metabolism (CMRGlc) and aerobic glycolysis (GI). For each PET session and independent metabolic measure, a "youthful pattern" was defined based on its correlation to average gray matter regional values calculated in a separate cohort of 33 young healthy adults. A Spearman rank correlation rho was then calculated for each PET session as compared to the group results from the younger cohort to calculate the "youthful index" of each metabolic measurement at the time of that PET session.
Results: Controlling for age, sex, and amyloid status, WMH volumes were associated with a reduced youthful GI ($p<0.001$). This was not true for the other metabolic measures ($p>0.05$).
Conclusions: WMH burden might be an important aspect of the loss of brain resilience to AD pathology. Loss of gray matter aerobic glycolysis might affect white matter metabolism, and provoke increased vulnerability to WMH.

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OD131 / #1412

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

CHARACTERIZATION OF BRAIN SHUTTLE ENABLED TRKB NEUROTROPHIN RECEPTOR AGONIST ANTIBODIES - TRANSLATION TO NON-HUMAN PRIMATES

Pawel Stocki[1], Aziz Gauhar[1], Shu-Fen Coker[1], Patrick Doherty[2], Frank Walsh[1], Lynn Rutkowski[1]
[1]Ossianix Inc, Pre-clinical Development, Stevenage, United Kingdom, [2]King's College London, Psychology And Neuroscience, London, United Kingdom

Aims: We previously reported on the TXB4 transferrin receptor 1 VNAR antibody that can transport a TrkB agonist antibody to the CNS and provided full neuroprotection in a mouse model of Parkinson's Disease. We characterized a new primate specific shuttle called TXP1 and then genetically fused it to the TrkB antibody for clinical translation.
Methods: TXP1 was first expressed as fusion to human Fc and characterized *in vitro* by SPR, ELISA, flow cytometry. Brain penetration was tested in monkeys after IV administration at 1.35 mg/kg. Brain and plasm concentrations were determined after cardiac perfusion using an Fc-capture ELISA. TXP1 was also genetically fused to the N-terminus of the heavy chain to generate a bivalent, bispecific TrkB agonist antibody and characterized *in vitro* by SPR, ELISA, flow cytometry and a reporter cell assay for agonist activity.
Results: TXP1 as human Fc fusion binds with high affinity to TfR1 and has a similar binding kinetic profile to human and monkey versions of the receptor. After systemic administration in monkeys, the TXP1-Fc fusion showed enhanced brain penetration by up to 34-fold depending on brain region when compared to an isotype control. When the TXP1 brain shuttle was fused to the TrkB agonist antibody, the resulting bispecific antibody retained binding and showed similar *in vitro* functional activity to both targets.
Conclusions: TXP1 is a high-capacity shuttle for delivery of antibodies and other products to the CNS. The shuttle should allow the delivery of TrkB agonist antibodies in NHPs and lead to clinical trials in neurodegenerative diseases.

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OD132 / #1968

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

SMALL MOLECULE MODULATION OF THE P75 NEUROTROPHIN RECEPTOR REDUCES TAU OLIGOMER TOXICITY AND PROMOTES SPINE RESILIENCE

Tao Yang[1], Yeonglong Ay[1], Sukhneet Kaur[1], Kevin Tran[1], Harry Liu[1], Stephen Massa[2], Frank Longo[1]
[1]Stanford University, Neurology And Neurological Sciences, Palo Alto, United States of America, [2]University of California, San Francisco, Neurology, San Francisco, United States of America

Aims: The accumulation of pathologic forms of tau protein is a key feature of Alzheimer's disease (AD). Oligomeric forms of tau promote dendritic spine degeneration; thus, methods for preventing this sequela could have significant therapeutic potential. The intracellular signaling networks regulated by the p75 neurotrophin receptor ($p75^{NTR}$) substantially overlap with those linked to pathologic forms of tau. Here we sought to examine whether modulation of $p75^{NTR}$ would reduce spinotoxic factors generated in tauopathy mice and/or directly increase resilience of dendritic spines to oligomeric tau.
Methods: Cultured hippocampal neurons, maintained for 21 days, were exposed for 24 hrs to hippocampal tau-enriched extracts from PS19 tauopathy mice that were treated with vehicle or the $p75^{NTR}$-modulator LM11A-31 by oral gavage at 6-9 months of age; or to recombinant tau oligomers or PS19 extracts, with or without LM11A-31 in the culture medium. Morphologic analyses, immunostaining and western blots were performed.
Results: Neurons exposed to extracts from vehicle-treated PS19 mice showed a significant reduction in spine density. Extracts derived from LM11A-31-treated mice induced significantly less spine loss. Decreased spine density was also induced by tau oligomers and untreated PS19 extracts and was reversed by addition of LM11A-31 *in vitro.* Further, in vitro immunostaining showed that adding pathologic tau resulted in increased levels of AT8 and p-tau217 signal and this increase was prevented by addition of LM11A-31. Western blotting showed reduction in cofilin phosphorylation triggered by addition of tau oligomers which was normalized by LM11A-31 treatment.
Conclusions: These finding support the possibilities that modulation of $p75^{NTR}$ signaling may reduce the accumulation of pathological tau species or other spinotoxic factors in vivo and/or provide resilience to degenerative effects of pathological tau and/or other related tissue factors.

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March 28 - April 1, 2023 | Gothenburg, Sweden

OD133 / #1671

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

FLUORINATED LIPOSOMES MODIFIED WITH TRANSFERRIN TO TARGET THE BRAIN AND THE AMYLOID-BETA PEPTIDE: AN INNOVATIVE STRATEGY AGAINST ALZHEIMER'S DISEASE

Meghna Dabur[1,2], Joana Loureiro[1,2], Maria Do Carmo Pereira[1,2]
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Aims: Millions of people worldwide die from Alzheimer's disease (AD), a neurological condition that progresses and cannot be cured. It has been challenging to create disease-modifying medications for AD; essentially, most of the attempts have ended in clinical trial failure. Fluorinated molecules exhibit hydrophobicity, lipophilicity and high metabolic stability and have been shown to be effective in preventing protein misfolding for amyloid-beta (Aβ), the prevalent pathogenic hallmark of AD. As a promising therapeutic approach to achieve the requisite physiochemical qualities for overcoming the blood-brain barrier (BBB) and postponing Aβ aggregation, a combination of nanotechnology with a fluorinated compound is addressed.
Methods: Liposomes were produced through the lipid film method using a mixture of phospholipids and fluorinated fatty acids. The liposomes' surface was modified with transferrin, and their stability was addressed using dynamic light scattering. The fatty acids fluorination was confirmed using Fourier transform infrared and nuclear magnetic resonance spectroscopy, and the conjugation of transferrin on the surface of the liposomes was verified and quantified using Bradford dye assay. The Aβ aggregation was monitored using the thioflavin-T fluorescence assay.
Results: All fluorinated liposomes formulations appeared to have low polydispersity and sizes below 200 nm, and there was no apparent aggregation of nanoparticles over two months. No significant variations in physiochemical properties were identified in the liposomes containing fluorine nor in the liposomes containing the polymer polyethylene glycol with transferrin. The Aβ aggregation was delayed in the presence of fluorinated liposomes as well as fluorinated liposomes containing transferrin on their surface.
Conclusions: The developed fluorinated liposomes can be a promising nanocarrier to target the brain and prevent or treat AD. Furthermore, this formulation may result in the creation of more novel nano-fluorinated therapeutics in the future.

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OD134 / #1983

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

ACTIVE IMMUNOTHERAPY REDUCES NOTCH3 DEPOSITION IN BRAIN CAPILLARIES IN A CADASIL MOUSE MODEL

Helena Karlström[1], Daniel Oliveira[1], Kirsten Coupland[1], Wenchao Shao[1], Shaobo Jin[2], Francesca Del Gaudio[2], Sailan Wang[1], Rhys Fox[2], Julie Rutten[3], Johan Sandin[1], Henrik Zetterberg[4], Johan Lundkvist[1], Saskia Lesnik Oberstein[3], Urban Lendahl[2]
[1]Karolinska Institutet, Neurobiology, Care Science, And Society., stockholm, Sweden, [2]Karolinska Institutet, Cmb, Stockholm, Sweden, [3]Leiden University Medical Center, Department Of Clinical Genetics, Leiden, Netherlands, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden

Aims: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common monogenic form of familial small vessel disease; no preventive or curative therapy is available. CADASIL is caused by mutations in the *NOTCH3* gene, resulting in a mutated NOTCH3 receptor, with aggregation of the NOTCH3 extracellular domain (ECD) around vascular smooth muscle cells. In this study, we have developed a novel active immunization therapy specifically targeting CADASIL-like aggregated NOTCH3 ECD.
Methods: We have immunized CADASIL TgN3R182C^{150} mice with NOTCH3 aggregates composed of CADASIL-R133C mutated and wild type EGF1-5 repeats bi-weekly for a total of four months followed by immunohistochemistry on brain, retina and kidney as well as ELISA and Simoa on serum.
Results: The results showed a marked reduction (38-48%) in NOTCH3 deposition around brain capillaries, increased microglia activation and lowered serum levels of NOTCH3 ECD. Active immunization did not impact body weight, general behavior, the number and integrity of vascular smooth muscle cells in the retina, neuronal survival, or inflammation or the renal system, suggesting that the therapy is tolerable.
Conclusions: This is the first therapeutic study reporting a successful reduction of NOTCH3 accumulation in a CADASIL mouse model supporting further development towards clinical application for the benefit of CADASIL patients.

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OD135 / #1170

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

DISCOIDIN DOMAIN RECEPTOR-1 IS A THERAPEUTIC TARGET IN NEURODEGENERATIVE DISEASES

Charbel Moussa[1], Max Stevenson[1], Rency Varghese[2], Michaeline Hebron[1], Xiaoguang Liu[1], Yasar Torres-Yaghi[3], Fernando Pagan[3], Scott Turner[1]
[1]Georgetown University Medical Center, Neurology, Washington, United States of America, [2]Georgetown University Medical Center, Oncology, Washington, United States of America, [3]MedStar Georgetown Hospital, Neurology, Washington, United States of America

Aims: The role of Discoidin Domain Receptors (DDR1/2) is poorly understood in neurodegeneration. DDRs are activated by collagen and whole genome CSF miRNA sequencing suggests that collagens are longitudinally increased in PD patients, whereas DDR1 inhibition via nilotinib reduces the level of collagens. We aimed to better understand the effects of DDR on collagen in neurodegenerative disorders.
Methods: We measured the effects of nilotinib on DDR activity in the CSF and performed unbiased next generation whole genome miRNA sequencing of miRNAs from AD and PD patients. We verified DDR1 effects via cross-breeding DDR1 knockout mice with transgenic models of PD and AD, that express alpha-synuclein and beta-amyloid, respectively.
Results: The levels of CSF pDDR1 (phosphorylated) were longitudinally increased in PD and AD patients, whereas oral nilotinib, 300mg, treatment for 12 months significantly reduced pDDR1 levels. There was a significant decrease in miRNAs, which negatively regulate gene expression, that control collagens between baseline and 12 months in AD and PD patients with placebo, but 12-month treatment with nilotinib increased miRNAs, suggesting significant reduction of collagens expression. DDR1 knockout in mice that express human A53T mutation of alpha-synuclein ($DDR^{-/-}$A53T) or vascular dementia models that express Dutch, Swedish and Iowa mutations of APP ($DDR^{-/-}$APP) showed significant reductions of blood vessel thickness and collagen 4 levels, in parallel with clearance of amyloid and alpha-synuclein.
Conclusions: Our data indicate that pharmacological inhibition of DDR1 via nilotinib in AD and PD patients or genetic knockout of DDR1 in mice reduces the level of collagens and vascular thickness, potentially repairing blood brain barrier dysfunction in neurodegenerative diseases. Collectively these data indicate that DDR1 inhibition is a therapeutic target in neurodegenerative diseases.

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OD137 / #797

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

GABA-A RECEPTOR MODULATING STEROIDS IMPAIR MEMORY, PROMOTES DEMENTIA, AND ANTAGONIZED BY GABA-A RECEPTOR MODULATING STEROID ANTAGONISTS.

Torbjörn Bäckström[1], Magnus Doverskog[2], Thomas Blackburn[2]
[1]Umeå University, Clinical Sciences, Umeå, Sweden, Sweden, [2]Umecrine Cognition AB, Management, Solna, Sweden

Aims: Gamma-amino butyric acid (GABA) is the main inhibitory neurotransmitter in the brain and GABA-ergic transmission is important for the regulation of learning and memory. The progesterone metabolite allopregnanolone (Allo) is a potent positive GABA-A receptor modulating steroid (GAMS). In animal models, Allo impairs memory and deteriorates memory and learning in transgenic mice given continuously at doses corresponding to low-grade stress. In humans, Allo impairs episodic memory and a GAMS, medroxyprogesterone acetate treatment for four years doubled the frequency of dementia in elderly women. Disorders like hepatic encephalopathy and primary biliary cholangitis are associated with elevated Allo levels and impaired cognition, and increased fatigue. **Objectives:** To block GAMS induced memory deterioration.
Methods: Methods: We have invented compounds that function as GABA-A receptor modulating steroid antagonists (GAMSA), but without intrinsic effects on the GABA-A receptors. They will be used to block the deteriorating effects of Allo.
Results: Results: The antagonistic effect is noted in most GABA-A subtypes investigated so far, especially the dominant GABA-A receptor subtype, alpha5, in the hippocampus and the subtype related to memory. *In vivo*, GAMSA inhibits Allo-induced anesthesia in rats, and sedation or saccadic eye velocity in humans. GAMSA, can inhibit Allo-induced memory disturbances in rats. A GAMSA (golexanolone, GR3027), restored learning and motor coordination in rat models of hepatic encephalopathy. GR3027 reverses neuroinflammation in the cerebellum and hippocampus in a rat model of neuroinflammation induced by hyperammonemia. In human's, vigilance, cognition, and pathological EEG was improved in patients with hepatic encephalopathy when treated with GR3027.
Conclusions: Conclusions: GAMSA seem to be possible to use as treatment for impaired cognition. **References:** Bengtsson, et al. *Neurobiology of Stress*, 2020;12,100206:1-20. Johansson et al. Psychopharmacology. 2018;235(5):1533-1543 Mincheva et al. Neurosci Ther. 2022;Jul26. doi:10.1111/cns.13926.

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OD138 / #2671

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

G-PROTEIN SIGNALING AS TARGET FOR ALZHEIMER'S DISEASE: SPATIAL EXPRESSION VALIDATION OF DEEP LEARNING AND NETWORK ANALYSIS BASED COMPUTATIONAL FRAMEWORK

Qun Lu[1], Daniel Zhang[1], Timothy Penwell[1], Rui Wu[2]
[1]The Brody School of Medicine at East Carolina University, Anatomy And Cell Biology, Greenville, United States of America, [2]East Carolina University, Computer Science, Greenville, United States of America

Aims: Unbiased evaluation of the presumptive Alzheimer's disease (AD)-associated genes through their underlying AD pathogenic pathways and interrelationship facilitates the identification of potential new targets for effective treatments. The recently available large-scale multi-omics datasets provide opportunities to use computational approaches for such studies. The objectives of this study are to apply deep learning and network analysis-based computational framework to identify and validate G-protein signaling as potential AD targets.
Methods: We applied a novel disease gene identification (DigID) computational framework that consists of both a semi-supervised deep learning classifier to predict AD-associated genes and a protein-protein interaction network-based analysis to prioritize the importance of these predicted genes in AD. The potential disease relevance of the novel genes was validated using spatial expression analysis and subcellular Super-resolution STochastic Optical Reconstruction Microscopy (STORM) approaches.
Results: The DigID predicted 1,272 AD-associated genes with high accuracy, and it revealed both known and potentially novel AD molecular mechanisms and therapeutic targets. Among the top ten most important AD-associated genes ranked by DigID, seven are the targets of FDA-approved or investigational drugs for AD treatment. The other three were identified as potential novel targets, including GNAI1 and GNB1, two G-protein subunit genes that are known to regulate synaptic signaling, and KNG1, a mediator of Aβ-associated brain inflammation and phagocytosis. Spatial expression analysis of the multi-omics studies demonstrated differential transcriptomic dysregulation in different sub-brain regions. Super-resolution STORM analysis further revealed their subcellular localization and molecular interactions with other well-established AD protein networks in neurons.
Conclusions: Our studies highlight the potential of applying DigID for the identification of novel AD associated-genes and G-protein signaling as therapeutic targets in AD. This study is supported by USPHS NIH GM146257 (OD031672) and Wooten Foundation MT7955.

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ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

PREVENTION OF COGNITIVE IMPAIRMENT AND SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE: A NOVEL PATHWAY CONNECTING NEUROTRANSMISSION TO AMYLOID LOAD

Ashiq Rafiq, Hong Bao, Ankit Seth, Jacob Miller, Alexis Stranahan, Ferenc Deak
Augusta University, Neurosci & Regen. Medicine, Augusta, United States of America

Aims: Rate of synaptic activity and particularly rate of vesicle endocytosis is critically important for the processing of amyloid precursor protein (APP) into beta-amyloid (Abeta), a source of major toxic component in Alzheimer's disease (AD). The exact molecular mechanism connecting synaptic transmission to APP processing is still unknown.
Methods: We used a variety of methods to address this question: Based on our previous studies on genetic association with AD risk, we generated a novel mouseline with lowered synaptobrevin/VAMP1 expression and crossed to Tg2576 mice expressing human APP with Swedish mutations. We studied these mice using behavioral assays, slice recordings of synaptic plasticity, fluorescence imaging of synaptic release. We visualized and quantified amyloid load with light sheet microscopy and ELISA assays.
Results: We have examined a specific class of proteins – the vesicular membrane associated proteins (VAMPs/synaptobrevins) and their role in synaptic release and Abeta production: a) in human genetic screens single nucleotide polymorphism (SNP) variants of the VAMP1 gene encoding syb1 are significantly associated with late onset AD; b) SNPs associated with increased expression of VAMP1 increase the risk of AD and SNPs associated with lower syb1 expression reduces the risk of AD; c) in neurons of VAMP1 KO mice Abeta40 and Abeta42 production is substantially reduced. d) Lower levels of syb1 protected 18 mo old Tg2576 mice from cognitive impairment in radial water maze assay and reduced amyloid formation in their brains.
Conclusions: Based on these observations, we conclude that syb1 is a key coupling protein between vesicular release and APP processing. We propose that variations in synaptobrevin-1 level alter the coupling of synaptic transmission to APP processing and therefore have profound effect on Abeta production and risk of late-onset AD.

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OD140 / #1510

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

SINGLE NUCLEUS INVESTIGATION OF THE MOLECULAR EFFECTS OF THE GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST SEMAGLUTIDE IN A MOUSE MODEL OF NEUROINFLAMMATION

Marie Bentsen[1], Mette Ludwig[2], Dylan Belmont-Rausch[2], Anna Secher[3], Stine Normann Hansen[3], Kristoffer Egerod[2], Anne-Mette Bjerregaard[4], Charlotte Hansen[5], Kevin Dalgaard[3], Myrte Merkestein[3], Dorte Holst[3], Charles Pyke[3], Franziska Wichern[6], Joseph Polex-Wolf[3], Tune Pers[2], Lotte Knudsen[1]
[1]Novo Nordisk, Chief Scientific Advisor Office, R&ed, Måløv, Denmark, [2]University of Copenhagen, Novo Nordisk Foundation Center For Basic Metabolic Research, Copenhagen, Denmark, [3]Novo Nordisk, Global Drug Development, Måløv, Denmark, [4]Novo Nordisk, Digital Science & Innovation, Måløv, Denmark, [5]Novo Nordisk, Medical & Science, Søborg, Denmark, [6]Gubra, Neuropedia, Hørsholm, Denmark

Aims: Glucagon-Like Peptide-1 receptor agonists (GLP-1RAs) are approved as diabetes and obesity treatments. The GLP-1RA semaglutide is currently being investigated as a disease-modifying treatment in early Alzheimer's disease (AD) in two phase 3a randomized, placebo-controlled trials (evoke/evoke+). The leading hypothesis for the disease-modifying effect of semaglutide is through an effect on neuroinflammation. Because neuroinflammation is part of the pathophysiology in AD, and Parkinson's disease (PD), we here investigate the molecular effects of semaglutide in a lipopolysaccharide (LPS) induced neuroinflammation mouse model at the single nucleus level.
Methods: Mice were treated daily subcutaneously with semaglutide (30nmol/kg) or vehicle for 28 days, and LPS or vehicle was administered on days 15-17. Single nucleus RNA-sequencing and immunohistochemistry was performed to assess transcriptional and morphological changes in the hippocampus 2h, 24h, 5d and 11d post-LPS administration, respectively.
Results: A total of 184,493 nuclei were sequenced of which 87,975 were neurons and 96,518 were glia cells. Most differentially expressed genes between semaglutide+LPS and vehicle+LPS hippocampal cells were observed in microglia and a neuron subtype 24h post-LPS. Among all cell populations, and across all four timepoints, glia cells displayed most differentially expressed genes, and the changes followed a dynamic cell type-dependent temporal pattern. Further, LPS-treated mice had infiltrating peripheral immune cells in hippocampi, which were not seen in vehicle treated mice. Semaglutide treatment reduced the proportion of infiltrating peripheral immune cells in response to LPS treatment.
Conclusions: In an LPS-induced neuroinflammation mouse model, subcutaneously administered semaglutide resulted in robust gene expression changes in both glia cells and neurons. It is currently being elucidated how these multi-cellular changes could affect biological pathways relevant for neuroinflammation related to AD and PD.

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ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

ANTIGEN SPECIFIC TREG ATTENUATES ALZHEIMER'S DISEASE

Pravin Yeapuri, Jatin Machhi, Yaman Lu, Mai Mostafa, Rana Kadry, Jake Cohen, Eugene Lu, Milan Patel, Shaurav Bhattarai, Krista Namminga, Katherine Olson, R. Lee Mosley, Howard Gendelman
University of Nebraska Medical Center, Pharmacology And Experimental Neuroscience, Omaha, United States of America

Aims: Immunotherapy for Alzheimer's disease (AD) has met with mixed results. Vaccines targeting amyloid-b (Ab) although effective in mouse models, have led to a number of adverse events (AEs) during humans therapeutic trials. The AEs were associated with the infiltration of pro-inflammatory T effector (Teff) cells. These results highlighted Teff's pathobiological role in AD. Indeed, our own prior work affirmed these data by demonstrating that Ab specific monoclonal Teff (Ab-Teff) accelerate AD pathology. We hypothesized that Ab specific anti-inflammatory regulatory T cells (Treg) could lead to neuroprotective outcomes.
Methods: We generated Ab-Treg by CRISPR-Cas9 knock-out of the murine endogenous T cell receptor (TCR) followed by electroporation of a plasmid encoding for Ab specific TCR. Antigen specificity was confirmed by tetramer staining. Ab-Tregs generated were adoptively transferred into APP/PS1 transgenic mice and evaluated over time for changes in behavior and neuroprotective outcomes.
Results: Ab-Treg clones showed transient expression of Ab-TCR up to 6 days following electroporation. Compared to natural Tregs (nTreg), adoptive transfer of Ab-Treg sustained Teff suppressive functions, reduced amyloid load, and precluded the emergence of reactive microglia in the hippocampus and cortex of APP/PS1 mice. Flow cytometry demonstrated increased Treg homing to disease affected brain regions. Ab-Treg's ability to target affected brain regions was confimed by F18 Fluorodeoxyglucose(FDG) radiolabelled cell tracing. Reduction in amyloid load correlated with increased cognitive function determined by Y maze, water maze and brain FDG glucose uptake.
Conclusions: We posit that antigen reactive Ab-Tregs may be harnessed as a celluar immunotheraphy for AD. Compared to nTreg, Ab-Treg can target amyloid rich sites in the brain leading to rapid amyoid clearance and improved cognitive functions.

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OD141a / #658

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN AD: PRECLINICAL STUDIES
30-03-2023 07:00 - 08:30

DISCOVERY AND NONCLINICAL DEVELOPMENT OF ALN-APP, AN INVESTIGATIONAL RNAI THERAPEUTIC

Jeff Kurz[1], Luke Muhumuza[1], Jeff Allen[1,2], Bret Bostwick[1], Kirk Brown[1]
[1]Alnylam Pharmaceuticals, Research, Cambridge, United States of America, [2]Myrtelle Inc, Research, Wakefield, United States of America

Aims: ALN-APP is an investigational, intrathecally administered RNAi therapeutic in development for Alzheimer's Disease (AD). Targeting the *APP* gene transcript, ALN-APP is designed to lower amyloid precursor protein (APP) production and thereby lower APP fragments in the central nervous system (CNS), including amyloid beta (Aβ) and other intracellular and extracellular APP cleavage products implicated in AD pathogenesis. Nonclinical studies were conducted to demonstrate the pharmacology and toxicology profile of ALN-APP and support the entry of ALN-APP into clinical trials.
Methods: Rat and monkey studies, up to several months in duration, were conducted to evaluate the pharmacology and toxicology of ALN-APP. Assays were developed to measure ALN-APP and its metabolites in serial (blood, cerebrospinal fluid [CSF], urine) or terminal tissue samples. Pharmacodynamic changes in CSF APP protein levels and tissue mRNA levels versus controls were evaluated following ALN-APP administration. Toxicology was evaluated by clinical signs and sample analysis from animals administered supra-pharmacologic doses of ALN-APP, along with terminal necropsy and histology.
Results: ALN-APP displayed dose-dependent pharmacologic activity in monkeys, measured by reduction of *APP* mRNA and protein levels; Aβ peptides were also reduced. The pharmacodynamic effects were durable, consistent with drug levels that persisted for months in CNS tissues following single administration. Repeat-dose ALN-APP administration was well-tolerated in rats and monkeys in 4-week studies.
Conclusions: ALN-APP inhibits *APP* mRNA and reduces APP protein in vivo, consistent with its therapeutic potential, and displays a safety profile supporting the single-ascending dose trial currently in progress in patients with early-onset AD (EOAD).

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OD142 / #1780

ON-DEMAND SYMPOSIUM: CEREBRAL CONSEQUENCES OF VASCULAR CHANGES 02
30-03-2023 07:00 - 08:30

LEPTOMENINGEAL CELL DIVERSITY AND INTERCELLULAR COMMUNICATIONS IN NORMAL AGING AND ALZHEIMER'S DISEASE

Yanling Wang, Nicola Kearns, Artemis Iatrou, Danny Flood, Chris Gaiteri, Zachary Mullaney, David Bennett
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Aims: Human meninges at the brain border serves as an immunologically active barrier to defend the brain from pathological stimuli and maintain brain homeostasis. Here, we perform the first single-nuclei characterization of leptomeninges to elucidate cell types and intercellular communications in normal aging and Alzheimer's disease (AD).
Methods: We performed single nuclei RNA-seq (snRNA-seq) and subsequent computational analysis on the dissected leptomeninges from control and AD postmortem individuals.
Results: We identify endothelial, mural, immune, and fibroblast major cell types and multiple subtypes within each cell type. Interestingly, we discover a distinct vascular and fibroblast representation of leptomeninges from those of cortical parenchyma. Furthermore, the border-associated macrophages (BAMs) in leptomeninges display distinct transcriptional profiles from parenchymal microglia, and most meningeal T cells express the core gene signature of tissue-resident memory T cells. Comparing gene expression between control and AD individuals, we detect differentially expressed genes (DEGs) in most cell types, especially in BAMs and fibroblasts. Those DEGs are associated with dysregulations of extra-cellular matrix (ECM), glucose metabolism, and immune responses. Notably, BAMs express distinct AD GWAS genes from parenchymal microglia, suggesting an essential role of these understudied immune cell types in AD pathogenesis. Gene set enrich analysis reveals that the AD gene signature of ex vivo fibroblasts is significantly enriched in the Aβ-induced genes from cultured meningeal fibroblast-like cells. Lastly, we detect overall increased cell interactions and aberrant communication networks centering around BAMs and fibroblasts in AD.
Conclusions: Our work provides a detailed molecular atlas of the human leptomeninges that will guide future work in understanding meningeal immunity and surveillance. In addition, we reveal cell-type-specific transcriptional responses and intercellular communication changes in AD leptomeninges, shedding significant insights into human border-associated mechanisms underlying AD pathophysiology.

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OD143 / #2199

ON-DEMAND SYMPOSIUM: CEREBRAL CONSEQUENCES OF VASCULAR CHANGES 02
30-03-2023 07:00 - 08:30

INTERACTION OF VASCULAR RISK AND APOE4 STATUS ON CSF AMYLOID LEVELS IN NON-DEMENTED OLDER ADULTS

Lene Pålhaugen[1,2], Arne Nakling[3], Bjørn-Eivind Kirsebom[4,5], Jonas Jarholm[1,2], Henk J M M Mutsaerts[6], Per Selnes[1,2], Tormod Fladby[1,2]
[1]University of Oslo, Institute Of Clinical Medicine, Oslo, Norway, [2]Akershus University Hospital, Department Of Neurology, Nordbyhagen, Norway, [3]University of Bergen, Institute Of Clinical Medicine, Bergen, Norway, [4]UiT The Arctic University of Norway, Department Of Psychology, Faculty Of Health Sciences, Tromsø, Norway, [5]University hospital of North Norway (UNN), Department Of Neurology, Tromsø, Norway, [6]Amsterdam University Medical Center, Amsterdam Neuroscience, Dept. Of Radiology And Nuclear Medicine, Amsterdam, Netherlands

Aims: Cerebral amyloid angiopathy (CAA) is not only common in Alzheimer's disease (AD) patients, but also in the older cognitively normal population. While reduced beta-amyloid (Aβ) 42 in cerebrospinal fluid (CSF) is a diagnostic measure for AD, several studies have found lower levels of both Aβ40 and Aβ42 in CAA, potentially explained by trapping of amyloid in the vasculature due to impaired clearance. The *APOE*ε4-allele is an important risk factor for both CAA and AD. In this study, we examined the interaction between vascular risk and *APOE*ε4 status on Aβ.
Methods: We computed the Framingham Risk Score (FRS) as a measure of vascular risk in 297 cognitively normal (CN) and 267 cognitively impaired (CI) non-demented individuals (median follow-up 2.3 years) in the Dementia Disease Initiation cohort. We assessed the FRS*APOE interaction on Aβ38, Aβ40 and Aβ42 with linear mixed models. We divided the participants in four risk groups combining low and high FRS and *APOE*ε4 status (FRS+/APOE+, FRS-/APOE+, FRS+/APOE- and FRS-/APOE-) and assessed differences in Aβ with time, fitting linear mixed models with risk group, time and risk group*time interaction as fixed independent variables. Age and sex were covariates.
Results: For CI, there were significant cross-sectional FRS*APOE interactions on both Aβ38 (p=0.010) and Aβ40 (p=0.030), with a negative association between Aβ40 and FRS (p=0.035) and Aβ38 and FRS (p=0.046) for *APOE*ε4-carriers. In CN FRS+/APOE+, Aβ42 decreased significantly in time (p=<0.001) and more than FRS-/APOE+ (p=0.032) and FRS-/APOE-

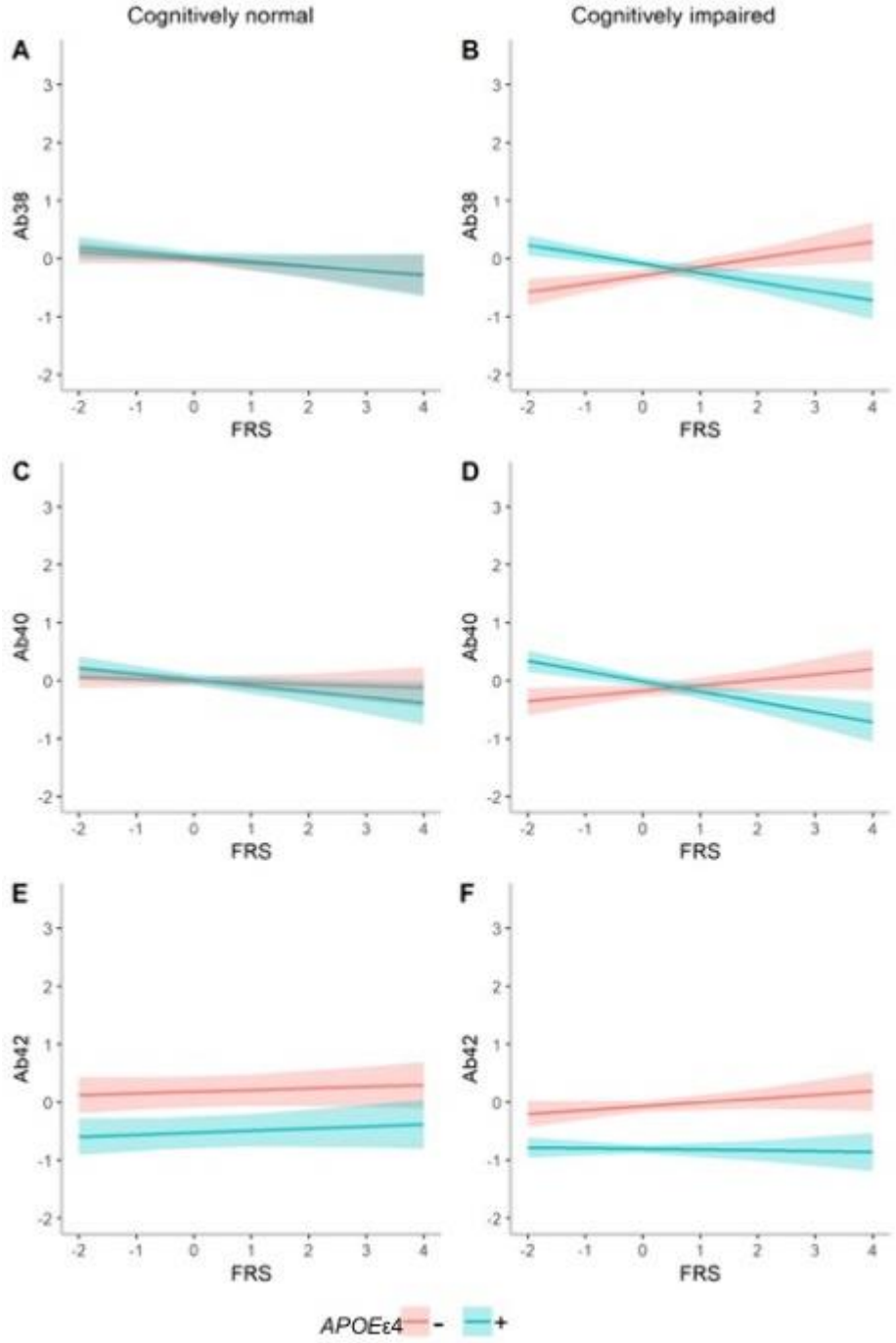

Figure 1. Adjusted fixed effects plots of cross-sectional FRS * *APOEε4* interaction on amyloid peptide levels in CSF. Aβ38, Aβ40 and Aβ42 were z-transformed using mean and standard deviation from cognitively normal individuals at baseline. FRS was z-transformed using mean and standard deviation from the whole cohort at baseline.

(p=0.005).

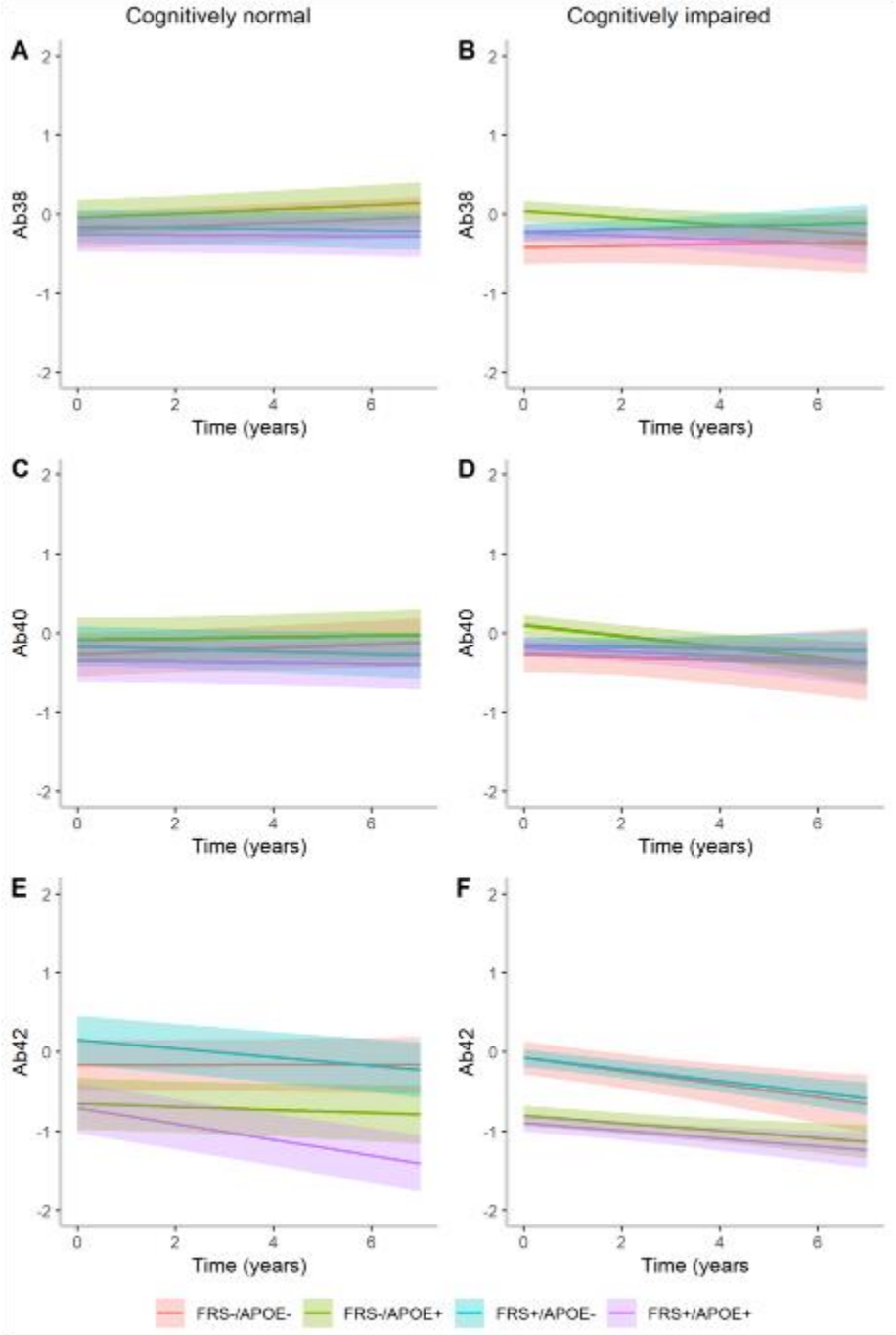

Figure 2. Adjusted fixed effects plots of FRS-APOE risk group * time interaction on amyloid peptide levels in CSF. Aβ38, Aβ40 and Aβ42 were z-transformed using mean and standard deviation from cognitively normal individuals at baseline. FRS was z-transformed using mean and standard deviation from the whole cohort at baseline.

Conclusions: Our findings are consistent with amyloid-beta precursor protein (APP) dysmetabolism in vascular dysfunction, with vascular trapping of amyloid in APOE-e4 carriers. A steeper decline in Ab42 with time in cognitively normal FRS+/APOE+ compared to FRS-/APOE+ supports the two-hit vascular hypothesis of AD.

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OD144 / #499

ON-DEMAND SYMPOSIUM: CEREBRAL CONSEQUENCES OF VASCULAR CHANGES 02
30-03-2023 07:00 - 08:30

ENDOTHELIAL EXPRESSION OF HUMAN APP GENERATES BLOOD AB AND INDUCES ROBUST CEREBRAL AMYLOID ANGIOPATHY IN APP KNOCK-IN MICE

Shinobu Kitazume[1], Yuriko Tachida[2], Saori Miura[1], Yui Muto[3], Hiroki Takuwa[4], Naruhiko Sahara[4], Akihiro Shindo[5], Yukio Matsuba[6], Takashi Saito[7], Yasushi Kawaguchi[3], Hidekazu Tomimoto[5], Takaomi Saido[6]
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Aims: The deposition of amyloid β (Aβ) in blood vessels of the brain, known as cerebral amyloid angiopathy (CAA), is observed in most Alzheimer's disease (AD) patients. Compared with the pathology of CAA in human cases, that in most mouse models of AD is not as evident, making it difficult to examine the contribution of CAA to the pathogenesis of AD. We and others previously demonstrated that human vascular endothelial cells express significant levels of amyloid precursor protein (APP). On the basis of the biochemical analysis that blood sAPP levels in rats and mice were markedly lower than those measured in human samples, we hypothesized that endothelial APP expression would be markedly lower in rodents, which could result in markedly lower levels of blood sAPP and subtle CAA pathology in most AD mouse models.
Methods: We have generated mice, EC-APP770^{+}, that specifically express human APP770 without Dutch/Iowa mutation in endothelial cells. We have also crossed the EC-APP770^{+}mice with AD model mice, *App*$^{NL\text{-}F/NL\text{-}F}$.
Results: The EC-APP770^{+}EC-APP770^{+} mice exhibited increased levels of serum Aβ and sAPP, indicating that endothelial APP makes a critical contribution to blood Aβ levels. Even though the aged mice did not exhibit apparent Aβ deposition in the cortical blood vessels, crossing these animals with APP knock-in mice, *App*$^{NL\text{-}F/NL\text{-}F}$, led to an expanded CAA pathology as evidenced by increased amounts of amyloid accumulated in the cortical blood vessels.
Conclusions: These results highlight an overlooked interplay between neuronal and endothelial APP in brain vascular Aβ deposition. The EC-APP770^{+}:*App*$^{NL\text{-}F/NL\text{-}F}$ mice would be useful to study the basic molecular mechanism causing possible breakdown of the blood-brain barrier by the administration of anti-Aβ antibodies.

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OD145 / #225

ON-DEMAND SYMPOSIUM: CEREBRAL CONSEQUENCES OF VASCULAR CHANGES 02
30-03-2023 07:00 - 08:30

FUNCTIONAL COVARIANCE CONNECTIVITY ANALYSIS OF GRAY AND WHITE MATTER IN OLFACTORY-RELATED BRAIN REGIONS IN CEREBRAL SMALL VESSEL DISEASE

Zenglin Cai[1], Yiqing Wang[1], Nizhuan Wang[2]
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Aims: Central anosmia can serve as a potential marker of early prodromal symptoms and progression in neurodegenerative diseases, the aim of this study was to assess whether functional connectivity of gray and white matter in olfactory-related brain regions is altered in cerebral small vessel disease (CSVD).
Methods: In this study, 21 patients with cerebral small vessel disease without olfactory impairment and 14 age-, gender-, and educational-matched controls were included. We applied the functional covariance connectivity (FCC) method to study the gray matter of the olfactory-related brain regions in Parkinson's disease. and functional covariance connections of white matter.
Results: The results of our study showed that the bottom of the temporal lobe, the limbic lobe, the right cerebellum, etc. in the gray matter of the patients with cerebral small vessel disease were abnormally connected with the bilateral anterior corona radiata and the left upper corona radiata in the white matter, indicating that the patients with cerebral small vessel disease had abnormal connections. There is potential brain damage in this area. The functional covariance connectivity strength of bilateral temporal lobe bases, limbic cortex and white matter, and the covariance connectivity strength of left upper corona radiata and gray matter function were significantly altered, with potential diagnostic value (data are still being processed).
Conclusions: These results suggest that alterations in the functional covariance connectivity of gray and white matter in olfactory-related brain regions may reflect changes in early olfactory function in patients with cerebral small vessel disease, suggesting that it may be a potential neuroimaging marker for early diagnosis.

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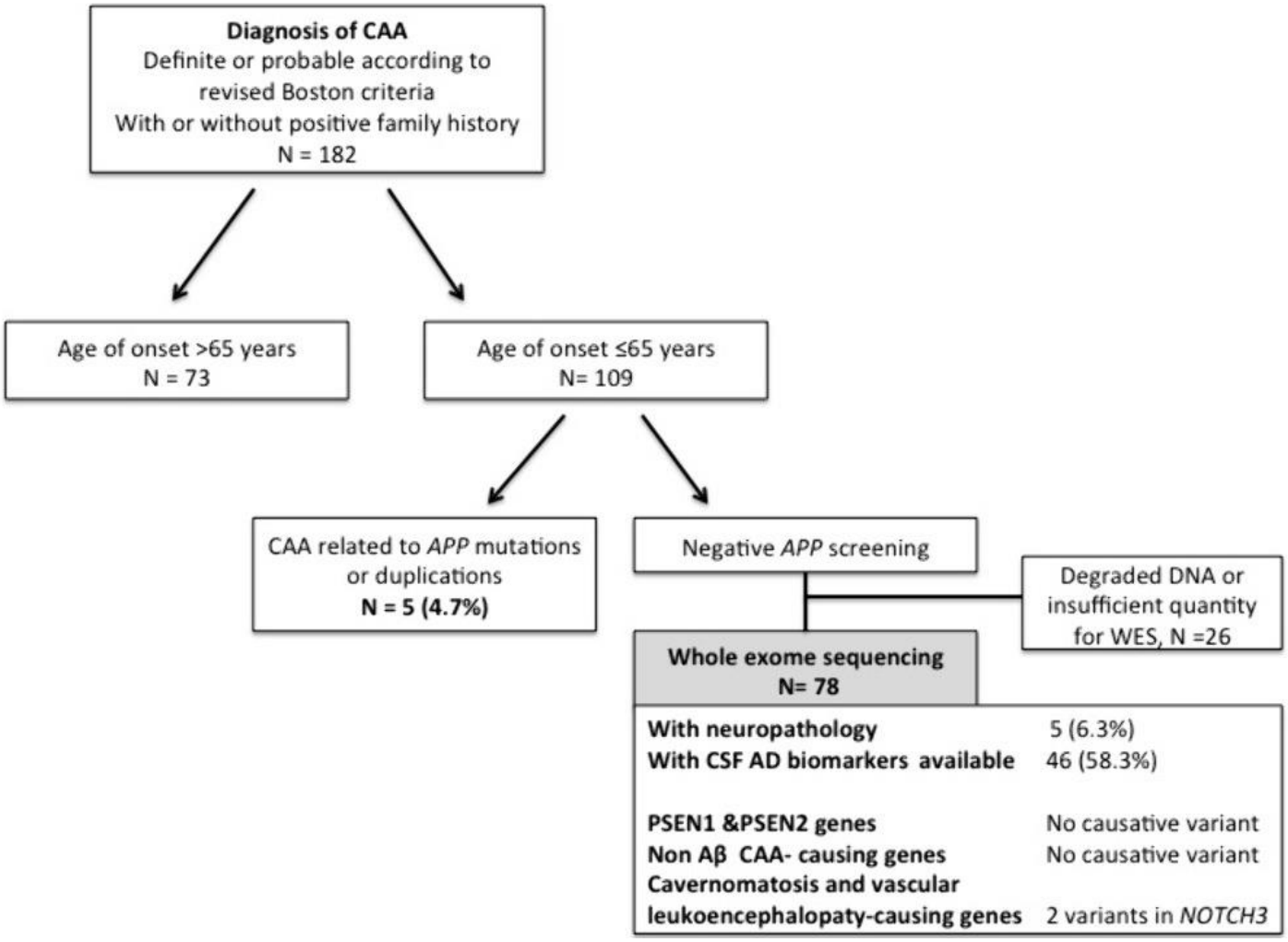
OD146 / #611

ON-DEMAND SYMPOSIUM: CEREBRAL CONSEQUENCES OF VASCULAR CHANGES 02
30-03-2023 07:00 - 08:30

INPUT OF EXOME SEQUENCING IN EARLY-ONSET CEREBRAL AMYLOID ANGIOPATHY

Lou Grangeon[1], Camille Charbonnier[2], Stephane Rousseau[2], Olivier Quenez[2], Aline Zarea[1], Anne Boland[3], Caa Genetics French Study Group[2], Gaël Nicolas[2], David Wallon[1]
[1]Rouen University Hospital, Neurology, Rouen, France, [2]Rouen University Hospital, Genetics, Rouen, France, [3]CNRGH, Genetics, evry, France

Aims: The genetic landscape of cerebral amyloid angiopathy (CAA) remains understudied. CAA shares with Alzheimer's disease (AD) some pathophysiological features and *APOE* genotypes as validated risk factors. However both conditions might share other genetic risk factors as those recently associated with AD**.** We aimed to assess the contribution of differential diagnosis genes to early-onset probable CAA as well as rare variants in genes associated with AD: *SORL1, TREM2*, *ABCA7, ABCA1* and *ATP8B4*
Methods: We conducted a whole exome analysis among 78 French patients with early-onset definite or probable CAA after negative genetic screening for *APP* mutations or duplications and compared their frequency to published early-onset AD case-control study
Results: Among 14 genes known to be involved in AD (*PSEN1, PSEN2*), non-Aβ CAA (*CST3, GSN, BRI2, TTR, PRNP*), cavernomatosis or vascular leukoencephalopathies, we detected distinct pathogenic variants in *NOTCH3* in two patients, who presented with spontaneous lobar intracerebral hematomas at 58 and 65 years old, suggesting that both patients developed CADASIL. Among the remaining 76 patients, 23.1% carried at least one *APOE* ε2 allele, 43.6% carried at least one *APOE* ε4 allele and 14 (19.7%) carried either a loss-of function (LOF) or a rare predicted damaging missense variants in *SORL1, TREM2*, *ABCA7, ABCA1* and *ATP8B4*. Five of these variants (6.6%) are well validated AD-risk factors (two *ABCA7* LOF, one *ABCA1* LOF,one *TREM2* R47H one*TREM2* R62H variants). The distribution of these rare variants were similar in early-onset CAA compared to the largest published early-onset AD case-control study.



Conclusions: CADASIL should be considered as a differential diagnosis of probable CAA. In addition to *APOE*, the identification of rare AD risk factors in CAA patients suggests putative shared genetic determinism that should be further assessed in larger studies

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OD147 / #722

ON-DEMAND SYMPOSIUM: CEREBRAL CONSEQUENCES OF VASCULAR CHANGES 02
30-03-2023 07:00 - 08:30

CEREBRAL VASCULAR TRANSCRIPTOME PROFILING REVEALS INTERMITTENT FASTING MODULATES CHRONIC CEREBRAL HYPOPERFUSION-INDUCED DISEASE PATHWAYS

Quynh Nhu Dinh, Yibo Fan, Nishat Tabassum, Cecilia Lo, Grant Drummond, Christopher Sobey, Thiruma Arumugam, T. Michael De Silva
La Trobe University, Department Of Microbiology, Anatomy, Physiology And Pharmacology, Centre For Cardiovascular Biology And Disease Research, Melbourne, Australia

Aims: Chronic cerebral hypoperfusion (CCH) is a major contributor to the development of vascular dementia (VaD), the second most common form of dementia. The pathophysiology of VaD is not well understood, making it difficult to develop effective therapies. Intermittent fasting (IF) modulates numerous signalling pathways and has been shown to be neuroprotective against VaD. To identify potential mechanistic pathways, this study aimed to understand the transcriptomic changes induced by CCH in cerebral arteries and the effect of IF on these transcriptomic changes.
Methods: Male C57Bl/6 mice were subjected to either ad libitum (AL) feeding or IF (fasting between 16:00-8:00). After 3 months of AL or IF, experimental CCH was induced in mice through bilateral carotid artery stenosis (BCAS) surgery to model VaD. RNA was extracted from cerebral arteries and transcriptomic changes were assessed using RNA sequencing after 1, 14, 21 and 30 days of BCAS or sham (control) surgery.
Results: IF mice had lower body weight and plasma glucose, and higher plasma ketone levels compared to AL mice ($n=10$, $P<0.05$). In cerebral arteries, BCAS induced differential expression of genes related to endothelial cell migration and cytoplasmic pattern recognition receptors (1 day after BCAS), angiogenesis, stress and inflammation (14 days after BCAS), morphogenesis and cytokinesis (21 days after BCAS), and vascular structure, hypoxia, inflammation and DNA repair (30 days after BCAS) ($n=4$, P-adjusted <0.05). IF altered expression of genes involved in inflammation and cellular stress which suggests a possible reversal of the transcriptomic changes induced by BCAS ($n=4$, P-adjusted <0.05).
Conclusions: CCH induces transcriptomic changes in cerebral arteries from as early as day 1 which may be reversed by IF. Novel pathways identified in this study could be targeted as a potential therapeutic for VaD.

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OD148 / #2643

ON-DEMAND SYMPOSIUM: CEREBRAL CONSEQUENCES OF VASCULAR CHANGES 02
30-03-2023 07:00 - 08:30

CARDIOVASCULAR RISK ASSESSMENT: A KEY ALERT FOR ALZHEIMER'S DISEASE SCREENING IN THE ELDERLY POPULATION

Gemma Garcia-Lluch[1], Juan Pardo Albiach[2], Lucrecia Moreno Royo[3], Miguel Baquero[1], Carmen Peña-Bautista[1], Consuelo Cháfer-Pericás[1]
[1]Medical Research Institute of Hospital La Fe, Research Group In Alzheimer Disease, Valencia, Spain, [2]Universidad CEU Cardenal Herrera, Valencia, Spain, Embedded Systems And Artificial Intelligence Group, Valencia, Spain, [3]Universidad CEU Cardenal Herrera, Valencia, Spain, 3department Of Pharmacy, Valencia, Spain

Aims: This study aims to assess whether cardiovascular risk in the elderly is associated with pathological CSF AD biomarkers.
Methods: The present work included patients between 50 and 75 years old who were cognitively healthy (controls) or were in the early stages of AD (cases). CSF biomarkers included t-tau, p-tau, and Aß42. Patients were classified according to the ratio t-tau/Aß42. A medical history review was performed to obtain total and HDL cholesterol levels, blood pressure levels, smoking habit, antihypertensive treatment, and diabetes status. The ERICE scale was used to calculate the patient's cardiovascular risk. A two-sample t-test and Pearson's Chi-squared test were performed to check group differences. A substudy with patients whose diagnosis included Aß42/Aß40 ratio and neurofilaments was also performed.
Results: Two hundred and thirty-one patients were included. One hundred seventy-seven patients had AD (76,62 %), and 54 patients were cognitively healthy (23,38 %). AD patients had higher cardiovascular risk and systolic blood pressure levels than cognitively healthy patients (p-value < 0,05). Moreover, a correlation between cardiovascular risk and pathological values of Aß42 was observed. On the other hand, one hundred and four patients were included in the substudy. As a result, 80 patients had AD (77%), and 24 were cognitively healthy (23%). AD patients showed higher punctuations on cardiovascular risk (p-value < 0,001). Finally, higher cardiovascular risk showed a correlation with pathological levels of the ratio t-tau/Aß42 and Aß42/Aß40, Aß42, and neurofilament levels (p-value < 0,02).
Conclusions: Cardiovascular risk assessment may be helpful in preclinical AD diagnosis, as it is associated with pathological CSF AD biomarkers.

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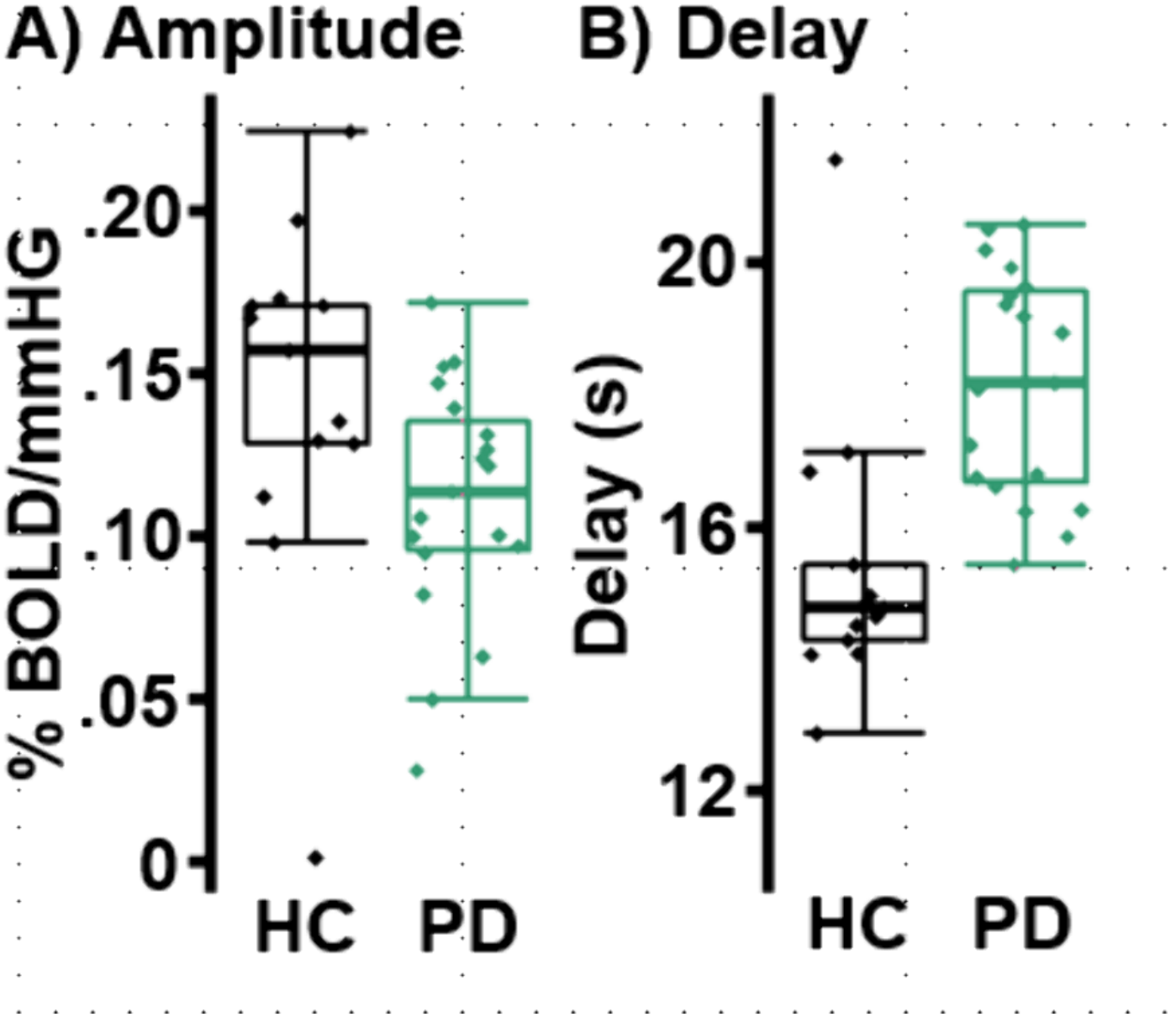
OD149 / #2657

ON-DEMAND SYMPOSIUM: CEREBRAL CONSEQUENCES OF VASCULAR CHANGES 02
30-03-2023 07:00 - 08:30

REDUCED AND DELAYED CEREBROVASCULAR REACTIVITY IN PARKINSON'S DISEASE

Sephira Ryman[1,2], Nicholas Shaff[1], Stephanie Nitschke[1], Kayla Julio[1], Christopher Wertz[1], Andrew Mayer[1], Andrei Vakhtin[1], Gerson Suarez-Cedeno[2], Amanda Deligtische[2], Erik Erhardt[3], Sarah Pirio Richardson[2]
[1]Mind Research Network, Translational Neuroscience, Albuquerque, United States of America, [2]Nene and Jamie Koch Comprehensive Movement Disorders Center, Department Of Neurology, Albuquerque, United States of America, [3]University of New Mexico, Mathematics And Statistics, Albuquerque, United States of America

Aims: Parkinson's disease (PD) patients have unique cerebrovascular risk factors and cerebrovascular related dysfunction which may contribute to the progression of the disorder. MRI cerebrovascular reactivity paradigms provide an opportunity to measure the ability of the cerebral vessels to dilate or constrict in response to challenges. The current study evaluates our hypothesis that PD patients exhibit a significant reduction in the amplitude of and latency in cerebrovascular reactivity relative to health controls (HC).
Methods: 19 PD and 13 age and sex-matched HC participated in the study. Participants were asked to inhale gas enriched in CO_2 to elicit a vasodilatory response while undergoing bold oxygen level-dependent (BOLD) MRI. Amplitude of whole brain cerebrovascular reactivity was quantified as the change in BOLD response per unit change in end-tidal CO_2 (%BOLD/mmHG). Latency of the fitted BOLD response was also calculated for each individual. An analysis of covariance (ANCOVA) was used to evaluate group differences between PD and HC in the amplitude and latency of cerebrovascular reactivity accounting for age and sex.
Results: A significant main effect of group was observed for whole brain cerebrovascular reactivity amplitude ($F_{(1, 28)}$ = 4.380; p = 0.046) and latency ($F_{(1, 28)}$ = 16.346; p < 0.001). PD patients exhibited reduced whole brain amplitude (0.144 +/- 0.055 %BOLD/mmHG) and increased latencies in cerebrovascular reactivity (15.40 +/- 2.17 seconds(s)) relative to HC (0.111 +/- 0.037 %BOLD/mmHG; delay 18.20 +/- 1.72
s).



Conclusions: PD patients exhibited reduced amplitude and increased latency in cerebrovascular reactivity suggesting poor cerebrovascular regulation. Future research is necessary to understand how cerebrovascular dysregulation impacts motor and non-motor symptoms over time.

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OD150 / #805

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

IMPLICATION OF ASTROCYTIC PHAGOCYTOSIS IN RODENT MODELS OF PRIMARY TAUOPATHIES

Karine Cambon[1], Nathan Louvel[1], Anastasie Maté De Gérando[1], Isabel Paiva[2], Gwennaëlle Auregan[1], Charlène Josephine[1], Mylène Gaudin- Guerif[1], Martine Guillermier[1], Anne-Sophie Herard[1], Caroline Jan[1], Fanny Petit[1], Emilie Faivre[3], David Blum[3], Laurette Boutillier[2], Philippe Hantraye[1], Marie-Claude Gaillard[1], Gilles Bonvento[1], Alexis-Pierre Bemelmans[1]
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Aims: In primary Tauopathies, abnormal forms of Tau are present in astrocytes in addition to neurons. Astrocytes can internalize neuronal Tau species and accumulate them. Given their capacity to eliminate synapses, astrocytes likely internalize Tau species while phagocytosing pathological synapses. Here we tested the hypothesis that 1) Tau pathology up-regulates phagocytosis in astrocytes and 2) silencing MER Proto-Oncogene, Tyrosine Kinase (MERTK)- mediated phagocytosis alleviates pathology.
Methods: We modelled Tau pathology using AAV gene transfer to overexpress hyperphosphorylated Tau (soluble form using human WT tau, or aggregated form using pro-aggregating vector TauProAggr) in the hippocampus of adult C57Bl/6J mice. RNAseq analysis was performed on isolated astrocytes 3 months after AAV injection. In addition, we designed an AAV encoding artificial miRNA to silence MERTK specifically in astrocytes. Mice were co-injected in the hippocampus with AAVs-CBA-Tau and either AAV-GFA-mirShMERTK or mirShControl. Three months later Tau pathology and astrocytic reactivity were assessed in the hippocampus using immunohistology, confocal microscopy and image analysis.
Results: Gene ontology analysis revealed that hTauProAggr triggered the up-regulation of 281 genes associated with immune response and phagocytosis-related pathways, compared to controls. Interestingly, phagocytosis was not induced in hTauWT group. In hTauProAggr- injected mice, MERTK silencing reduced overall hippocampal AT100- and AT8-positive tauopathy and strongly decreased astrocyte reactivity. In contrast, this treatment did not alter pathology nor astrocyte reactivity in hTauWT model.
Conclusions: Our data show the presence of Tau aggregates induces astrocytic phagocytosis whereas soluble Tau does not. Silencing MERTK-mediated phagocytosis reduces Tau pathology and may have overall beneficial effects.

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OD151 / #560

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

PURINERGIC P2Y12 RECEPTOR-MEDIATED ENDOCYTIC ACCUMULATION OF TAU OLIGOMERS AND LYSOSOMAL DEGRADATION IN MIGRATORY MICROGLIA

Subashchandrabose Chinnathambi
National Chemical Laboratory, Neurobiology Group, Biochemical Sciences Division, Pune, India

Aims: Microglia can directly interact with pathogenic Tau species by purinergic P2Y12 receptor and mediate membrane-associated actin remodelling and MTOC polarization for migration, invasion and phagocytosis. Here, we studied the P2Y12 receptor-mediated endocytosis of Tau monomer and oligomers via localized F-actin polymerization in a time-dependent manner.
Methods: • Immunofluorescence analysis and high-resolution confocal microscopy. P2Y12-mediated actin remodelling, formation of actin microstructures such as- podosome and filopodia were studied by Fluorescence microscopy. • Co-IP and Western Blot. The P2Y12-Tau interaction, expression of receptors, actin-associated proteins and endocytosis Rabs were studied by western blot. • Tau deposits degradation and Tau endocytosis assay. P2Y12-mediated Tau deposits degradation by forming actin microstructures and P2Y12-driven Tau endocytosis and lysosomal degradation were studied by confocal microscopy.
Results: The internalization of Tau was studied by β-arrestin-1-mediated receptor desensitization where Tau was found to colocalize with P2Y12 and β-arrestin-1 on cell surface and microglial cytosol. Similarly, the endocytic trafficking of Tau was studied in association with Rab5+ early, Rab7+ late and Rab11+ recycle endosomal vesicle, followed by the lysosomal degradation via Lamp2A association. Tau monomer was found to be internalized faster than oligomers and then followed endosomal trafficking and lysosomal degradation. Henceforth, the degradation of these Tau oligomers by alternative pathways can be intervened and targeted in order to prevent the spreading of Tau species by migratory microglia.
Conclusions: Microglia phagocytose Tau oligomers by P2Y12 and F-actin-mediated endocytosis The blockage of P2Y12 signalling exhibits the reduced level of Tau phagocytosis Microglia endocytose Tau by P2Y12-mediated and β-arrestin1-assisted desensitization Endocytosed Tau localizes with Rab5-associated early endosomes Tau oligomers accumulate in Rab7-containing late endosomes but monomer traffics through lysosomal degradation Tau oligomers follow through Rab11+recycling endosomes slowly than monomer

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OD152 / #1665

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

LIPID DROPLET-MEDIATED MICROGLIAL DYSFUNCTION IN ALZHEIMER'S DISEASE

Priya Prakash[1], Palak Manchanda[1], Evangelia Paouri[2], Kanchan Bisht[1], Kaushik Sharma[1], Prageeth Wijewardhane[1], Caitlin Randolph[1], Matthew Clark[3], Jonathan Fine[1], Elizabeth Thayer[1], Richard Prayson[4], Chi Zhang[3], Dimitrios Davalos[2], Gaurav Chopra[1]
[1]Purdue University, Chemistry, Integrative Neuroscience Institute, West Lafayette, United States of America, [2]Lerner Research Institute, Cleveland Clinic, Neurosciences, Cleveland, United States of America, [3]Purdue University, Chemistry, West Lafayette, United States of America, [4]Cleveland Clinic, Anatomic Pathology, Cleveland, United States of America

Aims: Several microglia-expressed genes have emerged as top risk variants for Alzheimer's disease (AD). Impaired microglial phagocytosis is one of the main proposed outcomes by which these AD-risk genes may contribute to neurodegeneration, but the mechanisms translating genetic association to cellular dysfunction remain unknown. Here we show that microglia form lipid droplets (LDs) upon exposure to amyloid-beta (Aβ), and that their LD load increases with proximity to amyloid plaques in brains from human patients and the AD mouse model 5xFAD.
Methods: LD formation is dependent upon age and disease progression, and is more prominent in the hippocampus in mice and humans. Despite variability in LD load between microglia from male versus female animals and between cells from different brain regions, LD-laden microglia exhibited a deficit in Aβ phagocytosis. Unbiased lipidomic analysis identified a substantial decrease in free fatty acids (FFAs) and a parallel increase in triacylglycerols (TAGs) as the key metabolic transition underlying LD formation.
Results: We show that Aβ alone is sufficient to induce LD formation in microglia and that this conversion requires a specific metabolic conversion of FFAs to TAGs (the building blocks of LDs). This conversion is likely protective for the brain and microglia, as we recently showed (in collaboration with the late Ben Barres' group) that long-chain saturated FFAs can be neurotoxic (Nature 599,102–107, 2021), but it is not without cost for microglial abilities. We demonstrate that a key enzyme for the conversion of FFAs to TAGs, promotes microglial LD formation, is increased in microglia from 5xFAD and human AD brains, and that inhibiting it improved microglial uptake of Aβ.
Conclusions: These findings identify a new lipid-mediated mechanism underlying microglial dysfunction that could become a novel therapeutic target for AD.

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ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

USING SINGLE NUCLEUS PROFILING TO IDENTIFY DIFFERENTIAL NEURONAL AND MICROGLIAL SIGNATURES IN PARKINSON'S DISEASE

Zena Chatila[1], Archana Yadav[1], Xena Flowers[2], Taekyung Yun[1], Zoe Pelly[1], Andrew Teich[3], Rui Costa[4], Philip De Jager[5], Estela Area Gomez[6], Gabriela Martins[4], Roy Alcalay[7], Jean Paul Vonsattel[3], Vilas Menon[1], Elizabeth Bradshaw[1], Serge Przedborski[8]
[1]Columbia University, Neurology, New York, United States of America, [2]Columbia University, Neurology, Taub Institute, New York, United States of America, [3]Columbia University, Department Of Pathology And Cell Biology, New York, United States of America, [4]Columbia University, Zuckerman Mind Brain Behavior Institute, New York, United States of America, [5]Columbia University Medical Center, Center For Computational & Translational Neuroimmunology, Department Of Neurology, New York, United States of America, [6]Centro de Investigaciones biologicas "Margarita Salas", Biomedicine, CSIC, Spain, [7]Tel Aviv University, Sackler Faculty Of Medicine, Tel Aviv, Israel, [8]Columbia University, Neurology, Pathology & Cell Biology, And Neuroscience, New York, United States of America

Aims: The loss of dopaminergic (DA) neuron subpopulations in Parkinson's disease (PD) is accompanied by activated microglia and pro-inflammatory cytokine expression, suggesting that microglial-mediated neuroinflammation may contribute to PD-neurodegeneration. The molecular basis for this differential neuronal susceptibility, and microglial contribution to this phenomenon, remains to be established. Here, we investigate changes in neuronal and microglial subsignatures in post-mortem human tissue using single nucleus RNA-sequencing (snRNA-seq) to identify candidate genes/pathways involved in PD-neurodegeneration.
Methods: We applied snRNA-seq using the 10x Genomics Chromium platform to generate an unbiased transcriptomic dataset in 19 sporadic PD cases across the substantia nigra (SN), ventral tegmental area, substantia innominata, and hypothalamus, and in the SN of 14 controls.
Results: We found that DA-neuronal clusters fell into two major clades expressing either SOX6 or CALB1, and confirmed the expression of multiple DA-neuron subtype markers recently reported in a snRNA-seq study (Kamath et al. 2022). While DA-neuronal populations were depleted in the SN in PD, we found an AGTR1+ signature that was enriched in PD with higher expression of DAB1, suggesting pathway-specific dysregulation within this DA-subgroup. In parallel, our analysis revealed a microglial subpopulation enriched in the SN in PD, which differentially expresses genes such as TMEM163, which is part of a GWAS PD-associated locus. We also found a microglial subpopulation present in the SN of controls that is depleted in the SN in PD; this cluster has higher expression of heat-shock proteins that are relevant for antigen-presentation and may be protective against alpha synuclein proteinopathy.
Conclusions: With this genomic data, we aim to generate a multimodal signature of PD differential susceptibility and neuronal-microglial interactions, which may ultimately be used to develop biomarkers and candidate molecules/pathways to therapeutically target specific intercellular interactions.

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ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

ALZHEIMER'S ASSOCIATED NEURONAL AND MICROGLIAL PHENOTYPES ARE NORMALIZED WITH RETROMER VIRAL VECTORS

Yasir Qureshi[1,2], Suvarnambiga Kannan[2], Beth Stevens[3], Scott Small[2]
[1]Retromer Therapeutics, Gene Therapy, New York, United States of America, [2]Columbia University, Taub Institute, New York, United States of America, [3]Boston Children's Hospital, Kirby Center For Neurobiology, Boston, United States of America

Aims: The neuron's early endosome, a central trafficking station of the endolysosomal network, has proven to be an organelle fundamental to Alzheimer's disease (AD). A combination of genetic and functional studies have implicated endosomal trafficking as a pathogenic biological pathway in the disease. We aim to understand further this pathway using a mouse model defficient in one of the core retromer components.
Methods: We have developed a mouse model in which VPS35 is genetically depleted selectively in hippocampal and forebrain neurons, allowing survival into adulthood. In parallel, we have optimized a VPS35 repletion strategy using AAV9-VPS35, overcoming the autoregulation observed for VPS35 expression, and showing that exogenous VPS35 can bind other retromer core proteins critical for retromer function. We then combined the VPS35 neuronal-selective knockout (VPS35 nsKO) mice with the AAV9-VPS35 protocol and completed an extensive series of VPS35 depletion-repletion studies to strengthen the mechanistic link between retromer-dependent endosomal recycling and AD's known cellular phenotypes.
Results: The VPS35 depletion-repletion studies strengthen the causal link between the neuronal retromer and AD-associated neuronal phenotypes, including the acceleration of amyloid precursor protein cleavage and the loss of synaptic glutamate receptors. Moreover, the studies show that the neuronal retromer can regulate astrocytic activation, and a distinct, dystrophic, microglia morphology, phenotypic of hippocampal microglia in AD. Finally, by crossing these mice with tau KO mice we show that the neuronal and, in part, the microglial responses to VPS35 depletion were found to occur independent of tau.
Conclusions: Showing that the neuronal retromer can regulate AD-associated pathologies in two of AD's principal cell types strengthens the link, and clarifies the mechanism, between endosomal trafficking and late-onset sporadic AD

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OD155 / #854

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

PROTECTIVE ANTI-INFLAMMATORY EFFECTS OF PHOTOBIOMODULATION WITH RED/NIR LIGHT IN A MOUSE MODEL OF LPS-INDUCED SYSTEMIC AND BRAIN INFLAMMATION

Annelise Barron[1], Shirin Shamloo[1], Erwin Defensor[2], Jennifer Lin[2], Gaku Ogawa[2], Laura Vidano[2], Mehrdad Shamloo[2], John Fortkort[1]
[1]Stanford University, Bioengineering, Stanford, United States of America, [2]Stanford University, Neurosurgery, Stanford, United States of America

Aims: Neuroinflammation is associated with various neurological disease states. Photobiomodulation (PBM), the therapeutic use of specific wavelengths of light, has already shown anti-inflammatory properties in a range of applications. The current study was aimed at evaluating the effects of PBM on Lipopolysaccharide (LPS)-induced peripheral and central inflammation in mice as an experimental model for neurodegenerative diseases.
Methods: Group housed mice were administered PBM for 30-minute daily sessions for 12 days, 5 days at a time. Mice received either no light therapy, only red/NIR Light at 640 and 880 nm (RL), or red/NIR light plus 40 Hz gamma frequency flicker (RLG). On day 11, mice were dosed IP with either vehicle or LPS (1 mg/kg). Brain tissue and plasma were collected 24 hours after LPS/vehicle injection after the final PBM treatment. The samples collected were investigated for the inflammatory response with qPCR and Luminex assay.
Results: PBM significantly reduced the gene expression of IL18 and IL6 in naïve non-LPS stimulated mice brains. LPS induced a significant upregulation of IL33R, IFN-a, SRANKL, and IL15 in the brain, but PBM-RL prevented the induction of IL33R, IFN-α, SRANKL, IL15, and IL7RA after the LPS challenge. Systemically, we saw upregulation of IL10 and CCL4 by LPS challenge in LPS + RL groups, and downregulation of IL-1β, IFN-γ, and IL18 induction in LPS + RL/RLG groups.
Conclusions: This study demonstrates the neurological and systemically protective effect of short Red/NIR light treatments following LPS-triggered local and systemic inflammation. In future studies, implementing a longer period between LPS administration and tissue collection will be useful to allow for the investigation of the immune pathways modulated by light stimulation, and to further explore the therapeutic potential of LPS against neurodegenerative disorders.

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OD156 / #1644

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

LIPOPOLYSACCHARIDE (LPS) IS A POTENT NEUROTOXIC GLYCOLIPID IN ALZHEIMER'S DISEASE (AD)

Walter Lukiw
LSU Neuroscience Center, Neurology, Neuroscience, New Orleans, United States of America

Aims: Lipopolysaccharides (LPSs) are microbiome-derived glycolipids that are among the most potent pro-inflammatory neurotoxins known. In *Homo sapiens* LPSs originate from gastrointestinal (GI)-tract resident facultative-anaerobic Gram-negative bacilli including *Bacteroides-fragilis* and *Escherichia-coli.* LPSs have been abundantly detected in aged human brain and there has been found an increased abundance of LPS in Alzheimer's disease (AD)-affected neurons. Microbiome-generated LPS and other endotoxins cross GI-tract-biophysiological-barriers into the systemic-circulation and across the blood-brain barrier into the brain. Further evidence indicates that LPS up-regulates the pro-inflammatory transcription factor complex NF-kB (p50/p65), and NF-kB-sensitive microRNAs. These up-regulated miRNAs in turn down regulate a family of neurodegeneration-associated mRNA targets that include the mRNA encoding the neuron-specific neurofilament light (NF-L) chain protein. While NF-L has been reported to be up-regulated in peripheral biofluids progressive and lethal pro-inflammatory neurodegenerative disorders, NF-L is significantly down-regulated within neocortical neurons and this may account for neuronal atrophy, loss of axonal caliber and alterations in neuronal cell shape, modified synaptic-architecture and network deficits in neuronal-signaling capacity.
Methods: Culture of *Bacteroides fragilis* and *Escherichia coli*; human neuronal-glial (HNG) cell primary culture; transfection; 3'-UTR expression vectors (pLight Switch-3'-UTR); gel-shift assay; characterization of NF-kB (p50/p65); isolation/purification of LPS; immunohistochemical analysis; miRNA/mRNA/18S RNA sequencing; bioinformatics/statistical analysis
Results: LPS is detected in aged and AD brain; in HNG cells LPS induces NF-kB and a small family of NF-kB-sensitive microRNAs including miRNA-30b; miRNA-30b down-regulates expression from the neurofilament light (NF-L) chain gene; lack of sufficient NF-L leads to neuronal atrophy/cytoskeletal and synaptic/disorganization;
Conclusions: LPS contributes to the biological mechanism of AD. This is the first example of a microbiome-derived neurotoxic-glycolipid having significant detrimental miRNA-mediated actions on the expression of NF-L, an abundant filamentous protein known to be important in the maintenance of neuronal- and synaptic-homeostasis.

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OD157 / #1837

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

PLCG2 VARIANTS ELICIT DIFFERENTIAL MICROGLIAL RESPONSES AND DISEASE PATHOLOGY IN ALZHEIMER'S DISEASE

Stephanie Bissel[1], Andy Tsai[2], Evan Messenger[2], Peter Lin[2], Chuanpeng Dong[1], Miguel Moutinho[2], Yunlong Liu[1], Adrian Oblak[3], Kwangsik Nho[2], Bruce Lamb[3], Gary Landreth[2]
[1]Indiana University School of Medicine, Medical And Molecular Genetics, Indianapolis, United States of America, [2]Indiana University School of Medicine, Stark Neurosciences Research Institute, Indianapolis, United States of America, [3]Indiana University School of Medicine, Medicine, Indianapolis, United States of America

Aims: Recent studies have highlighted that many genetic risk variants for Alzheimer's disease (AD) are predominately expressed in microglia and are associated with innate immune responses. Among these risk genes is phospholipase C gamma 2 (PLCG2), a key signaling hub protein that regulates immune effector function. Notably, coding missense variants in *PLCG2* are linked to altered AD risk. The hyperfunctional P522R variant of *PLCG2* confers protection against AD, and we have identified a novel variant encoding the less active M28L variant that is associated with elevated AD risk. However, the contribution of *PLCG2* variants on AD pathogenesis is unknown.
Methods: To systematically explore the effect of *PLCG2* variants in AD, we created mice harboring the *PLCG2* variants and crossed them with 5xFAD amyloidogenic mice and aged them to 4 and 7.5 months of age.
Results: Primary murine microglia isolated from variant mice showed differential uptake capacity of fluorescently labeled amyloid-beta peptide. The less active M28L risk variant disrupted protein interactions between PLCG2 and upstream signaling elements, diminished microglial response to plaques, suppressed cytokine concentrations, downregulated disease-associated microglial gene expression, and exacerbated plaque deposition. Conversely, the protective, hypermorphic P522R variant altered microglial disease-associated populations, stimulated microglial response to plaques with altered cytokine levels, decreased plaque deposition, and ameliorated the impairment of synaptic plasticity and Y-maze alternation.
Conclusions: Collectively, our study provides evidence that the M28L variant had accelerated and exacerbated disease-related pathology, while the P522R variant appeared to mitigate disease severity and progression. Overall, our findings suggest that *PLCG2* plays an important role in AD pathophysiology.

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OD158 / #1745

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

NOT ALL LIPIDS ARE EQUAL: DIFFERENTIAL IMPACT OF LIPIDS ON MICROGLIA STATES AND FUNCTIONS.

Martine Therrien[1], Nicolas Weider[2], Dan Meyer[2], Eugenio Mattei[3], Trevor Atkeson[1], Sulagna Ghosh[1], Juan Lorenzo Pablo[2], Bradley E. Bernstein[2], Charles B. Epstein[2], Steven Mccarroll[2], Anna Greka[2], Beth Stevens[4]
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Aims: Objectives: Microglia activation is a pathological hallmark of neurodegenerative diseases (NDs), and they express multiple risk genes associated with late-onset Alzheimer's Disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Specific microglial states were identified in AD, PD, and ALS; however, it is unknown which signaling pathways induce state change and the impact of these states on disease pathobiology and progression. Emerging genetic and genomic data is pointing toward altered lipid metabolism; however, it is unclear how different types of lipid microglia state and function.
Methods: Methods: To answer these questions, we calculated a novel polygenic score and applied it to the CIRM biobank to answer these questions. We then selected 50 iPSC lines based on their genetic susceptibility to AD. Using the iPSC-derived microglia platform our lab has recently developed (Dolan*, Therrien* et al BioRxiv 2022), we characterized the impact of 48 different lipids across these lines with high and low genetic risk of AD.
Results: Results: From these 48 lipids, we observed that not all lipids impact microglia states and function similarly. While some lipids affected microglia functions without affecting their viability, others were particularly toxic to microglia. Moreover, these lipotoxic phenotypes were altered based on their genetic susceptibility to AD.
Conclusions: Conclusions: Our data identified key environmental elements altering microglia and how AD risk genes affect states and functions. This work will open the door to identifying modulators of microglia states and highlight new therapeutic avenues for AD and other neurodegenerative diseases.

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OD159 / #2482

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

REACTIVE ASTROCYTES AS THE CAUSE OF ALZHEIMER'S DISEASE

C. Justin Lee
IBS (Institute for Basic Science), Center Or Cognition And Sociality, Daejeon, Korea, Republic of

Aims: Reactive astrocytes have emerged as one of the key components of the neuroinflammation and possible causes of various neurodegenerative diseases including Alzheimer's disease, Parkinson's diseases and Hunting's diseases. We have hypothesized that reactive astrocytes become neurotoxic and contribute to the cause of these neurodegenerative diseases.
Methods: Utilizing the cutting edge in vitro and in vivo animal models, we have examined the detailed mechanism of how reactive astrocytes become neurotoxic. We have also confirmed the mechanistic insights in Alzheimer's disease patients' brain samples.
Results: We have discovered that reactive astrocytes protein degradation pathways, starting from Abeta-induced amyloid receptor-mediated endocytosis, leading to autophagic plasticity, fusing into lysosomes, degradating toxic proteins into amino acids and ammonia, merging into urea cycle and ending with putrescine degradation pathway to produce toxic byproducts of H2O2, ammonia, and GABA. From these mechanistic insights we have identified MAOB and H2O2 as molecular targets and developed highly potent and selective drug candidates, KDS2010(Seremabi) and AAD2004(Crisdesalazine), which are now in phase I clinical trials.
Conclusions: We have delineated the detailed molecular and cellular mechanisms of how reactive astrocytes contribute to neurodegenerative diseases. The novel concepts and tools that we have developed have been extremely valuable in developing novel therapeutic approaches to diagnose and cure the various neurodegenerative diseases such as Alzheimer's disease.

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OD160 / #2017

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

CONSTRUCTION OF IMMUNE CELL NETWORKS PROMOTING CLONAL CYTOTOXIC T CELLS IN THE LEPTOMENINGES OF NEURODEGENERATIVE DISEASES

Ryan Hobson[1], Samuel Levy[1], Chitra Singal[1], Xena Flowers[2], Benjamin Ciener[2], Delaney Flaherty[2], Harrison Xiao[2], Andrew Teich[2], Vladislav Korobeynikov[2], Neil Shneider[1], Elizabeth Bradshaw[1], Wassim Elyaman[1]
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Aims: Several studies have highlighted impaired meningeal lymphatic flow in both animal models of neurodegeneration and in idiopathic Parkinson's disease. Although dynamic changes in meningeal immunity functionally alter amyloid-beta and alpha-synuclein clearance in mice, a comprehensive view of the meningeal immune landscape in human neurodegeneration is currently unavailable.
Methods: Here, we used single-cell RNA and T-cell receptor (TCR) sequencing to characterize CD45+ immune cells from fresh leptomeninges from Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).
Results: Multiple myeloid and lymphoid clusters were identified in all neurodegenerative samples including meningeal macrophages expressing CD14 and C1QA and the resident meningeal macrophage marker LYVE-1. Additional myeloid populations expressing VCAN and interferon response genes may represent monocyte-derived macrophage precursors. Lymphoid populations represented the majority of total cells and were composed of both CD8+ effector memory T-cells and a mixed population of NK cells and NK-like T-cells. Ligand/receptor network analyses using CellChat identified several statistically significant intercellular interactions including osteopontin signaling between meningeal macrophages and both clonally expanded cytotoxic CD8 T and NK/NK-like T-cells. TCR sequence analysis revealed up to 500 unique TCR clonotypes in each sample, many of which were hyperexpanded with 25-50% of the TCR repertoire being occupied by the top 20 clonotypes and some of which had high TCRb chain sequence homology to EBV-specific TCRs.
Conclusions: In this study, we provide evidence for disrupted myeloid homeostasis and broad T-cell clonal expansion in the leptomeninges across neurodegenerative diseases. Network analyses suggest that meningeal macrophages in neurodegeneration may promote long-term clonally expanded T-cell survival through osteopontin signaling. These data recapitulate findings across several animal studies and will be useful in developing immunomodulatory interventions to treat neurodegeneration.

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OD161 / #927

ON-DEMAND SYMPOSIUM: DISEASE MECHANISMS, PATHOPHYSIOLOGY: ASTROCYTES, MICROGLIA, IMMUNE PROTECTION, NEUROINFLAMMATION
30-03-2023 07:00 - 08:30

THE ROLES OF GFAP HYPERPALMITOYLATION IN INFANTILE NEURONAL CEROID LIPOFUSCINOSIS

Eryan Kong
Xinxiang Medical University, Institute Of Psychiatry And Neuroscience, XinXiang, China

Aims: To understand the pathological mechanism of INCL from the angle of protein palmitoylation as such disease is caused by a natural mutation in PPT1, an enzyme catalyzing the process of depalmitoylation.
Methods: Genetical modifications in mice genome to create knockout or knockin mice models; Biochemical methods to evaluate levels of protein palmitoylation as well as total protein levels; Behavior studies to assess the ability of mobility and learning/memory in mice;
Results: 1. GFAP is palmitoylated; 2. PPT1 depalmitoylates GFAP; 3. The lelvel of GFAP palmitoylation is exaggerated in PPT1-deficient mice; 4. Hyper-palmitoylated GFAP enhances the proliferation of astrocytes; 5. Blocking GFAP palmitoylation in PPT1-deficient mice alleviates the neurodegenerative pathology; 6. Targeting GFAP palmitoylation by small molecular might bring beneficial effect for PPT1-deficient mice;
Conclusions: Hyper-palmitoylated GFAP caused by the loss-of-funciton of PPT1 induces astrogliosis, manifested by increased level of astrocytes proliferation; therefore, inhibiting GFAP palmitoylation in mice and INCL patient might bring good news for the devastating disease.

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OD162 / #956

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

CHEMICAL IMAGING OF AMYLOID AGGREGATION DYNAMICS USING ISILK

Jörg Hanrieder[1], Wojciech Michno[2], Katie Stringer[3], Frances Edwards[3]
[1]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [2]Uppsala University, Public Health And Caring Sciences, Uppsala, Sweden, [3]University College London, Neuroscience, Physiology And Pharmacology, London, United Kingdom

Aims: It is of critical importance to our understanding of Alzheimer's disease (AD) pathology, to determine how key pathological factors including beta-amyloid (Aβ) plaque formation are interconnected and implicated in nerve cell death, clinical symptoms and disease progression. Exactly how Aβ plaque formation begins and how the ongoing plaque deposition proceeds and initiates subsequent neurotoxic mechanisms is not well understood. The primary aim of our research is to elucidate the biochemical processes underlying early Aβ plaque formation in brain tissue.
Methods: We will use an array of advanced chemical imaging modalities including hyperspectral microscopy and mass spectrometry imaging that allows to delineate vivo Aβ build up and deposition at cellular length scales. Specifically we advanced the integration of conformation sensitive hyperspectral microscopy with MSI modalities to elucidate plaque morphology associated changes in Aβ signatures. We further pioneered means for amyloid chronology based on imaging stable isotope labelling kinetics (iSILK). Herein, third generation genetic AD mice (APP knock in: NLF and NLGF) are labelled metabolically with stable isotopes to follow the fate of aggregating Aβ species from before and throughout the earliest events of precipitating plaque pathology.
Results: Using integrated SILK imaging and hyperspectral microscopy allowed to visualize Aβ aggregation dynamics within single plaques across different brain regions. We show that formation of structurally distinct plaques is associated with differential Aβ peptide deposition. Specifically, in both models Aβ1-42 is forming an initial core-structure followed by radial outgrowth and late secretion and deposition of Aβ1-38. These data, for the first time, describe a detailed picture of the earliest events of precipitating amyloid pathology at scales not previously possible.
Conclusions: The results bring considerable novel information about the deposition mechanism of Aβ and its toxic interactions with the surrounding.

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OD163 / #1308

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

BETA-AMYLOID IS ONLY SEEN IN THE EXTRACELLULAR COMPARTMENT IN DIAGNOSTIC BRAIN BIOPSIES FROM IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS SUBJECTS

Sylwia Libard[1,2], Monika Hodik[1,3], Kristina Cesarini[4], Anca Dragomir[1], Irina Alafuzoff[2]
[1]Uppsala University, Department Of Immunology, Genetics And Pathology, Uppsala, Sweden, [2]Uppsala University Hospital, Department Of Pathology, Uppsala, Sweden, [3]Uppsala University, Biovis Platform, Uppsala, Sweden, [4]Uppsala University Hospital, Department Of Neurosurgery, Uppsala, Sweden

Aims: To study cellular compartmentalisation of beta-amyloid in diagnostic surgical brain biopsies from idiopathic Normal Pressure Hydrocephalus (iNPH) subjects using light microscopy (LM) and electron microscopy (EM).
Methods: During 2018 and 2019 brain tissue samples for both LM and EM were obtained from 12 iNPH patients. Three of the subjects displayed representative grey matter in both the LM and EM samples. Following, the tissue samples from these three iNPH patients were immunohistochemically (IHC) stained both for LM and EM with various beta-amyloid antibodies (Ab) and amyloid precursor protein (APP) Ab and assessed in regard to compartmentalisation.
Results: Overall five of the twelve subjects displayed beta-amyloid in their biopsy and moreover all three with representative EM material were in this cohort. In LM, high level of extracellular beta-amyloid aggregates was visualized in all subjects with 4G8, 6F/3D, unmodified (um) 7H3D6 and in two subjects with pyroglutamylated beta-amyloid (N3pE). The N3pE was moderate in one biopsy. The phosphorylated (p) beta-amyloid (1E4E11) was expressed at low level in one subject and moderate level in two biopsies. The APP was expressed in all samples. Using the EM-IHC the beta-amyloid 4G8, 6F/3D and N3pE was detectable in all three samples whereas the um and p variants were absent. The beta-amyloid staining was located extracellularly with no signal seen within the intracellular compartment. The APP was seen in both intracellular and extracellular compartment.
Conclusions: All beta-amyloid markers studied here displayed extracellular localisation using both LM and EM reflecting the pathological extracellular accumulation of beta-amyloid in the human brain. No intracellular beta-amyloid pathology was detected. The APP was visualized both intra- and extracellularly which corresponds to the localisation of the protein in membranes of cells and organelles.

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OD165 / #1440

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

AMYLOID-BETA PEPTIDES SIGNATURE IN BRAIN OF DOWN SYNDROME, SPORADIC ALZHEIMER'S DISEASE AND FAMILIAL ALZHEIMER'S DISEASE WITH APP DUPLICATION

Elena Camporesi[1], Amal Kasri[2], Gunnar Brinkmalm[3], Elena Gkanatsiou[1], Susana Boluda[2], Charles Duyckaerts[2], Lev Stimmer[2], Yannick Vermeiren[2], Sarah Pape[4], Peter De Deyn[5], Henrik Zetterberg[6], Andre Strydom[4], Marie-Claude Potier[2]
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Aims: To investigate the amyloid-beta (Aβ) pathology present as plaques or cerebral amyloid angiopathy (CAA) and shared across Alzheimer's disease (AD), Down syndrome (DS) and cases carrying a duplication of the *APP* gene (DUP-APP), we aimed at studying qualitative and quantitative differences of the Aβ peptides profile.
Methods: The study included soluble (tris-buffered saline, TBS) and insoluble (70% formic acid, FA) brain extracts from frontal cortex and hippocampus of sporadic AD (n=6), familial AD cases with DUP-APP (n=4), Down syndrome (n=3), DS with dementia (DS-D, n=8) and controls (CTRL, n=15). Using a combination of 6E10 and 4G8 antibodies, Aβ peptides were immunoprecipitated from both fractions. Eluates were analysed by mass spectrometry (MS), using both MALDI and LC-MS techniques.
Results: Generally, the FA fraction is enriched with Aβ peptides compared to the TBS fraction. In both fractions, the DUP-APP group showed a global higher abundance of Aβ peptides when compared to all the other groups. Interestingly, the $A\beta_{2\text{-}x}$ peptides were particularly increased in the DUP-APP group compared to all the other groups. When compared to AD cases, $A\beta_{1\text{-}37/38/39/40}$ peptides were increased in the DUP-APP group, while the $A\beta_{1\text{-}42}$ peptide was lower. The DS-D group also had increased $A\beta_{1\text{-}37/38/39/40}$ peptides compared to AD, while DS without dementia group had a pattern more similar to the CTRL group
Conclusions: The high abundance of $A\beta_{1\text{-}37/38/39/40}$ in the DUP-APP brains suggests the concomitant presence of higher CAA pathology in this disease. This information, together with the different Aβ peptides signature of sporadic AD, DS-D and DUP-APP cases revealed by the MS analysis, will be useful in the development of pathology-specific biomarkers and might inform selection for therapeutic interventions.

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OD166 / #1566

POSTERS: A01.E. DISEASE MECHANISMS, PATHOPHYSIOLOGY: CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
28-03-2023 07:00 - 23:59

INTRACELLULAR ABETA ACCUMULATION IN HIPPOCAMPAL NEURONS LEADS TO ENDOSOMAL/LYSOSOMAL LEAKAGE

Lars Tjernberg, Sophia Schedin Weiss, Yang Gao
Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, Solna, Sweden

Aims: There are different pools of the 42-residue amyloid β-peptide (Aβ42) in hippocampal neurons. We hypothesize that some of these pools are physiologically relevant whereas others are toxic. Intraneuronal Aβ is partly derived from internalization of extracellular Aβ, and can oligomerize in the late endosomes/lysosomes. However, it is still unknown how intracellular oligomerized Aβ42 causes toxicity to the cells. Here, our aim was to explore the mechanisms of cytotoxicity of intracellular Aβ in neurons.
Methods: Mouse primary hippocampal neurons were treated with different concentrations of monomeric Aβ42 - with or without fluorescent labels - for different time periods. Intracellular accumulation of internalized Aβ42 was monitored over time by lattice light sheet microscopy. Aβ42 concentrations in neuronal vesicles were determined by live cell imaging. Immunocytochemistry and Airyscan microscopy were used to detect the loss of endosomal/lysosomal integrity in neurons.
Results: Monitoring uptake of Aβ42 during 24 h showed that the majority of Aβ42 was transported to the soma region where it accumulated in late endosomes/lysosomes. Treatment with 1 nM Aβ42 for 20 days caused three orders of magnitude higher concentrations in late endosomes/lysosomes as compared to the cell culture medium. Aβ42 induced endosomal/lysosomal leakage when the concentration reached micromolar levels in those vesicles.
Conclusions: These data together with our previous studies suggest that extracellular Aβ42 is endocytosed, gradually accumulates in late endosomes/lysosomes where it polymerizes and damages vesicle integrity. The damaged vesicle may release Aβ42 and other lysosomal components into the cytosol and thereby generate toxicity. Thus, the late endosomal/lysosomal pool of aggregated Aβ42 may be a target for AD treatment.

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OD167 / #1256

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

INTRACELLULAR ABETA ACCELERATES TAU PRETANGLE FORMATION SPECIFICALLY IN ENTORHINAL STELLATE CELLS

Clifford Kentros[1], Valentina Dimaria[2], Miguel Murteira De Carvalho[2], Maria Letizia Potenza[2], Asgeir Kobro-Flatmoen[2], Menno Witter[2]
[1]Norwegian University of Science and Technology, Kavli Institute For Systems Neuroscience, Trondheim, Norway, [2]Norwegian University of Science and Technology, Kavli Institute For Systems Neuroscience, Ntnu, Trondheim, Norway

Aims: Alzheimer`s Disease (AD) is characterized by two pathological signs: extracellular amyloid plaques, composed primarily of aggregations of Amyloid-beta peptide (Abeta), and neurofibrillary tangles (NFTs), intracellular aggregates of hyperphosphorylated microtubule-associated protein tau (p-tau). While the parent gene of Abeta is clearly associated with AD, the anatomical progression of plaques does not strongly correlate with dementia. Conversely, the progression of NFTs clearly correlates with dementia, starting in LII stellate neurons of the entorhinal cortex (EC, Braak stage 1) in prodromal patients, then spreading (apparently transynaptically) through the EC (stage 2) and then to other memory areas (hippocampus and subiculum, 3-4), and eventually to neocortex (5-6), but there is no genetic linkage between tau and AD. This suggests that EC stellate neurons are particularly vulnerable to the pathological interactions between tau and Abeta underlying AD pathogenesis and may "seed" AD-related tauopathy throughout the brain.
Methods: To explore this possibility, we injected AAVs expressing wildtype human-Tau (Htau) via the Synapsin promoter near the rhinal fissure of 1-month-old AD rats (McGill-R-Thy1-APP model) and wildtype (wt) controls. Since these AD rats express Abeta in all neurons, this enables investigation of the interactions between Htau overexpression and Abeta in various neuronal cell types of the EC and adjacent cortices.
Results: Htau overexpression led to p-tau in both AD and wt rats (pSer396+ 2 months post-injection), interestingly almost exclusively in entorhinal stellate neurons. Five months post-injection, however, only the AD rats showed evidence of pretangle formation (i.e. were AT8+), again almost exclusively in stellate cells.
Conclusions: These data suggest that EC stellate neurons have an innate predilection for the pathological interactions between Abeta and tau leading to AD, providing an anatomically appropriate model of the earliest stages of AD pathogenesis.

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OD168 / #1756

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

AMYLOID CORRELATES WITH LATER TAU ACCUMULATION FOR INDIVIDUALS IN EARLY BRAAK STAGES

Stijn Servaes[1], Joseph Therriault[1], Cécile Tissot[1], Firoza Lussier[1], Gleb Bezgin[1], Yi-Ting Wang[1], Jenna Stevenson[1], Nesrine Rahmouni[1], Alyssa Stevenson[1], Vanessa Pallen[1], Peter Kunach[1], Jaime Fernandez-Arias[1], Arthur Macedo[1], Seyyed Hosseini[1], Tharick Pascoal[2], Serge Gauthier[1], Pedro Rosa-Neto[1]
[1]McGill University Research Centre for Studies in Aging, Neurology, Montreal, Canada, [2]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America

Aims: Accumulation of tau neurofibrillary tangles in Alzheimer's disease (AD) follows a stereotypical pattern – known as Braak staging - as suggested by post-mortem and tau-PET imaging studies. As individuals show different rates of tau accumulation, depending on their initial stage, this potentially biases drug effects on tau pathology over time. We hypothesized that amyloid would be a driving force behind tau deposition in later Braak regions for those that were at the early stages of the disease.
Methods: Individuals in Braak stage I (n = 22) or II (n = 14) with baseline and 24-month follow-up were recruited from the Translational Biomarkers of Aging and Dementia (TRIAD) cohort. All individuals underwent amyloid ([^{18}F]AZD4694) and tau ([^{18}F]MK6240) PET imaging. Differences in standardized uptake value ratios between the two time-points in Braak I-III were used to separate fast accumulators of tau from slow accumulators, using the standard deviation of a Young group (n = 8). Pearson R's were calculated between tau deposition in Braak regions IV-VI and the neocortical amyloid load, within both these groups. Furthermore, a voxelwise analysis was performed to identify specific regional differences while correcting for age, sex and presence of ApoE4.
Results: Fast accumulators had stronger increases in tau accumulation in Braak region V, compared to slower accumulators. Furthermore, the level of tau deposition in this region was associated with the amyloid load in the neocortex, but only in the fast accumulator group (figure 1). This was confirmed in a voxelwise analysis, after correcting for control variables (figure 2).

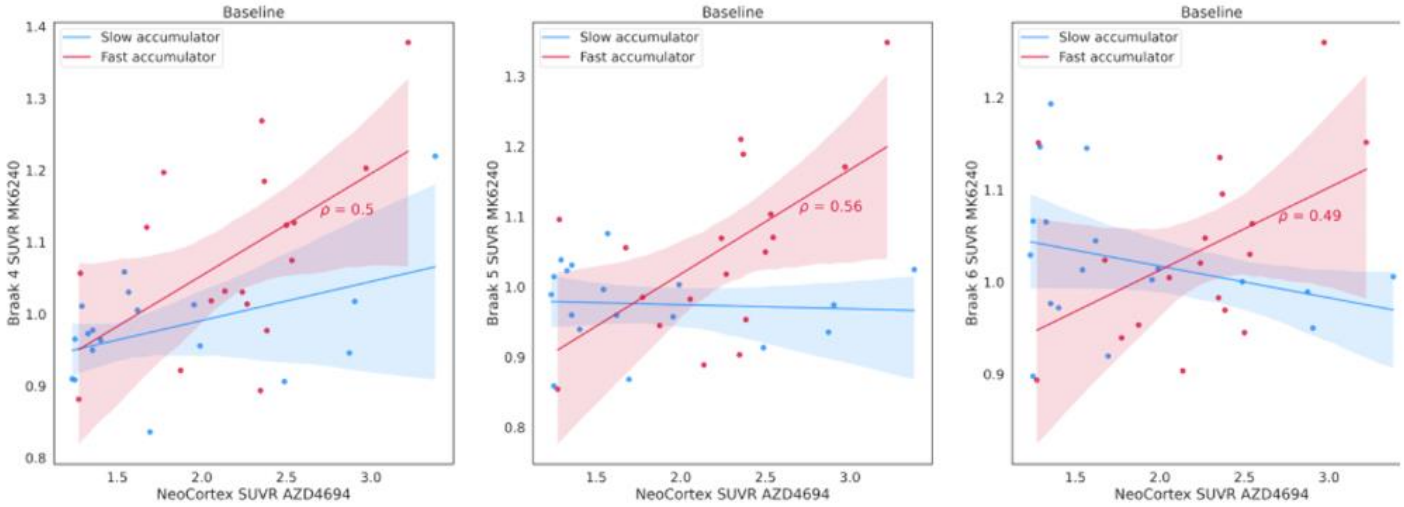

Figure 1: Association between amyloid load and late Braak region tau deposition

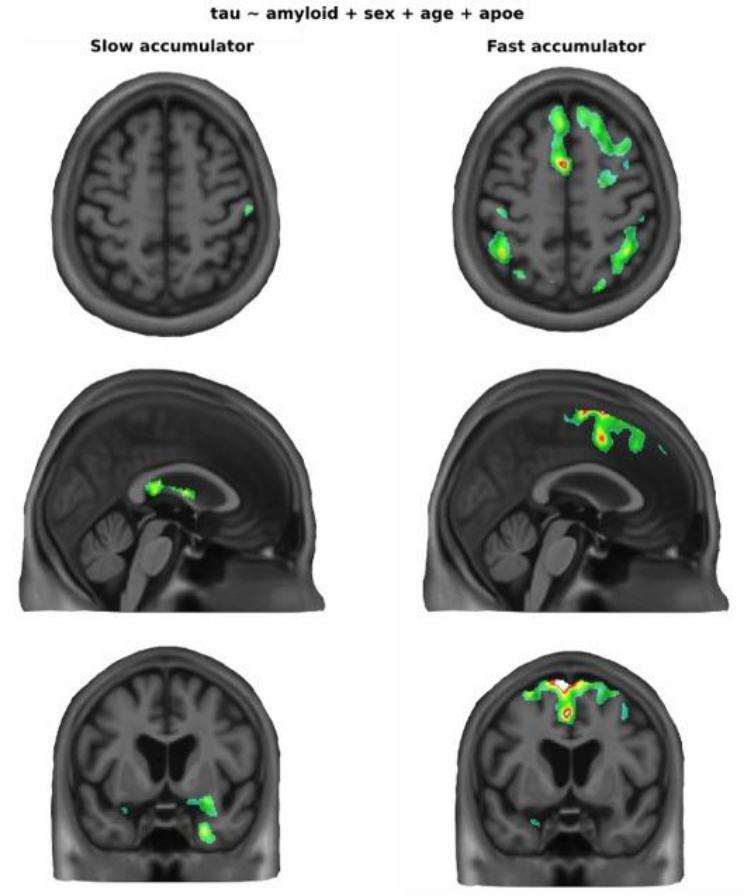

Figure 2: Voxelwise analysis revealing clusters showing a significant relationship between amyloid and tau

Conclusions: Tau deposition in later Braak regions is associated with a higher amyloid load in individuals in early Braak stages that accumulate tau at a more rapid rate.

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OD169 / #781

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

CROSS-SEEDING OF AMYLOID-BETA BY FOOD PROTEIN AMYLOIDS

Mahafuzur Rahman[1], Rodrigo Pires[1], Anja Herneke[2], Vasantha Gowda[1], Maud Langton[2], Henrik Biverstål[3], Christofer Lendel[1]
[1]KTH Royal Institute of Technology, Department Of Chemistry, Stockholm, Sweden, [2]Swedish University of Agricultural Sciences, Department Of Molecular Sciences, Uppsala, Sweden, [3]Karolinska Institutet, Department Of Biosciences And Nutrition, Huddinge, Sweden

Aims: The deposition of amyloid-β (Aβ) into senile plaques is an established hallmark of Alzheimer's disease but the events that trigger the conversion from the soluble form into insoluble amyloid are not understood. Many proteins that are not associated with disease are known to form amyloid with similar structural characteristics as the disease-associated deposits. This has raised the question about potential cross-seeding by amyloid encountered in our surrounding. We here investigate cross-seeding of Aβ(1-42) by 16 types of amyloid fibrils derived from food proteins or peptides, including milk, egg, legumes, oat and potato.
Methods: Amyloid-like fibrils were produced from the food-derived proteins and peptides. Thioflavin T fluorescence was used to investigate the kinetics of Aβ aggregation with and without the addition of food amyloid seeds. The amyloid fibril structures were visualized by atomic force microscopy.
Results: We found that none of the investigated protein fibrils accelerated the aggregation of Aβ. In two cases we observed decrease aggregation rates, which appear to be related to electrostatic interactions between the food protein seeds and Aβ in aggregated form.
Conclusions: The results suggest that food-derived amyloid is not a major risk factor for development of Aβ pathology.

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OD170 / #2465

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

RAPID FORMATION OF ABETA PROTOFIBRILS UNDER ENDO-LYSOSOMAL CONDITIONS

Wolfgang Hoyer[1,2], Marie Schützmann[1], Filip Hasecke[1], Sarah Bachmann[3], Mara Zielinski[2], Gunnar Schröder[2], Hans Zempel[3]
[1]Heinrich-Heine-Universität Düsseldorf, Institut Für Physikalische Biologie, Düsseldorf, Germany, [2]Forschungszentrum Jülich, Institute Of Biological Information Processing (ibi-7), Jülich, Germany, [3]University of Cologne, Institute Of Human Genetics And Center For Molecular Medicine Cologne (cmmc), Cologne, Germany

Aims: Protofibrils are soluble, toxic Abeta aggregates that constitute an important AD drug target, e.g., in immunotherapy with the antibody lecanemab. Here we identify physiological conditions that promote protofibril formation.
Methods: The condition dependence of protofibril assembly was determined utilizing Abeta42 as well as the dimeric Abeta construct dimAb that facilitates analysis of the protofibril formation kinetics. Protofibril formation, clustering, and release were imaged by atomic force microscopy. The structure of the smallest protofibril subunits was investigated by cryo-EM. The capacity of protofibrils to bind to dendritic spines, to induce Tau missorting, and to impair neuronal function were studied in primary mouse neuronal cell cultures.
Results: Protofibrils form in a reaction that is distinct from amyloid fibril nucleation. The rate of protofibril assembly is accelerated 8,000-fold upon pH reduction from extracellular to endo-lysosomal pH, at the expense of amyloid fibril formation. The pH-induced promotion of protofibril assembly and the high endo-lysosomal Abeta concentration together enable extensive protofibril formation of Abeta42 under physiological conditions. At endo-lysosomal pH, Abeta42 protofibrils cluster into dense aggregates, which release individual protofibrils upon a pH shift to extracellular pH. Exploiting the enhanced protofibril formation of dimAb we furthermore demonstrate targeting of protofibrils to dendritic spines, potent induction of Tau missorting, a key factor in tauopathies, and impaired neuronal activity.
Conclusions: The results suggest that the endosomal/lysosomal system is a major site for the assembly of pathomechanistically relevant protofibrils.

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OD171 / #2424

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

HOW AMYLOID BETA FIBRILS GROW AND HOW POTENTIAL DRUGS SUPPRESS THEIR GROWTH

Peter Vekilov
University of Houston, William A. Brookshire Department Of Chemical And Biomolecular Engineering, Houston, United States of America

Aims: To elucidate the molecular mechanism of incorporation of peptide chains from the solution into the fibril tips as they acquire the conformation typical of the fibril bulk and highlight mechanisms of action of potential drugs.
Methods: We employ time-resolved *in situ* atomic force microscopy to quantify the kinetics of growth of individual fibrils. The kinetic data allows us to identify the steps of the molecular mechanism of peptide incorporation and evaluate the governing thermodynamic and kinetic parameters. We characterize fibril structure by cryogenic electron microscopy. We explore Aβ40 fibrils with four distinct structures. We measure the toxicity of fibrils formed in the presence of bexarotene to neurons.
Results: The incorporation of an incoming peptide chain into fibrils of the four structures divides into two steps, association to the tip with a few contacts (docking), followed by restructuring to attain the conformation typical of the fibril bulk (locking). Surprisingly, the second step is delayed by the formation of an intermediate complex supported by transient contacts that need to unravel before the incoming chain folds into the bulk fibril conformation. The relative rates of the two steps determine whether the fibril growth rate correlates linearly with the peptide concentration or the correlation saturates and fibril growth rate becomes insensitive to increasing peptide concentration. We demonstrate that bexarotene, a medication with anti-amyloid activity, suppresses amyloid fibrillization by promoting an alternative fibril structure. Remarkably, growth remains stunted even in drug-free solutions. We find that the bexarotene fibrils kill primary rat hippocampal neurons less efficiently than normal fibrils.
Conclusions: Drug-driven polymorph transformation presents a mode of action to irreversibly suppress toxic aggregates not only in Alzheimer's, but also potentially in myriad diverse pathologies that originate with protein condensation.

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OD172 / #982

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

AMYLOID-BETA INDUCES ROCK2 STABILISATION LEADING TO NEURODEGENERATION AND COGNITIVE IMPAIRMENT

Rebeca Lapresa[1,2], Jesus Agulla[1,2], Sonia Gonzalez-Guerrero[1,2], Juan Pedro Bolaños[1,2], Angeles Almeida[1,2]
[1]Instituto de Investigación Biomédica de Salamanca (IBSAL), Hospital Universitario De Salamanca, Salamanca, Spain, [2]Instituto de Biología Funcional y Genómica (IBFG), Csic-usal, Salamanca, Spain

Aims: Alzheimer's disease (AD) is the main cause of dementia and one of the most lethal and burdening diseases. The main mechanisms responsible for the cognitive decline developed by the patients are synaptic and neuronal loss, triggered by Amyloid-beta (Aβ). Cdh1, the main cofactor of the E3 ubiquitin ligase anaphase promoting complex/cyclosome (APC/C) in neurons, is essential for neuronal survival and homeostasis. These processes are highly dependent on the maintenance of dendritic stability. One key protein involved in dendritic integrity regulation is ROCK2. Previous studies of our group demonstrate that APC/C-Cdh1 complex maintains dendritic integrity in cortex and hippocampus by regulating ROCK2 levels, preserving cognitive function[1]. We have also demonstrated that Cdk5 hyperactivation directly phosphorylates and inactivates Cdh1[2]. Our working hypothesis is that Cdk5-APC/C-Cdh1-ROCK2 pathway is involved in Aβ neurotoxicity.
Methods: To assess this issue, we used an $A\beta_{25-35}$toxicity model in primary neurons, and in intracerebroventricularly-injected mice.
Results: We describe that $A\beta_{25-35}$ oligomers induce Cdk5-mediated phosphorylation of the APC/C-cofactor, Cdh1, leading to inhibition of APC/C and, eventually, neuronal apoptosis. Moreover, we show that $A\beta_{25-35}$-induced APC/C-Cdh1 inhibition causes ROCK2 accumulation and activation in neurons. Moreover, using a ROCK2 selective inhibitor, we were able to reduce the Aβ-induced memory impairment in vivo[3].
Conclusions: Our results demonstrate that the Cdk5-APC/C-Cdh1-ROCK2 novel axis is involved in Aβ neurotoxicity and modulates neuronal response to Aβ damage, making them potential molecular targets for AD therapy. Funded by Instituto de Salud Carlos III (PI21/00727 and RD21/0006/0005, co-funded by the European Union - FEDER/FSE+ and NextGenerationEU -); FEDER; Junta de Castilla y León (CSI151P20; co-financed with FEDER funds) and Bodegas R. López de Heredia-Viña Tondonia. [1]Bobo-Jimenez et al. PNAS, 2016 [2]Maestre et al. EMBO J, 2008 [3]Lapresa et al., Front Pharmacol, 2022

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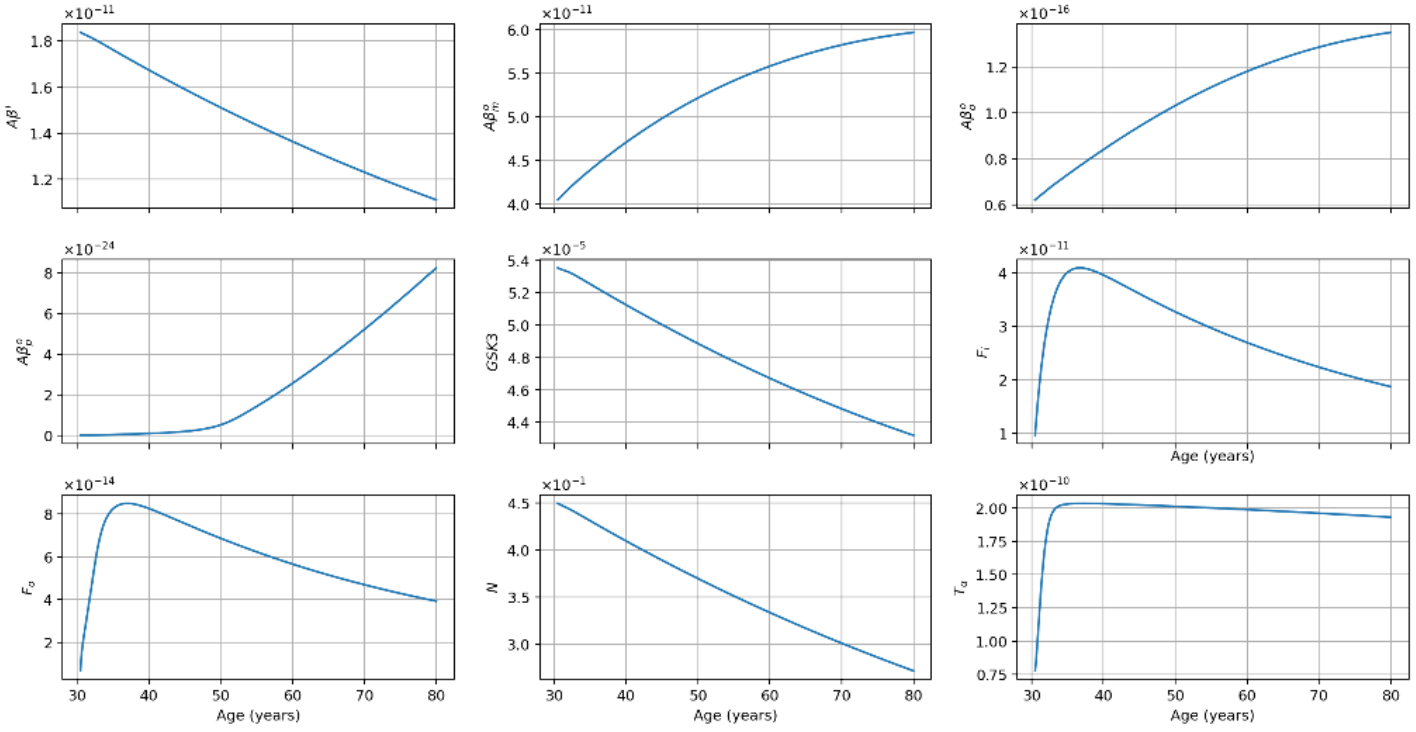
OD173 / #1859

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

COMPUTATIONAL MODEL OF AMYLOID-BETA, TAU PROTEIN AND INFLAMMATION IN ALZHEIMER'S DISEASE

Eleonore Chamberland[1], Simon Duchesne[2], Nicolas Doyon[1]
[1]Laval University, Department Of Mathematics And Statistics, Québec, Canada, [2]Laval University, Radiology And Nuclear Medicine Dept., Québec, Canada

Aims: What really triggers Alzheimer's disease (AD)? The solution is likely a dynamic interaction of various pathways, including beta-amyloid, hyperphosphorylated tau proteins, and inflammation cytokines, modulated by risk factors such as genetics and sex. However, testing such a multifactorial hypothesis is logistically near impossible to perform in humans in practice. Computational models could solve this problem by offering a means to untangle causal relationships. We present our work towards building such a computational model in AD.
Methods: We developed a dynamic mathematical system of a normal brain evolving to a diseased state. The model has nineteen variables, including neurons, activated astrocytes, microglia and macrophages, and some cytokines, beta-amyloid, tau proteins, linked together by ordinary differential equations instantiated with parameters extracted from the literature. Due to its importance in AD, we separated beta-amyloid accumulation into its intracellular monomer and extracellular monomer, oligomer, and plaques components. The effect of sex and presence of APOE4 were factored in via selected parameters. The model is also sensitive to insulin, given diabetes as a known risk factor. The model, implemented in Python, was solved over one million steps, representing aging from 30 to 80 years old. It used an implicit multi-step method based on a backward differentiation formula for the derivative approximation.
Results: Our model can successfully relate all variables with respect to age. Parameters are being reviewed to ensure our mathematical relationships adequately represent reality. Validation with observational study data is forthcoming. Example of some curves given by the model.



$A\beta^{I}$: Intracellular beta-amyloid monomer; $A\beta_m^e$: Extracellular beta-amyloid monomer; $A\beta_o^e$: Extracellular beta-amyloid oligomer; $A\beta_p^e$: Extracellular beta-amyloid plaques; *GSK3*: Glycogen synthase kinase-3; F_i: Intracellular NFTs; F_e: Extracellular NFTs; *N*: Neurons; T_α: TNF-α.

Conclusions: Mathematical models are powerful tools that allow us to manipulate variables of interest and their relationship on a scale multiple orders of magnitude greater in sillico than in vivo.

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OD174 / #2696

ON-DEMAND SYMPOSIUM: A-BETA TOXICITY
30-03-2023 07:00 - 08:30

GENOME-WIDE SCREEN IDENTIFIES CURLI AMYLOID FIBRIL AS A BACTERIAL COMPONENT PROMOTING HOST NEURODEGENERATION

Chenyin Wang, Chun Yin Lau, Fuqiang Ma, Chaogu Zheng
University of Hong Kong, School Of Biological Sciences, Hong Kong, Hong Kong PRC

Aims: Growing evidence indicates that gut microbiota play a critical role in regulating the progression of neurodegenerative diseases such as Parkinson's disease. The molecular mechanism underlying such microbe–host interaction is unclear.
Methods: In this study, by feeding Caenorhabditis elegans expressing human α-syn with Escherichia coli knockout mutants, we conducted a genome-wide screen to identify bacterial genes that promote host neurodegeneration.
Results: The screen yielded 38 genes that fall into several genetic pathways including curli formation, lipopolysaccharide assembly, and adenosylcobalamin synthesis among others. We then focused on the curli amyloid fibril and found that genetically deleting or pharmacologically inhibiting the curli major subunit CsgA in E. coli reduced α-syn–induced neuronal death, restored mitochondrial health, and improved neuronal functions. CsgA secreted by the bacteria colocalized with α-syn inside neurons and promoted α-syn aggregation through crossseeding. Similarly, curli also promoted neurodegeneration in C. elegans models of Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease and in human neuroblastoma cells.
Conclusions: Overall, our studies indicate that bacterial components, such as curli, can have direct neurodegenerative effects.

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OD175 / #2677

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

ROLE OF SEX FOR CLINICAL CORRELATIONS OF SUBSTANTIA NIGRA NEURON LOSS IN LEWY BODY DEMENTIA

Ece Bayram, Irene Litvan
University of California San Diego, Neurosciences, La Jolla, United States of America

Aims: Lewy body, Alzheimer's pathology, substantia nigra neuron loss levels are associated with clinical features in Lewy body dementia (LBD). However, clinical correlations of Lewy body and Alzheimer's pathologies differ by sex; and we aimed to investigate whether there are sex differences for clinical associations of substantia nigra neuron loss in LBD.
Methods: Data was obtained from the National Alzheimer's Coordinating Center Uniform Data Set (UDS) and Neuropathology Data Set for UDS visits conducted between September 2005 and August 2019. Analysis included 42 women and 99 men with limbic or neocortical Lewy body pathology and available substantia nigra neuron loss data, excluding those with other neuropathologic diagnoses, from 27 AD Research Centers. Interactions between sex and substantia nigra neuron loss for likelihood of LBD core features during life, dementia likelihood and severity at last visit (CDR® Dementia Staging Instrument-Sum of Boxes [CDR-SOB]) were assessed with linear models controlling for age at last visit.
Results: Women and men had similar years of education; women were older at last visit and at death than men. Men were more likely to have a clinical LBD diagnosis during follow-up, had a higher likelihood and worse dementia at last visit, and had higher levels of substantia nigra neuron loss. There were no sex interactions with substantia nigra neuron loss for clinical associations. More neuron loss was associated with higher likelihood of dementia, cognitive fluctuations, visual hallucinations, REM sleep behavior disorder and parkinsonism for men; cognitive fluctuations, hallucinations and parkinsonism for women.
Conclusions: More severe substantia nigra neuron loss is associated with a higher likelihood of LBD core clinical features. Although women have less substantia nigra neuron loss than men, clinical correlations do not significantly differ for women and men.

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OD176 / #821

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

PROTEIN PHEWAS OF LRRK2 VARIANTS IDENTIFIED NOVEL CAUSAL PROTEINS AND PATHWAYS FOR PARKINSON'S DISEASE

Bridget Phillips[1], Dan Western[1], Yichen Sun[1], Laura Ibanez[2], Lihua Wang[1], Chengran Yang[1], Priyanka Gorijala[1], Yun Ju Sung[1], Carlos Cruchaga[1,2]
[1]Washington University in St. Louis, Psychiatry, St. Louis, United States of America, [2]Washington University in St. Louis, Neurogenomics And Informatics Center, St. Louis, United States of America

Aims: Leucine-rich repeat kinase 2 (LRRK2) common gene variants (tagged by rs76904798) are associated with sporadic PD. In a previous study we found that rs76904798 was associated with CSF GRN levels, but a comprehensive unbiased analysis of associated proteins remains incomplete due to prior focus on cis protein QTL (pQTL). Using the largest aptamer-based CSF proteomics study to date (7,006 SomaScan7K proteins, 3,107 individuals), we performed a phenome-wide association study (PheWAS) to identify proteins associated with LRRK2 variants and PD.
Methods: SNP selection using Conditional and Joint Association Analysis (GTCA-COJO) and PLINK LD r2 scores identified 11 other independently associated SNPs. Fine mapping was performed between each significant analyte and PD GWAS via colocalization analysis, Transcriptome-wide Association Studies (TWAS), and Mendelian randomization (MR). These analytes were further analyzed based on PD risk association, brain cell type specificity, and FUMA gene pathway annotation.
Results: 26 proteins passed FDR correction, with 11 implicated with PD before like GRN and GPNMB. TWAS/FUSION analyses also indicate 12 proteins were significant and positively associated with PD risk, like novel proteins C1QTNF1 and SDCBP2, and half were validated by the PPMI data. In addition, MR analyses indicate that proteins like GREM2, GRN, and C1QTNF1 are also causal for PD risk. Cell-type enrichment analyses indicate enrichment of microglia-specific proteins (Enrichment fold 7.35, $P=4.14\times10^{-10}$). Enrichment analyses indicate enrichment for GO_MYELOID_LEUKOCYTE_ACTIVATION ($P=1.57\times10^{-4}$) and GO_LEUKOCYTE_ACTIVATION_INVOLVED_IN_INFLAMMATORY_ RESPONSE ($P=2.8\times10^{-3}$) pathways.
Conclusions: Trans QTL can identify novel proteins interaction in an unbiased manner. This study linked LRRK2 variants with both PD implicated, GRN and GPNMB, and novel, ITGB2 and C1QTNF1, proteins that have support in our TWAS, MR, and PPMI validation. Proteins being enriched in microglia and the lysosome pathway suggest involvement in neuroinflammation.

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OD178 / #289

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

LRRK2 G2019S PROMOTES ASTROCYTIC INFLAMMATORY RESPONSE INDUCED BY OLIGOMERIC A-SYNUCLEIN THROUGH NF-KB PATHWAY

Fen Wang[1], Kai-Jie He[2], Jinbao Zhang[1], Jun-Yi Liu[3], Chun-Feng Liu[2,4]
[1]The Second Affiliated Hospital of Soochow University, Department Of Neurology, Suzhou, China, [2]Soochow University, Institute Of Neuroscience, suzhou, China, [3]Dushu Lake hospital affilicated to Soochow University, Department Of Neurology, Suzhou, China, [4]The Second Affiliated Hospital of Soochow University, Department Of Neurology, suzhou, China

Aims: Neuroinflammation is implicated in the progression of Parkinson's disease (PD). Leucine-rich repeat kinase 2 (*LRRK2*) is a potential therapeutic target for PD and may play a role in the regulation of inflammatory pathways. However, the underlying mechanism remains unclear. The present study investigated the mechanism of the astrocytic inflammatory response in *LRRK2 G2019S* mutation induced by oligomeric α-synuclein (O-αS).
Methods: We established an O-αS induced inflammation model in *LRRK2 G2019S* mutant. Immunofluorescence or immunohistochemical staining was used for detecting activation and morphological changes of glial cells in mouse striatum, followed by morphological and fluorescence intensity analyses. The inflammatory levels of primary astrocytes with different treatments were detected by quantitative and semi-quantitative experimental approaches.
Results: Astrocytes are pivotal mediators of α-syn toxicity since they internalize and store α-syn released from damaged neurons. We found that *LRRK2 G2019S* enhanced the activation of astrocytes treated by O-αS *in vivo*. Morphological analysis showed that the astrocyte morphology of *LRRK2 G2019S* changed greatly, and the cell bodies were swollen and branched. However, the morphology of microglia did not change compared with the control group. *LRRK2 G2019S* mediated dopaminergic neuronal loss in the O-αSinduced mouse model. *In vitro*, *LRRK2 G2019S* aggravated astrocytic inflammation induced by O-αS through the nuclear factor-κB pathway, and inhibition of LRRK2 kinase activity reduced production of inflammatory factors.
Conclusions: *LRRK2 G2019S* is an important contributing factor leading to astrocytic inflammation, and inhibition of *LRRK2* kinase activity is a viable strategy for suppressing neuroinflammation in the pathogenesis of PD.

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OD179 / #2185

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

STRAIN-SPECIFIC ALPHA-SYNUCLEIN ANTIBODIES DISTINGUISH BETWEEN SYNUCLEINOPATHIES

Simona Ghanem[1], Ilham Abdi[1], Daniel Erskine[2], Nour Majbour[1], Nishant Vaikath[1], Omar El-Agnaf[1]
[1]Hamad Bin Khalifa University, Qatar Biomedical Research Institute (qbri), Doha, Qatar, [2]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom

Aims: Multiple System Atrophy (MSA), Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB) are synucleinopathies that vary in their clinical and pathological phenotype. PD is characterized by the presence of alpha-synuclein (α-Syn) in Lewy bodies and neurites whereas in MSA, α-Syn is found in glial cytoplasmic inclusions (GCIs). The aim of this study is to explore the hypotheses that the pathological and clinical differences of these synucleinopathies is due to the presence of distinct α-Syn strains with unique conformation, seeding and propagation properties.
Methods: A panel of in-house antibodies that target different forms of α-Syn was generated. Antibodies were fully characterized by Dot blot, western blot analysis, and immunohistochemistry on postmortem brain tissues. Sandwich-based ELISAs were developed and optimized using the panel of antibodies and evaluated for their direct quantification capability in biological samples, human CSF and brain lysates. Diverse aggregation assays, including real-time quaking-induced conversion (RT-QuIC) on brain homogenates from PD, MSA, and DLB cases as well as healthy controls were also conducted.
Results: Cell-based models and immunohistochemistry on post-mortem brain tissues using our novel antibodies showed unique binding characteristics capable of distinguishing α-Syn pathology found in Lewy bodies (LBs) and Lewy neurites (LNs) which are predominantly found in PD and DLB, from α-Syn in GCIs which is the main pathology seen in MSA cases. Similarly, sELISAs conducted on CSF samples and brain lysates showed distinct segregation between MSA cases from PD, DLB, and healthy controls.
Conclusions: The strain specific α-Syn antibodies will elucidate the pathogenic mechanisms underlying these synucleinopathies and potentially help in the identification of disease associated specific biomarkers.

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OD180 / #759

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

ALPHA-SYNUCLEIN SEEDING ACTIVITY IN DEMENTIA WITH LEWY BODIES

Carmen Peña-Bautista[1,2], Rakesh Kumar[3], Consuelo Cháfer-Pericás[2], Axel Abelein[3], Daniel Ferreira[1]
[1]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society (nvs), Stockholm, Sweden, [2]Instituto de Investigación Sanitaria La Fe, Neurología, Valencia, Spain, [3]Karolinska Institutet, Department Of Biosciences And Nutrition, Stockholm, Sweden

Aims: Dementia with Lewy bodies (DLB) is a common dementia but the field is still lacking a specific biomarker of its core pathology: alpha-synuclein. Recently, the alpha-synuclein seeding activity detection method called Real-time quaking induced conversion (RT-QuIC) has shown great potential for the assessment of alpha-synuclein in vivo. In this presentation we provide an updated overview of the state-of-the-art research with regard to RT-QuIC in DLB.
Methods: Following the PRISMA guidelines, we conducted a systematic review of publications until August 2022. Twenty-one publications were finally analysed.
Results: RT-QuIC using cerebrospinal fluid generally showed high accuracies for DLB diagnosis, with sensitivities (SN) from 75 to 100 % and specificities (SP) from 83 to 100 %, compared to controls; SN 65-100% and SP 84-100% compared to Alzheimer's disease, and SN 86-100 % and SP 0-15 % compared to Parkinson's disease. Similar results were found for brain homogenates and other tissues (skin, submandibular gland). The low diagnostic discrimination between DLB and Parkinson's disease could be improved with the use of different RT-QuIC parameters for example AUC, Imax or Lag phase and by characterizing RT-QuIC products (proteinase K–resistant and fibrillary alpha-synuclein species). We also observed a good diagnostic performance of RT-QuIC for the early stages of idiopathic REM sleep behaviour disorder and mild cognitive impairment. Several factors could influence RT-QuIC results, including DLB subtype, co-pathologies, sample type or assay conditions (buffer, temperature, sample volume, and seeding substrate).
Conclusions: RT-QuIC can detect alpha-synuclein seeding activity with high accuracy and early in the disease. However, RT-QuIC cannot differentiate between DLB and Parkinson's disease at the moment. The recent data on biochemical or morphological characterization of RT-QuIC products and RT-QuIC kinetics holds promise and deserves further investigation.

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OD181 / #412

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

ALPHA SYNUCLEIN NITRATION AND AGGREGATION IN NEURONS IS CONTROLLED BY THE NOVEL ENZYME SYNUCLEIN NITRASE

Robert Brendza, Sarah Wright, Selim Boudoukha, Rustem Esanov, Sami Hussain, Edward Vertudes, Marie Whitmore, Irene Griswold-Prenner, Vu Dang
Nitrase Therapeutics Inc, Research And Development, Brisbane, United States of America

Aims: Alpha synuclein (αSyn) aggregation plays a key role in the pathology of Parkinson's disease. Recent studies indicate that nitration of αSyn promotes aggregation of the protein. Nitrase Therapeutics has identified an enzyme, Synuclein Nitrase, that specifically catalyzes the nitration of αSyn. We report here studies in mice designed to determine if αSyn nitration by Synuclein Nitrase plays a role in αSyn nitration and aggregation in vivo.
Methods: Using a methamphetamine model, we reduced Synuclein Nitrase activity or levels using either a small molecule pan-Nitrase inhibitor (NB001) or Synuclein Nitrase knockout to investigate the role Synuclein Nitrase plays in αSyn nitration. A preformed fibrils (PFF) model of synucleinopathy was used to investigate the consequence of Synuclein Nitrase knockout on αSyn aggregation both in cultured iPSC-dopaminergic neurons and in mice.
Results: Methamphetamine increased levels of nitrated αSyn in mouse red blood cells and brain. The increase was blocked by Synuclein Nitrase knockout or treatment with NB001. In wild-type iPSC-dopaminergic neurons, PFF induced phospho-αSyn aggregates; Synuclein Nitrase knockout reduced this aggregation. Likewise, Synuclein Nitrase knockout attenuated the PFF induced formation and spreading of phospho-αSyn pathology to specific, distal brain regions.
Conclusions: Nitration of αSyn is controlled by Synuclein Nitrase as shown by the decrease in nitration of αSyn in Synuclein Nitrase knockout mice and by a chemical inhibitor in WT mice. In addition, inhibition or removal of Synuclein Nitrase reduced the formation of phospho-αSyn aggregates in *in vitro* and *in vivo* models. These data suggest that development of a Synuclein Nitrase therapeutic could result in significant disease-modification of Parkinson's disease.

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OD182 / #2048

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

STRUCTURES OF LIPIDIC A-SYNUCLEIN FIBRILS AND PRE-FIBRILLAR AGGREGATION INTERMEDIATES

Vrinda Sant[1], Leif Antonschmidt[1], Kumar Movellan[1], Kai Xue[1], Evgeny Nimerovsky[1], Magdeline Nathan[1], Stefan Becker[1], Loren Andreas[1], Christian Griesinger[1,2]
[1]Max Planck Institute for Multidisciplinary Sciences, Nmr Based Structural Biology, Goettingen, Germany, [2]University of Goettingen, Cluster Of Excellence "multiscale Bioimaging: From Molecular Machines To Networks Of Excitable Cells" (mbexc), Goettingen, Germany

Aims: The ability of oligomeric α-Synuclein (αS) aggregation intermediates to nucleate on lipid membranes and disrupt them has been proposed to be a mechanism for toxicity in neurodegenerative diseases. However, structural characteristics responsible for toxicity remain elusive due to difficulty isolating oligomers from brain tissue and their low population, and transient nature makes even *in vitro* preparations challenging to study. Two high-resolution structures have been determined: a toxic oligomer and the fibril endpoint, both in complex with lipid membranes.
Methods: We aggregate recombinant αS along with small unilamellar vesicles. Aggregation kinetics are monitored by Thioflavin T fluorescence and lipid bound intermediates at different time points are isolated by centrifugation. These are characterized mainly with solid-state nuclear magnetic resonance (NMR). Toxicity of aggregation species are probed with cell viability assays in SH-SY5Y neuroblastoma cells.
Results: A pre-fibrillar αS oligomeric aggregation intermediate (I1) is isolated at the end of the lag phase during the formation of an L2-fibril polymorph. The lipidic L2-fibril resembles topological folds amplified from patients with Parkinson's disease and Lewy Body Dementia and sub-structures from fibril filaments from human brains with Lewy Pathology. The pre-L2-fibril intermediate, I1, shows impacted cell viability as opposed to the fibril. A high resolution structural model of I1 which shows distinct differences to the L2-fibril has been determined and will be discussed.
Conclusions: A toxic early aggregate embedded in membranes can be isolated and characterized with high resolution.

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OD183 / #1475

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

DEVELOPMENT OF A NOVEL OPTOGENETIC-BASED MODEL OF A-SYNUCLEIN AGGREGATION TO STUDY A-SYNUCLEINOPATHIES

Abid Oueslati
University Laval- CHUL, Molecular Medecine, Québec, Canada

Aims: Parkinson's disease (PD) is characterized by dopaminergic neuronal loss and presence of proteinaceous inclusions Lewy bodies. These inclusions are constituted of a pre-synaptic protein, alpha-synuclein (a-syn). Evidence suggests for a central role of a-syn aggregation in PD. However, how these aggregates precipitate dopaminergic neuronal loss remain elusive. This is due to the lack of proper models to undertake such investigations. To overcome this limitation, our group created a cellular and animal model of PD mimicking authentic LBs features. Using our new optogenetic-inducible a-syn aggregation, we aim to dissect how these inclusions interfere with physiological functions of dopaminergic neurons leading to neuronal loss.
Methods: Our optogenetic versatile strategy allows for spatiotemporal control of alpha-syn aggregation both in vivo and in living cells. This approach is based on the use of a mutant form of the Arabidopsis thaliana photoreceptor cryptochrome 2 (CRY2). When stimulated with blue light, CRY2 undergoes reversible and robust protein clustering. Fusing this system to a-syn, CRY2 clustering triggered aggregation of a-syn prompting formation of LB-like inclusions in living cells. We refer to this system as light-inducible protein aggregation (LIPA).
Results: LIPA has allowed for real-time induction of a-syn inclusions with remarkable spatial and temporal resolution both in vitro and in vivo. Results showed that LIPA-induced aggregates auto-perpetuate for several days, faithfully mimicking authentic features of LBs and induced significant dopaminergic neuronal loss and behavioural impairment in vivo.
Conclusions: LIPA provides a dependable and invaluable tool to generate, visualize and dissect the role of protein aggregates in neurodegenerative disorders.

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OD184 / #1270

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

IMMUNOLOGICAL CHARACTERIZATION OF POLYMORPHIC ALPHA SYNUCLEIN OLIGOMERS

Kenya Moore[1], Nicha Puangmalai[1], Sagar Gaikwad[1], Cynthia Jerez[1], Rakez Kayed[2]
[1]University of Texas Medical Branch, Mitchell Center For Neurodegenerative Disease, Galveston, United States of America, [2]University of Texas Medical branch, Neurology, Galveston, United States of America

Aims: Characteristic proteinacious aggregates are the pathological hallmark of many neurodegenerative diseases. Specifically an intermediate state of aggregates, oligomers, are now considered the most toxic species. We have established recombinant polymorphic alpha synuclein (α-Syn) oligomers prepared with physiologically relevant inducers/buffers: artificial cerebrospinal fluid, docosahexaenoic acid, and dopamine. Utilizing our lab-generated α-Syn toxic conformation antibodies (SynTCs), we employ multiple methods to investigate the biochemical and biophysical properties of these distinct oligomers. In additon, we investigate the celluar effects of therapetuically targeting α-Syn oligomeric polymorphs in regards to seeding propensity and cytotoxicity.
Methods: We biochemically characterized polymorphic α-Syn oligomers using dot blotting, western blotting, and indirect Enzyme-linked Immunosorbent Assay (ELISA). We performed biophysical characterization with isothermal titration caloritmetry. α-Syn monomer, α-Syn oligomeric polymorphs (Syn O DA, Syn O DHA, Syn O aCSF), α-Syn fibrils, tau, and amyloidβ were tested to assess binding selectivity. To investigate the cellular effects, human neuroblastoma cells and primary cortical neurons isolated from mice over expressing α-Syn were exposed to α-Syn oligomeric polymorphs alone or SynTC-immunodepleted α-Syn oligomeric polymorphs. Immunocytochemistry and cell-based assays were used to evaluate enodgeous aggregation and cytotoxicity before and after the immunodepletion of α-Syn oligomeric polymorphs.
Results: Immunoblotting and indirect ELISA revealed distinct immunoreactivity detected by SynTCs for each α-Syn oligomeric species. α-Syn oligomeric polymorphs exhibit distinct binding profiles to each SynTC as observed in isothermal titration calorimetry. Importantly, when immunodepleted by SynTCs, the seeding propensity and mediated cellular toxiciity of α-Syn oligomeric polymorphs is differentially reduced in both SH-SY5Y cell and primary cortical neurons.
Conclusions: These results demonstrate the biological significance of the conformational heterogeneity of α-Syn oligomers and the importance of conformation specific antibodies. Therapeutics that can target conformational heterogeneity and reduce protein aggregate mediated toxicity have promising immunotherapeutic potential.

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OD185 / #592

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

QUANTIFICATION OF ASYN SEEDS IN PATIENTS' BIOFLUIDS BY SINGLE MOLECULE SEED AMPLIFICATION ASSAY

Jyoti Rukhaya[1], Preeti Manandhar[1], Derrick Lau[1], Kathryn Hill[2], Antony Cooper[2], Yann Gambin[1], Emma Sierecki[1]
[1]UNSW, School Of Biomedical Sciences, Kensington, Australia, [2]UNSW, Garvan Institute Of Medical Research, Darlinghurst, Australia

Aims: Our aim was to validate a unique method for the quantification of a-syn seeds in patients' biofluids, based on single molecule confocal spectroscopy, named single molecule Seed Amplification Assay (smSAA). Our goal is to **establish smSAA as a routine assay to quantify seed concentration in CSF** and **validate smSAA use in blood**.
Methods: smSAA relies on the extreme sensitivity provided by single molecule confocal spectroscopy. Single molecule fluorescence methods, with a million-fold improvement in sensitivity compared to traditional plate readers, have the power to detect the original seeds in the biosamples. Our assay directly counts the number of seeds but also measures their individual size to create a multidimensional fingerprint of the sample. To distribute this method, we created a plug-and-play device that offers extreme sensitivity to quantify a-syn seeds with simple operation by non-specialists. This instrument is 3D-printed and all optical alignments and data analysis are automated, allowing the faithful duplication of the method.
Results: We established an optimised protocol for smSAA that detects a-syn seeds with attogram sensitivity. Our data show that smSAA accurately measures seed concentration in CSF samples and retains the diagnostic sensitivity and specificity of standard SAAs. Further we prove that smSAA is reliable and reproducible across multiple users and multiple centres. We also show proof-of-concept that smSAA is compatible with serum and plasma samples.
Conclusions: Our new detection method for a-syn seeds is highly sensitive and can detect seeds in CSF, even before amplification. smSAA is quantitative and linear in the nM-fM range. This gain of sensitivity allows for a fast experiment, using minute amount of sample, dramatically reducing consumption of precious biosamples and monomeric a-syn.

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OD186 / #1025

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

INTRA-STRIATAL INJECTIONS OF MISFOLDED ALPHA-SYNUCLEIN PROTEIN IN MICE IMPAIRS STIMULUS-RESPONSE LEARNING, MOTOR FUNCTION AND MIMICS PARKINSON'S DISEASE PATHOGENESIS

Oren Princz-Lebel[1], Vania F. Prado[2], Marco. Prado[3], Lisa Saksida[2], Timothy Bussey[3]
[1]Neuroscience Program, Physiology And Pharmacology, London, Canada, [2]Western University, Robarts Research Institute, London, Canada, [3]The University of Western Ontario, Robarts Research Institute, London, Canada

Aims: Using a mouse model, we aimed to assess whether synucleinopathy is necessary or even sufficient to reproduce the cognitive and motor abnormalities often seen in patients with Parkinson's disease.
Methods: We injected recombinant human α-synuclein pre-formed fibrils or saline control unilaterally in the dorsal striatum of M83 heterozygous male and female mice. We assessed cognitive function using the Visuomotor Conditional Learning (VMCL) task, an established stimulus-response learning task which uses the Bussey-Saksida touchscreens. At both 8 weeks and 14 weeks post-injection, we assessed motor function using the Accelerator Rotarod, Open Field, Catwalk and Grip Force tasks. Following behavioural assessments, brain and spinal cord tissue was collected for immunohistochemistry and western blots to measure severity of synucleinopathy and neurodegeneration of vulnerable neurons.
Results: Mimicking the pathogenesis often seen in patients with Parkinson's disease, we found severe and robust cognitive impairments prior to the onset of major motor impairments. At 9-12 weeks post-injection of α-synuclein pre-formed fibrils, we found male and female mice were significantly impaired at acquiring the VMCL task, showing ~30% decrease in accuracy compared to mice injected with saline control. At 14-16 weeks post-injection, we also found signficant motor impairments, with stronger severity in male mice. In addition, with immunohistochemistry and western blots, we found robust signs of synucleinopathy and neurodegeneration in the brains and spinal cords of α-synuclein injected mice.
Conclusions: Our results implicate misfolded α-synuclein protein as a key mechanism underlying cognitive and motor dysfunction in a Parkinson's disease-relevent progression. In addition, our molecular work highlights the ability of α-synuclein protein to seed across the central nervous system, instigating neurodegeneration of vulnerable neurons.

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OD187 / #1977

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

ALPHA-SYNUCLEIN STRAIN VARIABILITY IN BODY-FIRST AND BRAIN-FIRST PARKINSON'S DISEASE MODELS

Nathalie Van Den Berge[1], Mie Just[1], Therése Klingstedt[2], Priyanka Swaminathan[3], Marikken Sundnes[3], Mikael Lindgren[3], Peter R. Nilsson[2], Per Borghammer[4]
[1]Aarhus University, Clinical Medicine, Aarhus C, Denmark, [2]Linköping University, Department Of Physics, Chemistry And Biology, Linköping, Sweden, [3]Norwegian University of Science and Technology, Department Of Physics, Trondheim, Norway, [4]Aarhus University Hospital, Nuclear Medicine And Pet, Aarhus, Denmark

Aims: Pathogenic alpha-synuclein (asyn) aggregates are a defining feature of neurodegenerative synucleinopathies, such as Parkinson's disease (PD). These aggregates can propagate trans-synaptically along the brain-body axis, hereby affecting multiple cell-types and organs. Increasing data suggest that the clinical heterogeneity seen in patients with synucleinopathies could be explained by the presence of distinct asyn strains, which exhibit variable morphologies and pathological functions. Importantly, the cellular environment is known to impact strain morphology. We hypothesize, for the first time, that the changing cellular environments an asyn aggregate may encounter during its brain-to-body or body-to-brain propagation, may influence strain morphology, and hence its function or toxicity. Here, we aim to use rodent models of body-first and brain-first PD propagation to determine if asyn strain morphology is altered during spread along the brain-body axis.
Methods: Body-first PD and brain-first PD are recapitulated by injection of artificial asyn pathology in the gut and amygdala, respectively. Next, disease progression is evaluated at mid and advanced disease stages using imaging biomarkers and histology against asyn pathology in several organs (brain, gut, heart, skin). Structural variations in aggregated asyn are characterized using thiophene-based ligands, which create a "spectral fingerprint" that reflects the conformational properties of the pathology.
Results: Our preliminary findings show subtype-specific neuronal system dysfunction and emission spectra of hFTAA- and HS-68-binding to asyn-positive aggregates in the dorsal motor nucleus of the vagus, substantia nigra, stomach and heart.
Conclusions: These results indicate that aggregated asyn is able to change conformation upon crossing a synapse, due to the changing cellular environment during trans-synaptic propagation, and, that conformational properties correlate with disease initiation (gut or brain). This study contributes greatly to our understanding of PD subtypes, and the potential link between strain and phenotypic variability.

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OD188 / #966

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

THE SELECTIVE DETECTION OF ALPHA-SYNUCLEIN OLIGOMERS TO ANALYSE SMALL MOLECULE INHIBITORS OF THEIR FORMATION FOR THE TREATMENT OF PARKINSON'S DISEASE

Roxine Staats, Samata Pandey, Megan Pullein, Benedetta Mannini, Norhakim Yahya, Johnny Habchi, Luke Rajah, John Thomson, Scott Pollack
Wren Therapeutics, Discovery Research, Cambridge, United Kingdom

Aims: Oligomeric forms of alpha-synuclein are implicated in the progression of Parkinson's Disease and other alpha-synucleinopathies. Treatments targeting disruption of neurotoxic oligomers will rely on measuring oligomer levels accurately throughout development. Our objective is to develop precise, selective biomarker assays suitable for the preclinical and clinical development of such therapeutics.
Methods: An ELISA readout was developed to monitor the levels of oligomeric alpha-synuclein both in cell extracts and *in vivo* samples. The assay was designed to detect alpha-synuclein oligomers selectively (vs. monomer and fibrillar forms). Several anti-alpha-synuclein antibodies were evaluated to identify antibodies that, once tagged with capture and detection functionalities in an optimal format, could provide selective probes for oligomeric alpha-synuclein species. The assay was validated using both stabilised oligomers and samples from carefully defined cellular and in vivo conditions. A single molecule counting (SMC) assay format has also been explored to greatly increase detection sensitivity.
Results: Commercially-available and literature-described anti-alpha-synuclein antibodies were evaluated by ELISA in order to identify those with selectivity profiles (for oligomeric vs. monomeric alpha-synuclein) suitable for further characterisation. A range of capture and detection linkers was explored to optimise assay sensitivity and reproducibility in relevant *in vivo* matrices. The SMC format shows promise to enhance the assay even further.
Conclusions: We have developed a robust assay platform for the detection of alpha-synuclein oligomers to characterise the effects of potent, small-molecule inhibitors of alpha-synuclein oligomer generation in both an iPS dopaminergic cell model and a Parkinson's disease mouse model, confirming target engagement.

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OD189 / #1742

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

THE ANTIOXIDANT RUTIN COUNTERACTS THE PATHOLOGICAL IMPACT OF ALPHA-SYNUCLEIN ON THE ENTERIC NERVOUS SYSTEM IN VITRO

Anne Christmann[1], Manuela Gries[1], Patrik Scholz[2], Pascal Stahr[3], Jessica Ka Yan Law[4], Steven Schulte[1], Monika Martin[1], Rainer Lilischkis[1], Sven Ingebrandt[4], Cornelia Keck[3], Karl-Herbert Schafer[1]
[1]University of Applied Science Kaiserslautern, Department Of Informatics And Microsystems And Technology, Zweibrucken, Germany, [2]Bayer AG, Formulation Development, Leverkusen, Germany, [3]Philipps-University Marburg, Department Of Pharmaceutics And Biopharmaceutics, Marburg, Germany, [4]RWTH Aachen University, Institute Of Materials In Electrical Engineering, Aachen, Germany

Aims: Motoric disturbances in Parkinson's disease (PD) derive from the loss of dopaminergic neurons in the substantia nigra. Intestinal dysfunctions appear often long before the manifestation of neuronal symptoms, suggesting a strong correlation between gut and brain in PD. Oxidative stress is a key player in neurodegeneration causing neuronal cell death. Using natural antioxidative flavonoids like Rutin, might provide intervening strategies to improve or avoid PD pathogenesis.
Methods: Various formulations of Rutin were characterized by electron microscopy and by determining their radical scavenging activity. To explore potential effects of microRutin compared to nanoRutin upon the central and the intestinal nervous system, the so called enteric nervous system (ENS), during PD, its neuroprotective effects were assessed, using *in vitro* models, viability assays, immunostainings. To transfer the data to an applicable formulation of Rutin, the soluble Troxerutin was also tested.

Results: Our results demonstrated that Rutin inhibited the neurotoxicity induced by Syn administration by decreasing oxidized lipids and increasing cell viability in both, mesencephalic and ENS cells. For enteric cells, neuronal outgrowth, number of synaptic vesicles and tyrosine hydroxylase positive cells were significantly reduced when treated with Syn. This could be reversed by the addition of Rutin. nRutin revealed a more pronounced result in all experiments.
Conclusions: Our study shows that Rutin, especially the nanocrystals, are promising natural compounds to protect neurons from cell death and oxidative stress during PD. Early intake of Rutin may provide a realizable option to prevent or slow PD pathogenesis.

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OD190 / #2733

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

DOPAMINE NEURON SUBTYPE-SPECIFIC LRRK2 DYSFUNCTION IN THE NIGROSTRIATAL SYNAPSE

Loukia Parisiadou[1], Chuyu Chen[1], Oscar Moreno Ramos[2], Zachary Gaertner[2], Vanessa Promes[1], Natalia Lopez Gonzalez[2], Raj Awatramani[2]
[1]Northwestern University, Pharmacology, CHICAGO, United States of America, [2]Northwestern University, Neurology, Chicago, United States of America

Aims: LRRK2 mutation carriers exhibit pathological and clinical phenotypes similar to idiopathic Parkinson's disease (PD) patients, including dopamine (DA) neuron loss in the substantia nigra pars compacta (SNc). Within the SNc, cell loss in the ventral tier is more prominent than in the dorsal tier in PD brains. Despite early recognition of this pathological feature, we do not clearly understand the selective vulnerability of ventral tier neurons. Here, we studied DA neuron dysfunction in a cell-type-specific manner to fill this gap, focusing on LRRK2 function in the most vulnerable DA neuron subtype.
Methods: We used the LRRK2 mutant knock-in (KI) mouse model expressing the G2019S mutation, which revealed a decrease in evoked nigrostriatal DA release. As active zones like structures on the DA axon terminals mediate the fast kinetic signaling of DA, we assessed release site organization in identified control and mutant LRRK2 DA axons, leveraging our newly developed genetic intersectional strategies. We employed 3D structured illumination microscopy in control and mutant LRRK2 striatal sections.
Results: We demonstrated an increase in the volume of Bassoon clusters (a marker of DA release sites), suggesting the disorganization of these sites. The increase was specific for the vulnerable ventral subset of DA neurons. Functional studies combining optogenetics and genetically encoded DA sensors will examine the regional diversity of DA release defects in these mice. At the same time, single-nucleus RNA sequencing and cell type-specific proteomics will shed light on the involved molecular targets.
Conclusions: Our data show a LRRK2-mediated dysfunction, specifically in the vulnerable PD DA neuron cell type in a physiological penetrant mouse model. The precise elucidation of LRRK2 pathological events relevant to PD DA subsets will illuminate disease mechanisms with high specificity and mechanistic insights.

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OD190a / #2212

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, LRRK2, PATHOPHYSIOLOGY
31-03-2023 07:00 - 08:30

PREDICTING PARKINSON'S DISEASE PROGRESSION USING A MULTIMODAL COMBINATION OF BASELINE CLINICAL MEASURES, NEUROIMAGING AND BIOFLUID MARKERS IN EARLY PD

Lyndsey Collins-Praino[1], Benjamin Ellul[1], Angus Mcnamara[1], Irina Baetu[2], Stephan Lau[3,4], Mark Jenkinson[3,4]
[1]University of Adelaide, School Of Biomedicine, Adelaide, Australia, [2]The University of Adelaide, School Of Psychology, Adelaide, Australia, [3]The University of Adelaide, School Of Computer Science, Adelaide, Australia, [4]The University of Adelaide, Australian Institute Of Machine Learning, Adelaide, Australia

Aims: Understanding disease progression in Parkinson's disease (PD) is critical for disease management and therapeutic development. Given the subjective, labile nature of clinical measures, multimodal models incorporating objective biomarkers are needed. We assessed whether a combination of such markers predicts progression in motor or non-motor symptoms up to 5-year follow-up in early PD.
Methods: Data from the Parkinson's Progression Markers Initiative study were used. As a proxy marker of substantia nigra (SN) integrity, manual masking of the hypointense region adjacent to the SN was carried out in T2-weighted MRI. Two separate hierarchical clustering analyses were performed on motor and cognitive outcomes at five-year follow-up. The ability of clinical, neuroimaging (proxy SN integrity, DaT binding) and biofluid (alpha-syn, p-tau and IGF-1) markers to predict cluster membership at 5-year follow-up was assessed using logistic regression models.
Results: Two clusters were defined in the motor analysis (n= 117), with the second showing higher rigidity, worsened cognitive and motor function and increased mood dysfunction at 5-year follow-up compared to the tremor-dominant first group. Membership in this second cluster was predicted by male sex, lower DaT binding and CSF alpha synuclein levels at baseline; predictors accounted for 19.8% of the variance. In the non-motor analysis (n = 136), two distinct groups were defined, with the second demonstrating older age, worsened cognition and motor function and increased mood dysfunction. Membership in this second cluster at 5-year follow-up was predicted by higher age, lower UPSIT score, worse cognitive function and increased mood dysfunction at baseline; predictors accounted for 37.7% of the variance.
Conclusions: A multimodal combination of clinical measures and biomarkers has utility for predicting disease progression at five-year follow-up, with potential greater accuracy for non-motor outcomes.

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OD193 / #1953

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

IS SENESCENCE OF DOPAMINERGIC NEURONS AN AGE-RELATED DRIVER OF PARKINSON'S DISEASE?

Taylor Russo[1], Benjamin Kolisnyk[2], Aswathy Bs[1], Tae Wan Kim[3], Jacqueline Martin[1], Lorenz Studer[3], Markus Riessland[1]
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Aims: Cellular senescence is a mechanism to prevent uncontrolled cell division (tumorigenesis). As senescent cells persist in tissues, they cause local inflammation that can be harmful to surrounding cells, contributing to aging. Generally, neurodegenerative diseases, such as Parkinson's, are disorders of aging. The contribution of cellular senescence to neurodegeneration is still unclear. Determining the cell type-specific function of the neuroprotective master regulator and genetic risk factor for PD, SATB1, in human DA neurons, we identified senescence being crucial for the selective vulnerability of dopaminergic neurons.
Methods: We used human stem cell-derived DA neurons to investigate the neuroprotective role of the PD risk gene SATB1. We applied diverse sequencing methods (ChIP-seq, RNA-seq, ATAC-seq) and functional studies using imaging, biochemical methods and energy analyses.
Results: SATB1 is a DNA-binding protein associated with PD. We found that SATB1 prevents cellular senescence in post-mitotic dopaminergic neurons. Loss of SATB1 causes activation of a cellular senescence transcriptional program in dopamine neurons both in human stem cell-derived dopaminergic neurons and in mice. We observed phenotypes that are central to senescence in SATB1 knockout dopamine neurons in vitro and in vivo. Moreover, we found that SATB1 directly represses expression of the pro-senescence factor p21 in dopaminergic neurons. Additionally, we found that DA neuron senescence results in spreading of senescence to glial cells and triggers massive immune responses even before DA neuron degeneration occurs.
Conclusions: Our data implicate senescence of dopamine neurons as contributing factor in the pathology of PD in vitro and in vivo (mice and humans). Inflammation in the midbrain of PD patients was reported to occur before symptom onset and neurodegeneration. Senescence of DA neurons would cause these symptom and eventually leading to inflammaging resulting in DA neuron loss.

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OD194 / #2101

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

LEWY NEURITES IN THE RETINA OF PARKINSON'S DISEASE, LEWY BODY DISEASE, MULTIPLE SYSTEM ATROPHY AND OTHER NEURODEGENERATIVE DISEASES.

Frederique Hart De Ruyter[1], Tjado Morrema[1], Jurre Den Haan[1], Frank Verbraak[2], Johannes De Boer[3], Annemieke Rozemuller[1], Femke Bouwman[4], Jeroen Hoozemans[1]
[1]Amsterdam UMC, Pathology, Amsterdam, Netherlands, [2]Amsterdam UMC, Ophthalmology, Amsterdam, Netherlands, [3]VU University, Physics, Amsterdam, Netherlands, [4]Amsterdam UMC, Alzheimer Center Amsterdam, Amsterdam, Netherlands

Aims: There is increasing interest in using the retina as a source for biomarkers for different neurodegenerative diseases. Specific protein aggregates associated with neurodegenerative diseases are present in the retina and could be visualized in a non-invasive way. Previous studies have already established the presence of Lewy aggregates in the retina of Parkinson's disease and Dementia with Lewy bodies. In this study we assess the presence of retinal α-synuclein aggregates in neuropathologically characterized α-synucleinopathies, other neurodegenerative diseases and non-demented controls.
Methods: Post-mortem eyes were collected through the Netherlands Brain Bank from donors with PD (n=6), PDD (n=2), DLB (n=5), incidental LBD (n=2), MSA (n=2), as well as other neurodegenerative diseases (AD, FTLD-TDP, FTLD-tau, PSP, CBD, MS, n=29) and non-demented controls (n=14). Cross-sections of the superior-temporal quadrants were immunostained for phosphorylated a-synuclein (pS129) and assessed for the presence of aggregates and inclusions.
Results: As previously described, pS129 showed diffuse immunoreactivity in the retinal nerve fiber layer (RNFL) and structures resembling Lewy neurites mainly in the inner plexiform layer, as well as the ganglion cell layer, inner nuclear layer (INL) and sporadically in the outer plexiform layer. Lewy neurites were present in 75% of all synucleinopathies without variety between the clinical subtypes, and generally absent in controls. Lewy neurites were observed in 30% of other neurodegenerative diseases such as tauopathies and FTLD-TDP.
Conclusions: Presence of Lewy neurites positive for a-synuclein pS129 differentiates α-synucleinopathies from controls. However, Lewy neurite-like structures do not seem exclusively present in α-synucleinopathies, since their presence was also observed in other neurodegenerative diseases such as AD and FTLD-TDP. Our study provides additional insight into the use of α-synuclein pS129 aggregates in the retina as a biomarker for neurodegenerative diseases such as PD.

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OD195 / #2253

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

DISRUPTION OF RNA METABOLISM AND SYNAPTIC SIGNALING IN EARLY STAGES P.A53T-ASYN PATHOLOGY

Elissavet Akrioti[1], Panos Chandris[1], Katerina Segklia[1], Konstantina Charmpi[1], Paraskevi Koutsoudaki[2], Sofia Chavaki[2], Stuart Lipton[3], Rebecca Matsas[1], Era Taoufik[1]
[1]Hellenic Pasteur Institute, Neurobiology, Athens, Greece, [2]National and Kapodistrian University of Athens, School Of Health Sciences, Athens, Greece, [3]Scripps Research and UC San Diego, Neurodegeneration New Medicines Center, La jolla, United States of America

Aims: There is an imminent need to understand how αSynuclein (αSyn) triggers degeneration, how pathology evolves and what primary pathways are impaired. In our team we characterize molecular disturbances at the mRNA and protein level, in both p.A53T-αSyn mutant mice and 2D/ 3D cellular systems derived from patients bearing the p.A53T-αSyn mutation, to determine early events in αSyn-induced pathology.
Methods: To address our aims we exploit transcriptomics, proteomics and lipidomics pproaches in both mouse and human iPSC-derived p.A53T-αSyn neurons. We perform detailed immunocytochemical analysis to characterize synaptic contacts, neurotransmission receptors and neuronal subtypes, while we examine synaptogenesis defects in vitro by using a modified artificial synapse formation assay. Monosynaptic tracing of rabies virus is used to assess neuronal connectivity. Finally we combine live cell imaging with mRNA FISH, and proximity ligation assays to detect changes in αSynuclein RNA dynamics and binding partners.
Results: Omics approaches have revealed alterations in core cellular metabolic pathways including RNA metabolism, lipid and protein biosynthesis, and synaptogenesis. We report that mouse and human p.A53T-αSyn neurons display aberrant connectivity, alterations in the numbers of excitatory and inhibitory synaptic contacts, and a largely compromised network. The early occurrence of these defects is further supported by the partial inability of p.A53T-αSyn neurons to form artificial synaptic connections. Studies in Prnp-SNCA*A53T mice show that cortical and hippocampal expression of vGLUT1 and GABA are impaired long before the reduction of dopaminergic neurons in the substantia nigra. Synaptic dysfunction is reversed when a dual -allosteric NMDAR antagonist, NitroSynapsin is used.
Conclusions: Early synaptic dysfunction is a key feature of p.A53T-αSyn mediated pathology and present compromised neuronal connectivity and synaptogenesis mRNA trafficking and localization of αSynuclein are impaired in p.A53T-αSyn neurons NitroSynapsin reverses synaptopathy in p.A53T-αSyn neurons

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OD196 / #2252

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

DNA DAMAGE AND THE ASSOCIATED CHANGES IN THE NUCLEAR PROTEASOME OF DEMENTIA WITH LEWY BODY CASES

David Koss[1], Olivia Todd[2], Daniel Erskine[2,3], Johannes Attems[2], Tiago Outeiro[4]
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Aims: Many cellular processes are known to be impaired alongside alpha-synuclein (aSyn) modification and Lewy body (LB) aggregation in dementia with Lewy bodies (DLB). Though diverse, these impeded processes are unified by the requirement of accurate gene expression. Our recent work has demonstrated an upregulation of neocortical DNA damage in DLB cases. Such widespread genomic damage may compromise the gene expression necessary for cellular homeostasis and thus contribute to the cellular dysfunction underling neurodegeneration. Here, DNA damage and the associated nuclear proteasomal changes were investigated in DLB cases.
Methods: Post-mortem human temporal cortex sections were immunohistochemically quantified for oxidative DNA damage (8-oxo-dg), single strand (SSBs; XRCC1), double stand (DSBs: yH2.AX) breaks and aSyn phosphorylation (pS129) and comparisons made between DLB and controls (n=15 each) in neuronal and non-neuronal cells. Nuclear fractionates from frozen temporal cortex (n=9 for control and DLB) were subject to quantitative proteomics. Abundance comparisons for all identified proteins (~1800) were preformed between DLB and controls and underwent GO analysis.
Results: With oxidative DNA damage measures on-going, a wide-spread increase in neuron and non-neuronal DSBs but not SSBs was observed in DLB cases. Notably, DSB levels correlate with nuclear aSyn phosphorylation. GO analysis of the altered DLB nuclear proteosome found enrichment for DNA damage recognition and histone ubiquitination (biological functions), DNA end binding and ubiquitin activating enzyme activity (molecular functions) and non-homologous end joining (KEGG pathways). Comparisons of individual protein reported alterations in key mediators of DNA damage vulnerability, endonucleases and DNA repair regulators.
Conclusions: The data suggest in the cells of the DLB affected neocortex, there is increased vulnerability to DNA damage, which despite an upregulation of repair mechanisms, leads to a wide-spread increase in DSBs.

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OD198 / #1773

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

AGE, SEX, AND LIPID METABOLISM INTERSECT TO ELICIT COGNITIVE DECLINE IN THREE MOUSE MODELS OF GBA1-PARKINSON'S DISEASE (PD) AND DEMENTIA WITH LEWY BODIES (DLB)

Quinton Hake-Volling[1,2,3], Julianna Tomlinson[2,3], Thao Nguyen[1,2,4], Victoria Hamilton[1], Nathalie Lengacher[2,3], Graeme Taylor[1], Miroslava Cuperlovic-Culf[1,5], Michael Schlossmacher[2,3], Steffany Bennett[1,2,3]
[1]Neural Regeneration Laboratory, Ottawa Institute of Systems Biology, University of Ottawa, Department Of Biochemistry, Microbiology, And Immunology And Department Of Chemistry, Ottawa, Canada, [2]University of Ottawa, Brain And Mind Research Institute, Ottawa, Canada, [3]Ottawa Hospital Research Institute, Neuroscience Program, Ottawa, Canada, [4]Centre for Catalysis Research and Innovation, Department Of Chemistry And Biomolecular Sciences, Ottawa, Canada, [5]National Research Council, Canada, Digital Technologies, Ottawa, Canada

Aims: We sought to compare how age and sex interact in (1) Gba1$^{D409V/D409V}$ knockin mice representing a *GBA1*-PD-risk model with hallmark alpha-synuclein pathology, (2) SYNERGY mice, a humanized alpha-synuclein and *Gba1*-dependent mouse model expressing four copies of the human PD mutant *SNCA* allele placed on a murine *Snca*-null background and expressing human *Gba1*$^{D409V/D409}$ and (3) *Gba1*$^{D409V/D409V}$ knockin mice crossed to N5 TgCRND8 mice representing a PD-DLB model that combines both hallmark alpha-synuclein and amyloid-beta pathologies.
Methods: We used unbiased lipidomic approaches employing nanobore high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (nLC-ESI-MS/MS) coupled to ion mobility and novel bioinformatic pathway and machine learning-based approaches to map sex-specific network disruptions at 2, 4 and 6 months of age in plasma and temporal cortex. We linked these changes to performance in a panel of behavioural tests (nest building, Y-maze, and Morris Water Maze).
Results: We quantified and characterized the phospholipid and sphingolipid compositions differentially disrupted in plasma and brain of male and female mice of each genotype. We identified defining changes in metabolism that differentially associated with cognitive decline and pathology in male and female mice.
Conclusions: Ceramide, glycerophosphocholine and glycerophosphoserine metabolism is differentially disrupted in male and female mouse models of AD, PD and DLB.

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OD199 / #1254

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

ORGAN-ON-CHIP SYSTEM TO STUDY YOUNG ONSET PARKINSON DISEASE (YOPD)

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Cedars Sinai Medical Center, Board Of Governors Regenerative Medicine Institute, Los Angeles, United States of America

Aims: Parkinson disease (PD) is complex neurodegenerative disorder in which nigral dopaminergic neurons are progressively lost resulting in a reduction of striatal dopamine levels and aggregation of intracellular proteins leading to motor and non-motor symptoms over time. The underlying molecular changes in dopamine neurons are complex and likely involve the interplay of multiple cellular systems. We have previously shown improved neuronal maturity in microfluidic devices with the incorporation of multiple cell types including astrocytes and brain microvasculature endothelial cells (BMECs). These human iPSC-derived blood-brain barrier chips provide a platform for disease modeling and drug screening. The current objective is to develop this platform into a robust and reproducible human vascularized model of YOPD to identify early metabolomic, transcriptomic, and proteomic biomarkers, and test blood-brain barrier transport of candidate therapeutics.
Methods: The chip has two channels, separated by a porous membrane. The top (neural) channel contains patient-specific iPSC-derived dopaminergic neurons and primary human midbrain astrocytes. The bottom (vascular) channel contains iPSC-derived BMECs.
Results: Our data shows that iPSC-derived dopaminergic neurons and BMECs survive in the midbrain-chip at least for 28 days, with no sign of neuronal toxicity. Each channel was analyzed by immunostaining with specific cellular markers, including Tyrosine hydroxylase (TH) for dopamine neurons, GFAP for astrocytes, and occludin for BMECs. Single nuclei RNA-sequencing demonstrates the presence of multiple cell types within the midbrain-Chip.
Conclusions: Ongoing studies include transcriptomic, metabolomic, and electrophysiological assays. Previous results in iPSC-derived dopamine neurons from patients with YOPD showed elevated α-synuclein levels. We are now testing different approaches to modulate α-synuclein levels with target therapeutic compounds delivered across the human blood-brain barrier.

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OD200 / #1534

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

CONTRIBUTION OF INNATE IMMUNITY IN NEURODEGENERATION OF PARKINSON'S DISEASE

Jae-Jin Song, Hyejin Park, Valina Dawson, Ted Dawson, Tae-In Kam
Johns Hopkins University School of Medicine, Institute For Cell Engineering/department Of Neurology, Baltimore, United States of America

Aims: Pathologic α-synuclein can spread from cell to cell contributing to the progressive pathogenesis of Parkinson's disease (PD), which causes microglia- and astrocyte-mediated neuroinflammation in a non-cell autonomous fashion. However, what drives the abnormal assembly of pathologic α-synuclein and death in neurons as well as the neuroinflammation in non-neuronal cells that are activated by pathologic α-synuclein are not known.
Methods: We determine the role of microglia-astrocyte-neuron axis in α-synuclein neurodegeneration using primary cultures and α-synuclein preformed fibrils (PFFs)-injected mouse model of sporadic PD.
Results: We showed that misfolded α-synuclein activates microglia, which release IL-6. IL-6, via its trans-signaling pathway, induces changes in the neuronal iron transcriptome that promote ferrous iron uptake and decrease cellular iron export via cellular iron sequestration response (CISR). Genetic deletion of IL-6, or treatment with the iron chelator deferiprone, reduces pathological α-synuclein toxicity in a mouse model of PD. These data suggest that IL-6-induced CISR leads to toxic neuronal iron accumulation, contributing to α-synuclein-induced neurodegeneration. In addition, activated microglia induce neurotoxic reactive astrocyte by secreting IL-1α, TNF-α and C1q and that reactive astrocytes are found in postmortem brains of human neurodegenerative diseases including PD. We showed that pathological α-synuclein contributes to formation of neurotoxic reactive astrocytes and preventing α-synuclein-induced microglial activation and reactive astrocyte conversion protected against dopaminergic neurodegeneration and behavioral deficits in a mouse model of sporadic PD. More recently, we also found that reactive astrocytes formed by oligomeric amyloid-β (Aβ) contribute to neurotoxicity and synaptic degeneration in a mouse model of Alzheimer's disease (AD).
Conclusions: Taken together, these findings demonstrate that microglia and reactive astrocytes contribute to non-cell autonomous neurodegeneration and pathogenesis of PD.

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OD201 / #1430

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

IMAGING ALPHA-SYNUCLEIN OLIGOMER IN HUMAN PARKINSON'S DISEASE BRAIN TISSUES

Ru Tian[1], Bin Fu[2], Christina Toomey[3], Lucien Weiss[4], Sonia Gandhi[5], Steven Lee[2], Michele Vendruscolo[1]
[1]University of Cambridge, Center For Misfolding Diseases, CAMBRIDGE, United Kingdom, [2]University of Cambridge, Department Of Chemistry, CAMBRIDGE, United Kingdom, [3]University College London, Queen Square Brain Bank For Neurological Disorders, London, United Kingdom, [4]École Polytechnique de Montréal, Department Of Engineering Physics, Montreal, Canada, [5]UCL, Institute Of Neurology, London, United Kingdom

Aims: To date, the molecular origins of PD are not fully understood and no disease-modifying treatments are available. Lewy bodies are relatively inert, smaller soluble assemblies of α-synuclein, referred to as oligomers, are likely to be actively neurotoxic. Therefore, investigating the role of α-synuclein oligomers in PD is a matter of urgency. Given their heterogeneous and transient nature, exploring them at single-molecule level is necessary to define their properties and mechanisms of toxicity for diagnostic and therapeutic interventions. To address this problem, we are using state-of-the-art microscopy techniques to analyze α-synuclein oligomers in PD human brain tissue. Our aim is to generate the first oligomer PD brain map. In the broader context of the Aligning Science Across Parkinson's program, the PD brain map will enable us to develop new hypotheses, explore disease mechanisms and identify new therapeutic targets.
Methods: The images were on a fluorescence microscope with a highly inclined and laminated optical sheet (HILO) at different z positions. The data analysis was carried out with Fiji/ImageJ software for images display and analysis, and matlab codes for aggregates measurement and statistics analysis
Results: Autofluorescence was highly variable across brain regions and cases and was quenched effectively with Sudan Black at 0.1% for 10 minutes. A variety of alpha-synuclein aggregates were detected ranging from diffraction-limited spots (approx. 200nm) to Lewy bodies. Aggregates were visualized and the co-incidence of various alpha-synuclein antibodies was detected with multiple different cell types, additional aggregated proteins, and different post-translational modifications.
Conclusions: Initial analysis highlights that the oligomeric forms of alpha-synuclein in the form of diffraction-limited spots are phosphorylated and once larger may become ubiquitinated. Further investigation into the characteristics of these puncta will reveal what role these putative oligomers play in disease.

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OD202 / #1107

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

INCREASED SER31 TYROSINE HYDROXYLASE PHOSPHORYLATION IN SUBSTANTIA NIGRA, NOT STRIATUM, MITIGATES DOPAMINE LOSS AND DELAYS ONSET OF PARKINSONIAN SIGNS: NOVEL INSIGHT INTO A LONG-STANDING QUESTION

Michael Salvatore[1], Jason Richardson[2], Ella Kasanga[1], Walter Navarrete[1], Yoonhee Han[2], Robert Mcmanus[1], Vicki Nejtek[1]
[1]University of North Texas Health Science Center, Pharmacology & Neuroscience, Fort Worth, United States of America, [2]Florida International University, Robert Stempel School Of Public Health And Social Work, Miami, United States of America

Aims: We compared progression of tyrosine hydroxylase versus dopamine loss between striatum and substantia nigra against the timing of parkinsonian sign onset using hemi-parkinsonian 6-OHDA rat model, and if tyrosine hydroxylase phosphorylation mitigated dopamine loss, despite tyrosine hydroxylase loss.
Methods: 65 male Sprague-Dawley rats were used to assess changes in dopamine tissue content, tyrosine hydroxylase (TH) protein, ser31 and ser40 TH phosphorylation stoichiometry, D1 receptor in striatum and substantia nigra (SN), and TH-positive neurons following induction of nigrostriatal lesion by unilateral 6-OHDA infusion into medial forebrain bundle. To determine if unilateral 6-OHDA lesion affected dopamine-related measures contralateral to lesion, a sham-operated group was included. Locomotor functions were evaluated in a day 7 and day 28 post-lesion cohort. Parkinsonian signs (forelimb use, open-field activity) were evaluated pre-lesion and at day 7 post-lesion in both cohorts, and at day 14, 21, and 28 days in the day 28 cohort.
Results: Forelimb use deficits occurred 7 days after lesion induction, preceding locomotor activity deficits at day 21. At 7 days post-lesion, >90% TH and dopamine loss occurred in striatum, whereas in SN, no dopamine loss occurred despite ~60% TH protein loss, and TH cell loss of lesser degree. By day 28, nigral TH loss increased >80%, and progressed contralateral to lesion, but DA loss was significantly less in lesioned SN, with no loss in contralateral SN. Ser31, but not ser40, TH phosphorylation increased in the SN at both time points and contralateral SN at day 28. D1 receptor expression increased in SN ipsilateral to lesion by day 28.
Conclusions: Augmented dopamine signaling in substantia nigra, not striatum, through increased ser31 TH phosphorylation and D1 receptor expression, compensates for progressive TH protein and cell loss to mitigate severity of parkinsonian signs.

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OD203 / #645

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

GENETIC AND PHARMACOLOGICAL REDUCTION OF CDK14 MITIGATES SYNUCLEINOPATHY.

Konrad Ricke[1], Jean-Louis Parmasad[1], Benjamin Nguyen[1], Haley Geertsma[1], Amanda Bruce[1], Steve Callaghan[1], William Stanford[1], Morgan Stykel[2], Brodie Buchner-Duby[2], Nathalie Lengacher[3], Julianna Tomlinson[3], Eric Lian[4], Alvin Joselin[5], Jiyan Ma[6], Patrik Brundin[6], Scott Ryan[2], Michael Schlossmacher[7], Maxime Rousseaux[1]
[1]University of Ottawa, Department Of Cellular And Molecular Medicine, Ottawa, Canada, [2]University of Guelph, Department Of Molecular And Cellular Biology, Guelph, Canada, [3]University of Ottawa, Brain And Mind Research Institute, Ottawa, Canada, [4]Ottawa Institute for Systems Biology, Faculty Of Medicine, Ottawa, Canada, [5]Hotchkiss Brain Institute, Department Of Clinical Neurosciences, Calgary, Canada, [6]Van Andel Institute, Department Of Neurodegenerative Science, Grand Rapids, United States of America, [7]Ottawa Hospital Research Institute, Program In Neuroscience, Ottawa, Canada

Aims: Parkinson's disease (PD) is an incurable neurodegenerative disease characterized by the loss of dopaminergic neurons and the abnormal accumulation of α-Synuclein (α-Syn) protein. Multiplications of the α-Syn gene cause PD syndromes and α-Syn-overexpressing animal models replicate PD features. Decreasing total α-Syn levels, therefore, is an attractive approach to decelerate neurodegeneration in patients. We previously performed a genetic screen for α-Syn modifiers, and found CDK14, a brain-enriched kinase of largely unknown function as a regulator of α-Syn dosage. Here, we aim to explore the effect of reducing CDK14 on α-Syn pathology and its sequelae in cell and animal models of PD.
Methods: To test the potential therapeutic effects of CDK14 reduction, we genetically decreased Cdk14 in two PD mouse models and in human neuronal culture. Next, we utilized a new specific CDK14-inhibitor, FMF-04-159-2, to analyze if pharmacological inhibition of CDK14 affects α-Syn dosage *in vitro*. Finally, we delivered FMF-04-159-2 into mice expressing human α-Syn, to test whether CDK14 inhibition affects cerebral α-Syn content *in vivo*.
Results: We found that genetically targeting Cdk14 *in vivo* mitigated α-Syn pathology and neuropathological sequelae, without causing untoward phenotypes, and silencing *CDK14* in human neuronal culture decreased pathogenic α-Syn. Importantly, pharmacological CDK14 inhibition reduced α-Syn levels in human neurons. Similarly, intracerebral administration of FMF-04-159-2 into mice decreased amounts of pathogenic α-Syn without inducing any signs of discomfort.
Conclusions: Here, we show that genetic reduction of Cdk14 mitigated α-Syn pathology and neurotoxicity in two distinct PD mouse models. These benefits of decreasing CDK14 on α-Syn pathology translated from mouse to human neurons. Importantly, pharmacological CDK14 inhibition reduced α-Syn pathology *in vitro* and *in vivo*. We conclude that targeting CDK14 function holds promise as a potentially disease-modifying approach to treat PD.

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OD204 / #1416

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

THE NOVEL THERAPEUTIC LIGAND TARGETING FATTY ACID-BINDING PROTEIN 3 PREVENTS ALPHA-SYNUCLEIN ACCUMULATION AND COGNITIVE-MOTOR IMPAIRMENTS IN LEWY BODY DISEASE-MODEL MICE

Ichiro Kawahata[1], Kohji Fukunaga[2]
[1]Tohoku University, Cns Drug Innovation, Sendai, Japan, [2]BRI Pharma Inc, R/d, Sendai, Japan

Aims: Aging society leads to an increase in patients with Parkinson's disease (PD) and dementia with Lewy bodies (DLB), which are neurodegenerative disorders characterized by motor and memory impairments. Brain accumulation of the causative protein α-synuclein is a pathological hallmark of these Lewy body diseases. We previously demonstrated that FABP3 is critical for intracellular uptake of α-synuclein coupled with dopamine D2 receptors and the accumulated protein-induced neurotoxicity in dopaminergic neurons. Therefore, we generated FABP3-specific ligands and examined the potential therapeutic ability of the drug candidates.
Methods: We employed FABP3$^{-/-}$ or wild-type C57BL6 mice and orally administrated FABP3 ligands to examine the preventing ability of α-synuclein propagation and intracellular accumulation. The therapeutic effect on the motor and cognitive impairments was analyzed by behavioral tests. Primary cultured mesencephalic neurons were also prepared from the mice. All the experiments were practiced under the approval of the Institutional Laboratory Animal Care and Use Committee of Tohoku University.
Results: FABP3$^{-/-}$ mice showed no nigrostriatal propagation of ATTO fluorescence-labeled-α-synuclein and no intracellular accumulation of the protein in dopaminergic neurons *in vivo*. Furthermore, FABP3-specific ligand attenuated α-synuclein propagation and aggregation. Detailed analysis using primary midbrain dopaminergic neurons revealed that the ligand prevented α-synuclein uptake and neuronal toxicity. The ligand also ameliorated cognitive and motor impairments in Lewy body disease-model mice to recover to healthy control levels *in vivo*.
Conclusions: These data indicate that FABP3 is a novel therapeutic target for Lewy body diseases, and the FABP3 ligand is a potential therapeutic drug for PD and DLB to recover motor and memory impairments by preventing α-synuclein propagation.

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OD205 / #1030

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

COLONIC ORGANOTYPIC CULTURES ISOLATED FROM A PRODROMAL PD MOUSE MODEL SHOW ABNORMAL ELECTRICAL ACTIVITY LINKED TO A SUSTAINED CA2+ SIGNALING.

Jessica Grigoletto*[1], Fabiana Miraglia*[1], Caterina Sorteni[1], Mary Conrad[2], Eleonora Crocco[1], Rebecca Senter[2], Federico Cremisi[1], Antonino Cattaneo[1], Stewart Campbell[2], Emanuela Colla[1]
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Aims: To gain insight into the role of the brain-gut axis in Parkinson's Disease (PD), we investigated functional aspects of enteric organotypic cultures isolated from a transgenic (Tg) mouse model with demonstrated prodromal, intestinal dysfunction.
Methods: Enteric cultures were obtained from the colonic myenteric plexus of Prp-A53T α-synuclein (αS) Tg mice and controls and grew on poly-lysine coated slides chambers for up to 5 weeks.
Results: We have successfully established healthy enteric colonic cultures from young and adult αS Tg mice and controls. Cyto-architecture of colonies immunostained with neuronal, glial and muscle markers confirmed a cytoarchitectural organization typical of an organotypic culture, resembling the structure of the colon *in vivo*, with muscle cells lying underneath and neurons and glia growing on top. Characterization of cell types was also determined, confirming consistently a predominance of muscle cells (45±7%), followed by glia (37.3±0.9%) and neurons (17.7±6%). No major differences in cell composition, survival and cyto-organization were found between colonies isolated from Tgs and controls or from young vs older animals. Differently when spontaneous and chemical-evoked synaptic potential was assayed as a function of Ca^{2+} activity, colonies from Tgs showed electrical abnormalities linked to a sustained increased in Ca^{2+} signaling with aging followed by a scarce excitability once stimulated. Notably cultures from Tgs bear neuronal, aggregated αS and aggregation could be further increased by exogenous administration of αS pre-formed fibrils.
Conclusions: We believe that colonic organotypic cultures can be a valuable translational system to evaluate the impact of αS aggregation on enteric neuronal function.

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OD206 / #2560

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

MOTOR DYSFUNCTION AND CORTICAL ATROPHY IN MICE WITH CONSTITUTIVE NUCLEAR ACCUMULATION OF ENDOGENOUS ALPHA-SYNUCLEIN, INDEPENDENT OF PROTEIN AGGREGATION

Haley Geertsma, Terry Suk, Konrad Ricke, Kyra Horsthuis, Jean-Louis Parmasad, Zoe Fisk, Steve Callaghan, Maxime Rousseaux
University of Ottawa, Department Of Cellular And Molecular Medicine, Ottawa, Canada

Aims: A growing body of evidence suggests an accumulation of nuclear aSyn plays a role in the pathogenesis of Parkinson's disease (PD). However, previous efforts used to tease out the role of nuclear aSyn in neurodegeneration have relied on overexpression, affecting its aggregation propensity and thereby clouding data interpretation. I aim to create a model to better understand the role of nuclear aSyn and to determine its mechanisms of toxicity.
Methods: We engineered a mouse line in which endogenous aSyn is localized to the nucleus via a nuclear localization signal (NLS; *Snca*^{NLS}). We characterized these mice on a behavioral, histological, and biochemical level and recorded the progression of disease in young (2-3 months), mid-aged (8-9 months), and aged (18-19 months) mice.
Results: The *Snca*$^{NLS/NLS}$ mice exhibit age-dependent motor deficits in rotarod, adhesive test, and beam break, and decreased survival rate. Histological analyses revealed motor cortex atrophy, specific to layers 5/6, in the absence of midbrain dopaminergic neurodegeneration. Additionally, there was no significant aSyn pathology, suggesting these phenotypes are not tied to pathologically aggregated aSyn. We also sampled cortical proteomes of *Snca*$^{NLS/NLS}$mice to determine the molecular underpinnings of these pathologies. Interestingly, we found several dysregulated proteins involved in dopamine signaling, including Darpp-32, Pde10a, and Gng7, which we further confirmed were decreased in the *Snca*$^{NLS/NLS}$ cortical samples via immunoblotting.
Conclusions: These results suggest that chronic endogenous nuclear aSyn can elicit a neomorphic toxic effect in mice. This model raises key questions related to the mechanism of aSyn toxicity in PD and provides a new model to study an underappreciated aspect of disease. We are now exploring the molecular mechanisms underlying nuclear aSyn toxicity, to ultimately shed light on this pathway in the context of PD.

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OD207 / #2567

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

METABOLOMIC RESEARCH OF INFLAMMATORY COMPONENT ASSOCIATED TO ALZHEIMER DISEASE USING TRANSGENIC MOUSE MODEL APP/PS1/IL4-KO

Jose Luis Gomez-Ariza
University of Huelva, Chemistry, Huelva (Spain), Spain

Aims: To study the influence of inflammatory processes in the pathological mechanisms underlying Alzheimer disease and the discovery of potential diagnosis biomarkers.
Methods: Direct infusion mass spectrometry (DI-ESI-MS and FIA-APPI-MS) were applied for serum analysis (polar and non-polar extracts) of two transgenic mouse (C57BL/6 background): APP/PS1 and APP/PS1/IL4-KO, which are compared with age-matched wild-type mice (C57BL/6).
Results: Transgenic (APP/PS1/IL4 and APP/PS1) and wide type (WT) mice were clearly classified applying PLSDA multivariant analysis to DI-QTOF-MS data, which has been used to decipher the mechanisms associated to AD-type disorders in response with interlukin-4 deficiency. In this way, a number of metabolites are significantly perturbed in both APP/PS1/IL4 and APP/PS1 mice, including different amino acids (threonine, aspartic acid, tyrosine), eicosanoids (HEPE, prostaglandins, leukotriene B4) and other compounds (urea, citrulline, histamine, 1-methylhistamine, urocanic acid, dopamine), while only dopamine allowed to differentiate between the two transgenic lines. However, it is noteworthy that some of these metabolites suffered a gradual change between the three groups considered in this study (from WT to APP/PS1, and finally APP/PS1/IL4).
Conclusions: The depletion of interleukin 4 may potentiates the pathology in the APP/PS1 mouse model of AD. Metabolic fingerprinting revealed significant alterations in levels of 13 metabolites (urea, histamine, threonine, 1-methylhistamine, aspartic acid, urocanic acid, dopamine, citrulline, tyrosine, HEPE, prostaglandins and leukotriene B4), which could be related to abnormalities in different metabolic pathways. Thus, the most important failures might be associated with impaired biosynthesis of histamine, altered metabolism of amino acids, deregulated urea cycle and increased production of pro-inflammatory eicosanoids.

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OD208 / #1933

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

ENDOLYSOSOMAL PATHWAYS IN THE PROTEINOPATHIES: STRATEGIES TO INHIBIT AXONAL AGGREGATE FORMATION TO RESTORE NEURONAL FUNCTION

Sandra Encalada[1,2], Romain Chassefeyre[3], Tai Chaiamarit[3], Adriaan Verhelle[3], Yin Wu[3], Sammy Weiser Novak[4], Leonardo Andrade[4], Uri Manor[4], Rachel Botham[5], Leonard Yoon[5], Jeffery Kelly[5]
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Aims: Intra-axonal accumulations of misfolded protein aggregates inside dystrophic axons are a hallmark of virtually all neurodegenerative disorders. Importantly, these aggregates form at early disease stages, and have been linked to pathogenic events. How intra-axonal aggregates form will inform on strategies to inhibit their formation and circumvent neuronal dysfunction, but these pathways remain unidentified.
Methods: Using biochemical, ultrastructural and light imaging microscopy, genetics, and cell biological approaches, we uncovered an endolysosomal pathway that regulates the formation of toxic aggregates of a mutant prion protein (PrP^{mut}) along mammalian axons.
Results: In this **a**xonal **r**apid **e**ndosomal **s**orting and **t**ransport-dependent **a**ggregation (ARESTA) pathway, the endolysosomal GTPase Arl8b recruits kinesin-1 and Vps41(HOPS) onto Golgi-derived endosomes carrying misfolded PrP^{mut}, to promote their relocation from the neuronal soma into the axon, where they undergo homotypic fusion and aggregation inside enlarged endo-membranes that we call endoggresomes. Axonal endoggresomes impair calcium dynamics and reduce neuronal viability via selectively impairing the microtubule cytoskeleton and organelle-organelle interactions at endoggresome toxicity 'hubs' or axonal swellings along axons. Reducing the function of ARESTA components genetically and pharmacologically with lysosomal flux/autophagy small molecule activators inhibits endoggresome formation in axons of cultured neurons, and circumvents neuronal toxicity and neuronal death. In mouse models of PrP^{mut} disease that display prominent astroglyosis and neuronal degeneration, reducing the function of ARESTA components genetically inhibits formation of aggregates in mouse brains, and reduced brain pathological lesions.
Conclusions: These data strongly suggest that ARESTA is an anti-aggregation target amenable to therapeutic modulation.

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OD208a / #1547

ON-DEMAND SYMPOSIUM: ALPHA-SYNUCLEINOPATHIES: ALPHA-SYNUCLEIN PATHOGENESIS, DOPAMINE, ANIMAL MODELS, ORGANOIDS
31-03-2023 07:00 - 08:30

COMBINED TWO-PHOTON-BASED IMAGING OF STRIATAL DOPAMINERGIC FIBERS AND INTEGRATIVE ASSESSMENT OF SYNAPTIC MARKERS ALLOWS TO STAGE RETROGRADE DEGENERATION IN A-SYNUCLEIN TRANSGENIC MICE

Gaia Faustini[1], Viviana Brembati[1], Alberto Brugnoli[2], Michele Morari[2], Maria Grazia Spillantini[3], Marina Pizzi[1], Arianna Bellucci[1]
[1]University of Brescia, Department Of Molecular And Translational Medicine, Brescia, Italy, [2]University of Ferrara, Department Of Neuroscience And Rehabilitation, Ferrara, Italy, [3]University of Cambridge, Clinical Neuroscience, Cambridge, United Kingdom

Aims: Early prodromal phases of Parkinson's disease (PD) are characterized by pathological deposition of α-synuclein (α-syn) microaggregates at synaptic terminals of the nigrostriatal system. This phenomenon may be at the basis of a progressive synapse-to-cell-body degeneration, but we still ignore how the deposition of α-syn microaggregates can gradually trigger retrograde neuronal loss. In this study, we used a well-established model of PD, mice overexpressing the truncated form of α-syn on the C57BL/6JOlaHsd background (SYN120 tg), exhibiting progressive deposition of α-syn fibrillary microaggregates in nigrostriatal terminals with dopamine release deficits, to stage the retrograde degeneration of dopaminergic neurons.
Methods: Immunofluorescence, two-photon microscopy and microdialysis were used to study the nigrostriatal system of SYN120 tg and C57BL/6J mice at 8, 10 and 12 months of age.
Results: In 8- and 10-month-old SYN120 tg mice we detected an early loss of vesicular monoamine transporter 2 (VMAT2) without dopamine release deficits or alterations of tyrosine hydroxylase (TH) and dopamine transporter (DAT) immunolabeling compared to C57BL/6J animals. Later, 12-month-old SYN120 tg mice showed dopamine release drop and dopamine turnover perturbation accompanied by a paradoxical dysfunctional DAT increase confirmed by vertical microdialysis and a patchy striatal fibers deafferentation detected by 3D two-photon microscopy of whole dorsal striata.
Conclusions: These data support that the progressive accumulation of α-syn at nigrostriatal terminals in the prodromal stages of PD produces a very early loss of VMAT2 that anticipates the synaptic dopamine release deficits. Moreover, they support that the initial phase of pathological α-syn-induced dopaminergic dysfunction is characterized by dopamine turnover perturbation with accumulation of dysfunctional DAT and that these pre-degenerative synaptic alterations can initiate nigrostriatal deafferentation.

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OD209 / #1442

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN PD AND LBD PRECLINICAL AND CLINICAL DRUG DEVELOPMENT
31-03-2023 07:00 - 08:30

DISCOVERY OF THERAPEUTIC SMALL MOLECULES TARGETING ALPHA-SYNUCLEIN AGGREGATION

Elpida Tsika, Nadine Ait-Bouziad, Nicolas Dreyfus, Coralie Vallet, Leonida Maliqi, Lorène Aeschbach, Sylvain Pautet, Sebastien Menant, Johannes Brune, Irina Borovko, Alexis Fenyi, Clarisse Schumer, Thomas Jaquier, Nicolas Fournier, Heiko Kroth, Sonia Poli, Andrea Pfeifer, Marie Kosco-Vilbois
AC Immune SA, Research, Lausanne, Switzerland

Aims: Parkinson's disease (PD) and other neurodegenerative diseases (NDD) involve an accumulation of alpha-synuclein (a-syn) aggregates that correlates with clinical manifestations. The aim of our work is to discover cell-permeable, orally bioavailable and brain penetrant small molecules that inhibit aggregation and intracellular accumulation of pathological a-syn as a treatment for PD and NDDs.
Methods: Using our unique, proprietary Morphomer® platform, small molecules were designed, screened and characterized in assays to evaluate inhibition of a-syn aggregation. These included biochemical approaches to assess a-syn solubility and β-sheet content, and cell-based assays to study effects of accumulating a-syn aggregates within living cells. Pharmacokinetics, brain exposure and tolerability were evaluated in mice after single and repeated dosing while efficacy was demonstrated *in vivo* in a spreading model of a-syn using transgenic mice inoculated with human a-syn preformed fibrils (tg hPFF mice).
Results: Through iterative medicinal chemistry and screening cycles, several compound series were identified that reduced both β-sheet content and aggregate size, preventing the transition of a-syn into insoluble conformations. Certain compounds also reduced the formation of intracellular aggregates in neurons with nanomolar IC_{50} values and specifically bind to aggregated a-syn, over monomer, with nanomolar dissociation constants. An orally bioavailable and brain penetrant compound was progressed in vivo demonstrating reduction of a-syn pathology in the brains of tg hPFF mice.
Conclusions: Establishing robust screening assays and exploring our Morphomer® platform of small molecules with concerted medicinal chemistry efforts has led to the discovery of a brain penetrant compound that alters a-syn pathology in a mouse model of PD. This series and others will be further developed in order to identify an optimized lead candidate to move into IND enabling activities.

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OD210 / #861

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN PD AND LBD PRECLINICAL AND CLINICAL DRUG DEVELOPMENT
31-03-2023 07:00 - 08:30

GARDENIN A DECREASES NEUROINFLAMMATION, ACTIVATES ANTIOXIDANT RESPONSE AND IMPROVES COGNITIVE AND MOTOR FUNCTION IN A53T ALPHA SYNUCLEIN OVEXPRESSING MICE

Nora Gray[1], Wyatt Hack[1], Noah Kolarsky[1], Urmila Maitra[2], Lukasz Ciesla[2]
[1]Oregon Health & Science University, Neurology, Portland, United States of America, [2]University of Alabama, Biological Sciences, Tuscaloosa, United States of America

Aims: To investigate the neuroprotective, cognitive and motor effects the novel PD therapeutic agent Gardenin A in the A53T alpha synuclein (A53TSyn) mouse model of alpha synuclein accumulation. Previous work by our group has shown that oral treatment with Gardenin A protected dopaminergic neurons and improved mobility in a *Drosophila* model of PD. These effects appeared to be mediated by a combination of antioxidant and anti-inflammatory effects. Here we evaluate the effects of Gardenin A in a mammalian PD model.
Methods: Five month old A53TSyn mice were treated with Gardenin A orally at 0, 25 or 100 mg/kg. After two weeks of treatment cognitive and motor testing were initiated and treatment continued throughout the duration of testing for a total of four weeks. At the conclusion of treatment brain tissue was harvested synaptic, antioxidant and pro-inflammatory markers were evaluated by gene expression. Immunohistochemistry is also underway to investigate alpha synuclein pathology and dopaminergic activity. All results were compared to age-matched, vehicle treated WT littermates.
Results: High dose Gardenin A (100mg/kg) attenuated motor and cognitive deficits apparent in the A53TSyn mice. Gardenin A also increased expression of synaptic and antioxidant genes in the cortex of treated A53TSyn mice and decreased expression of pro-inflammatory genes. Immunohistochemical analysis of alpha synuclein pathology and dopaminergic activity is ongoing.
Conclusions: These data support the existing *Drosophila* evidence of a neuroprotective effect of oral Gardenin A in the context of PD and show that similar effects can be observed in a mammalian system and that the same underlying mechanisms may be responsible. Future studies are needed to further optimize this promising therapeutic agent for translation to clinical testing.

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OD211 / #2332

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN PD AND LBD PRECLINICAL AND CLINICAL DRUG DEVELOPMENT
31-03-2023 07:00 - 08:30

AG490 TREATMENT RECOVERS GLIAL MORPHOLOGY IN A MOUSE MODEL OF PARKINSON'S DISEASE

Ana Ferreira, Luiz Britto
Universidade de São Paulo, Physiology And Biophysics, São Paulo, Brazil

Aims: The Transient Receptor Potential Melastatin 2 (TRPM2) is a calcium channel activated by oxidative stress. TRPM2 has been suggested to be involved in neurodegeneration. However, little is known about its participation in Parkinson's disease (PD). The aim of this study was to evaluate the impact of TRPM2 in PD.
Methods: We used the TRPM2 inhibitor AG490 in the 6-hydroxydopamine (6-OHDA) mouse model of PD. Animals underwent stereotaxic surgery for 6-OHDA administration in the right striatum. AG490 was injected intraperitoneally from day 3 to 6 after surgery. The animals then underwent motor behavioral tests (apomorphine and rotarod test) (n=12/group) on days 3 and 6, and euthanasia on day 7. Immunofluorescence (n=6/group) was performed for dopaminergic neurons (tyrosine hydroxylase, TH)), for microglia (Iba-1), and for astrocytes (GFAP) in the substantia nigra. Morphological analyses were performed in FIJI software by Skeleton and FracLac plugins.
Results: On day 3, before treatment, animals that received 6-OHDA had motor deficits (+130 rotations, $p<0.001$; 3±0.78 number of falls, $p=0.040$; and 26±10 seconds to fall, $p=0.001$) and reduced number of TH-positive cells (54±3%, $p<0.01$), which indicated an impaired dopaminergic system. Morphological analyses revealed that the 6-OHDA group had impaired glial cells (reduced endpoint, branch length, fractal dimension, lacunarity, and circularity, but an increased density and span ratio, $p<0.01$) with ameboid-like shapes, which indicated an activated state of both microglia and astrocytes. On day 6, after treatment, the 6-OHDA+AG490 group showed improvement of motor behavior ($p=0.001$ for apomorphine and $p=0.044$ for rotarod), a higher number of TH neurons (73±2, $p<0.01$), and recovered microglia and astrocyte morphology ($p<0.01$).
Conclusions: AG490 treatment thus appears to protect glial morphology in a PD mouse model. Inhibition of TRPM2 might then represent a therapeutical possibility for PD.

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OD212 / #1677

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN PD AND LBD PRECLINICAL AND CLINICAL DRUG DEVELOPMENT
31-03-2023 07:00 - 08:30

PROTEOMIC AND PHOSPHOPROTEOMIC ANALYSIS OF METFORMIN-MEDIATED PROTECTION AGAINST METHAMPHETAMINE-INDUCED DAMAGE IN NONHUMAN PRIMATES: IMPLICATIONS FOR PARKINSON'S DISEASE

Jennifer Blackburn[1], Daniel Curry[2], Bernardo Xavier[3], Robert Roth[2], John Elsworth[1]
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Aims: There are currently no treatments that can preserve the dwindling population of dopamine (DA) neurons in Parkinson's disease (PD). As PD is a multifactorial disorder, therapies with pleiotropic actions may offer superior clinical potential, such as the anti-diabetic drug metformin. Metformin influences many cellular pathways, including AMP-activated kinase (AMPK) signaling, which plays a crucial role in maintaining cellular energetic homeostasis, and the Akt pathway, which regulates diverse functions including cell growth, survival, proliferation and differentiation. Preclinical studies have indicated that metformin can protect DA neurons from parkinsonian-like damage, however, the mechanism responsible is not known**.** Our obective is to delineate metformin's protective mechanisms on DA neurons in nonhuman primate brain
Methods: African green monkeys were treated daily with oral metformin for 4 weeks (12.5 mg/kg for 1 week, then 25 mg/kg for 3 weeks). A subset of monkeys were also treated with the dopaminergic toxin, methamphetamine (METH) one week prior to terminus (0.5 mg/kg on day 22, 1.0 mg/kg on day 23). In several brain regions, we performed label-free quantification of proteome and Ti-O2 enriched phosphoproteome analysis in addition to measurements of DA concentration by HPLC.
Results: Metformin treatment reduced METH-induced dopaminergic toxicity in selective brain regions, including substantia nigra (SN) and dorsolateral prefrontal cortex. In the SN we detected 3102 proteins and 2570 phosphoproteins with a false discovery rate <1%. Pathway analysis of differentially regulated proteins indicated that relevant metformin-induced changes depended on METH-exposure: AMPK and Akt pathways were only activated in monkeys treated with both metformin and METH, as were mTOR and Nrf2 signalling pathways.
Conclusions: Metformin preferentially promotes specific aspects of mitochondrial function, antioxidant function, cell growth and survival under conditions of dopaminergic stress in primate brain.

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OD214 / #1146

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN PD AND LBD PRECLINICAL AND CLINICAL DRUG DEVELOPMENT
31-03-2023 07:00 - 08:30

PRECLINICAL DEVELOPMENT OF NEU-723, A LRRK2 INHIBITOR FOR THE TREATMENT OF PARKINSON'S DISEASE

Stephen Wood
Neuron23, Discovery Research, S. San Francisco, United States of America

Aims: To develop a potent, selective, brain penetrant small molecule inhibitor of LRRK2 with drug-like properties for the treatment of Parkinson's Disease (PD).
Methods: Small molecule inhibitors of LRRK2 were optimized for potency and selectivity along with a host of pharmacokinetic (PK) properties using traditional medicinal chemistry and computational/structural chemistry methods. Structure-activity relationships were driven by data from biochemical, cellular and in vivo model systems.
Results: NEU-723 is a potent inhibitor of LRRK2 with a single digit nM IC_{50} in biochemical assays and a low double-digit nM IC_{50} in cellular assays, including ex vivo human PBMCs. It is equipotent on WT and the G2019S variant of LRRK2 and shows roughly equivalent potency across human, rodent and NHP LRRK2. NEU-723 displays high levels of selectivity across the kinome and also across the phosphodiesterase family. The molecule shows excellent PK properties with distribution to the CNS which leads to robust target engagement (TE) in preclinical in vivo studies. NEU-723 shows TE in brain and blood in rats and NHPs with EC_{50}s consistent with the cellular IC_{50}. In preclinical, 10d dose-range-finding tox studies, NEU-723 is well tolerated up to AUC-based exposure multiples of 60x in rats and NHPs. 28d GLP studies have been completed and the molecule is expected enter human clinical trials in Q1-2023.
Conclusions: NEU-723 is a potent and selective LRRK2 inhibitor both in vitro and in vivo. These properties, combined with favorable PK and preclinical safety profiles make it an excellent candidate for clinical development.

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OD215 / #2004

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN PD AND LBD PRECLINICAL AND CLINICAL DRUG DEVELOPMENT
31-03-2023 07:00 - 08:30

MONTELUKAST INDUCES HOMEOSTATIC MICROGLIA AND IMPROVES MOTOR COORDINATION AND BALANCE IN THE LINE 61 MOUSE MODEL OF PARKINSON'S DISEASE

Ludwig Aigner[1], Katharina Strempfl[2], Barbara Altendorfer[1], Heike Mrowetz[1], Stefanie Flunkert[3], Joerg Neddens[4], Nadine Paiement[5], Horst Zerbe[6], Rodolphe Poupardine[7], Per Svenningsson[8], Johan Wallin[8], Birgit Hutter-Paier[4]
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Aims: Increasing scientific evidence suggests that dysregulation of inflammatory leukotriene signaling is involved in the pathogenesis of various neurodegenerative disorders including Parkinson's Disease (PD). Leukotrienes, lipid mediators of inflammation, are originally known for their role in asthma. We investigated whether Montelukast (MTK), a cysteinyl leukotriene receptor antagonist and approved anti-asthmatic drug, could impact motor impairments in the Line 61 mouse model of PD.
Methods: Line 61 mice and non-transgenic littermates were treated daily orally with MTK (10mg/kg) or vehicle using a mucoadhesive film formulation. The treatment was started 2 weeks of age and continued for a total of 10 weeks. Motor behavior was assessed with the beam walk test in treatment weeks 5 and 10. Brains were collected for further immunohistochemical and biochemical analyses.
Results: Comparing MTK-treated and vehicle-treated Line 61 mice, the numbers of slips off the beam and slips per speed were significantly decreased already in treatment week 5 and traversing time significantly decreased by treatment week 10. Immunohistochemical analyses of the striatum and cerebellum show that MTK reduced soma sizes and increased ramification of microglia. Transcriptomic and qPCR analyses revealed that striatal and cerebellar levels of serum/glucocorticoid-regulated kinase 1 (SGK1), a possible activator of inflammatory NF-κB signaling, decreased after MTK treatment. Western Blot experiments for validating the levels of SGK1 and NF-κB-related proteins are ongoing.
Conclusions: Although microgliosis and neuroinflammation are not a prominent feature of the Line 61 mouse model, anti-inflammatory treatment via MTK seems to induce a homeostatic shift in microglia and might even affect NF-κB signaling downstream of SGK1. Together with the observed ameliorations in motor coordination and balance MTK could be a suitable drug candidate for repurposing in the treatment of PD.

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ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN PD AND LBD PRECLINICAL AND CLINICAL DRUG DEVELOPMENT
31-03-2023 07:00 - 08:30

ASO THERAPY FOR PRION DISEASE

Hien Zhao[1], Holly Kordasiewicz[1], Eric Minikel[2], Sonia Vallabh[2], Deborah Cabin[3], Jill O'Moore[3]
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Aims: To evaluate plasma neurofilament light chain (NfL) response, a disease biomarker of neuroaxonal injury, and survival effects in the RML prion mouse model following treatment with a PrP-lowering antisense oligonucleotide (ASO)
Methods: Groups of N = 12 wildtype C57BL/6N mice were inoculated with RML prions and received either PrP ASO or saline via CSF delivery at 60 days or 120 days post infection (dpi), while uninoculated mice were included as controls. These ASO dose levels correspond to roughly 20-60% *Prnp* mRNA knockdown based on prior studies (Minikel et al., 2020). At 60 dpi, plasma NfL is elevated, prion pathology is established and neuroinflammation is increasing; overt behavioral phenotypes typically develop by 125 dpi (Minikel et al., 2020). Plasma NfL was quantified from bleeds taken at 1-day pre-ASO treatment, then every 30 days onward. Animals were followed to the terminal disease endpoint, as defined by 20% weight loss compared to baseline 60 dpi, or death.
Results: Plasma NfL levels steadily rose through terminal illness in RML-inoculated mice treated with saline and remained unchanged in uninoculated animals. A dose-dependent delay in plasma NfL rise was observed in RML-inoculated mice treated with a single adminstration of ASO at 60 dpi, which corresponded to a dose-dependent extension in survival of up to 40%. In an RML-inoculated cohort where treatment was initiated at 120 dpi, plasma NfL levels fell significantly in ASO-treated mice compared to the pre-dose time point, suggesting a reversal of pathology driving the 35% - 53% increase in survival time to terminal endpoint.
Conclusions: These data support the use of plasma NfL as a disease biomarker indicative of disease state, as it correlates with disease course and with clinical benefit in prion mouse model following ASO-mediated PrP lowering.

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OD218 / #771

ON-DEMAND SYMPOSIUM: THERAPEUTIC TARGETS IN PD AND LBD PRECLINICAL AND CLINICAL DRUG DEVELOPMENT
31-03-2023 07:00 - 08:30

ROCK-PD: PHASE IIA STUDY OF SAFETY, TOLERABILITY, AND SYMPTOMATIC EFFICACY OF THE ROCK-INHIBITOR FASUDIL IN PATIENTS WITH PARKINSON'S DISEASE.

Andreas Wolff[1], Alexander Hapfelmeier[2,3], Dag Aarsland[4], Olivier Rascol[5], Richard Wyse[6], Yvonne Remane[7], Janine Zimmer[7], Anke Wirth[7], Helen Bidner[8], Paul Lingor[1,9]
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Aims: The Rho-kinase (ROCK) inhibitor fasudil has shown both symptomatic and disease-modifying effects in Parkinson's disease (PD) models in vitro, and in vivo and has been approved for the treatment of subarachnoid haemorrhage since 1995.
Methods: To investigate the safety, tolerability, and symptomatic efficacy of the ROCK-inhibitor fasudil in a randomized, placebo-controlled, national, multicenter, double-blind phase IIa study in patients with PD (EudraCT-No.: 2021-003879-34).
Results: Seventy-five patients with PD will be recruited in fifteen trial sites in Germany. Patients must be Hoehn & Yahr stages I-III, nonfluctuating, and stable on PD medication for 6 weeks. Patients will receive either fasudil in two dosages, or placebo for a total of 22 days. The screening visit is followed by three study visits during the 22-day treatment period, and two additional follow-up visits on days 36 and 50 after baseline. The combined safety and/or tolerability profile of oral fasudil over 22 days is the primary endpoint of this study. Secondary endpoints include tolerability alone over 22 days and the safety profile over 22 and 50 days. Further secondary endpoints will be change in motor and non-motor symptoms, including changes in MDS-UPDRS (I-IV), PDQ-8, NMSQuest, MoCA, BDI-II, and PGI-I/CGI-I, assessed at days 10 and 22 after baseline. For exploratory analysis, biomaterial will be collected to determine the pharmacokinetics of fasudil and its active metabolite, and to evaluate biomarkers of disease progression.
Conclusions: After positive evaluation by the responsible competent authority and the ethics committee, patient recruitment will start probably end of 2022.

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OD218a / #250

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

MICROGLIAL AUTOPHAGY PREVENTS SENESCENCE AND REGULATES HOMEOSTASIS OF ALPHA-SYNUCLEIN AND AMYLOID PLAGUES IN DISEASE MODELS

Zhenyu Yue, Insup Choi
Icahn School of Medicine at Mount Sinai, Neurology And Neuroscience, New York, United States of America

Aims: Dysfunctional autophagy has been implicated in the pathogenesis of Parkinson's disease and Alzheimer's disease (AD). Previous evidence suggested disruptions of autophagy-lysosome pathway in affected neurons of both diseases. However, whether and how deregulated autophagy in microglia, a resident macrophage in the brain, contributes to PD and AD progression remains elusive. We aim to (1) investigate the physiological role of autophagy in microglia; (2) understand how microglial autophagy regulates alpha-synuclein homeostasis; (3) dissect the function of microglial autophagy in regulating amyloid plague-related pathology.
Methods: We have performed an integrated study, including genetic mouse models, microglial culture and morphology, single cell (sc)RNAseq analysis, proteomics, bioinformatic analysis, immunofluorescent imaging, and electron microscopy,
Results: We show that autophagy-deficiency promotes senescence-associated microglia (SAM) as evidenced by reduced proliferation, increased *Cdkn1a*/p21^{Cip1}, dystrophic morphologies, and senescence-associated secretory phenotype (SASP). We report a neuroprotective role for microglia in the clearance of neuron-released α-synuclein via via TLR4-NF-κB-p62 mediated selective autophagy. We also show that autophagy is activated in disease-associated microglia (DAM) surrounding amyloid plaques in AD mouse models. Inhibition of microglial autophagy causes disengagement of microglia from amyloid plaques, suppression of DAM, and aggravation of neuropathology in AD mice. Pharmacological treatment removes autophagy-deficient, senescent microglia and alleviates neuropathology in AD mice.
Conclusions: Our study reveals a critical role for autophagy in preventing cellular senescence in microglia; microglial autophagy protects neuron by clearing neuron-released alpha-synuclein. Our study demonstrates that microglial autophagy regulates the homeostasis of amyloid plaques; removal of senescent microglia is a promising therapeutic strategy.

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OD219 / #1466

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

EFFECTS OF HUMAN TAU AND AGEING ON MITOCHONDRIA IN APP KNOCK-IN MICE

Takshashila Tripathi[1], Darcey Kirwin[1], Kritarth Singh[2], Sneha Desai[1], Nazar Stasyuk[1], Aishwarya Pathak[1], Jack Wood[1], Rui Wang[1], Aya Balbaa[1], Shenyi Jiang[1], Dervis Salih[3], John Hardy[3], Michael Duchen[2], Damian Cummings[1], Frances Edwards[1]
[1]University College London, Department Of Neuroscience Physiology And Pharmacology, London, United Kingdom, [2]University College London, Department Of Cell And Developmental Biology, London, United Kingdom, [3]University College London, Uk Dementia Research Institute, London, United Kingdom

Aims: EFFECTS OF HUMAN TAU AND AGEING ON MITOCHONDRIA IN APP KNOCK-IN MICE
Methods: Hippocampus from mice aged 2 months to 2 years were collected from wild type or NLF mice, both with or without heterozygous knock-in of human Tau. RNA-seq was performed followed by WGCNA network analysis, validated by RT-qPCR and immunohistochemistry for specific genes of interest. Phosphorylation of Tau was also assessed using immunohistochemistry. Measurement of oxygen consumption aims to elucidate mitochondrial function.
Results: Introduction of human Tau into NLF mice resulted in decreased expression of mitochondrial genes, in particular ATP synthase subunit *mt-Atp8*, with increasing age, while nuclear expressed mitochondrial genes for complex V tended to increase in expression. These effects have been validated using RT-qPCR and immunohistochemistry. This decrease is associated with decreased size of mitochondria without significant changes in density in aged 18-month-old NLF x humanTau mice. Moreover, the NLF x humanTau mice showed increased phosphorylation of Tau in dystrophic neurites in plaques and accumulation of PHF1 labelling in cell bodies in the CA1 region, suggestive of neurofibrillary tangle formation.
Conclusions: Inclusion of human Tau in NLF mice may represent a full model of Alzheimer's disease, possibly due to mitochondrial dysfunction caused by decreased mitochondrially-encoded gene expression, in particular complex V of the respiratory chain. Importantly these changes are strongly related to old age.

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OD220 / #1777

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

IMPAIRED AUTOPHAGY AND MITOPHAGY IN APOE4 N9 MICROGLIA CELLS

Rawan Bassal
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Aims: Autophagy is a self-digestion process of cellular constituents through an autophagosomic-lysosomal pathway . It is important for normal growth control and may be defective in diseases. Autophagy plays an important role in maintaining the balance between the formation and degradation of proteins, and as a cell-survival mechanism under stressful conditions such as absence of nutrients. It also permits the disposal of damaged organelles and protein aggregates in the cell. Thus, autophagy is important for normal cell growth, differentiation, and survival. Moreover, studies have demonstrated that enhancement of autophagy may induce degradation of harmful aggregates such as mutant huntingtin, alpha-synuclein and Aβ aggregates, indicating that at least in some neurodegenerative diseases enhancement of autophagy may rescue neuronal cells Our interest is in the crosstalk between apoE4 and PS1 mutation , a major risk factors for Alzheimer disease (AD) and autophagy. **Understanding the role of autophagy and mitophagy and its link to apoE4 expression in AD may help developing new therapeutic strategies.**
Methods: 1. To examine the effect of apoE3 apoE4 and PS1 mutation expression on autophagy in N9 microglial cell line. 2.To explore the effects of apoE3, apoE4 and PS1 mutation on mitochondrial dynamics of N9 microglial cell line, under basal and mitochondrial damage-inducing conditions (e.g., treatment with mitochondrial uncoupling agents). 3.To examine how PS1 mutation and apoE4-expression affect neuroinflammation in N9 microglial cells and the connection to impaired autophagy.
Results: 1. Impaired Autophagy in ApoE4 N9 microglia and PS1 N9 microglia. 2. mRNA levels of pro-inflammatory and anti-inflammatory cytokines related to PS1 mutation and apoE4-driven impaired autophagy. 3.The effect of autophagy modulation on Aβ removal in apoE3/apoE4 cells.
Conclusions: Impaired autophagy in ApoE4 and PS1 mutation N9 microglia cells.

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OD222 / #2119

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

IMPAIRED FATTY ACID DEGRADATION BY ASTROCYTIC MITOCHONDRIA INDUCES ALZHEIMER'S-RESEMBLING NEUROINFLAMMATION AND NEURODEGENERATION

Yashi Mi[1], Guoyuan Qi[1], Francesca Vitali[1], Yuan Shang[1], Adam Raikes[1], Tian Wang[1], Yan Jin[2], Roberta Brinton[1], Haiwei Gu[2], Fei Yin[1,3]
[1]University of Arizona, Center For Innovation In Brain Science, Tucson, United States of America, [2]Florida International University, Center Of Translational Science, Port St. Lucie, United States of America, [3]University of Arizona, Department Of Pharmacology, College Of Medicine, Tucson, United States of America

Aims: Astrocytes provide key neuronal support, and their phenotypic transformation is involved in neurodegenerative disorders including Alzheimer's disease (AD). Metabolically, astrocytes are highly glycolytic with low mitochondrial oxidative phosphorylation (OxPhos) activity, but the physiological significance of astrocytic OxPhos and its implication in neurodegeneration remains unclear.
Methods: We generated a mouse model with astrocyte specific OxPhos deficit by deleting the transcription factor A mitochondrial ($Tfam^{AKO}$). Behavioral, electrophysiological, structural, metabolic, and pathological characterizations of these mice were performed. Cell autonomous and non-autonomous mechanisms by which astrocytic OxPhos deficit modulates astrocyte reactivity, microglia activity, synaptic function, and myelin integrity were determined. The metabolic and transcriptomic signatures of $Tfam^{AKO}$ brains were subsequently compared to those of an amyloidosis model of AD (5xFAD) for shared mechanisms.
Results: Here we show that the brain critically depends on astrocytic OxPhos to degrade fatty acids (FAs) and maintain lipid homeostasis. Aberrant astrocytic OxPhos induces lipid droplet (LD) accumulation followed by neurodegeneration that recapitulates key features of human AD including neuroinflammation, synaptic loss, demyelination, and cognitive impairment. Mechanistically, when FA load overwhelms astrocytic OxPhos capacity, elevated acetyl-CoA levels induce astrocyte reactivity by enhancing STAT3 acetylation and activation. Intercellularly, lipid-laden reactive astrocytes stimulate neuronal FA oxidation and oxidative stress, activate microglia *via* IL-3 signaling, and inhibit the biosynthesis of FAs and phospholipids required for myelin replenishment. Moreover, a decline in astrocytic FA degradation precedes astrocytic LD accumulation in 5xFAD mouse brains.
Conclusions: Our findings provide new insights into the unique role of astrocytes in maintaining lipid homeostasis and protecting the brain against lipotoxicity. We further reveal a lipid-centric, AD-resembling mechanism by which astrocytic mitochondrial dysfunction progressively induces neuroinflammation and neurodegeneration.

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OD224 / #1802

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

INVESTIGATION OF TOPOISOMERASE IIB OVEREXPRESSION ON ALPHA SYNUCLEIN FORMATION AND AUTOPHAGY PROCESS IN VITRO PARKINSON DISEASE MODEL

Mohamed Khashan[1], Sevim Isik[2]
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Aims: It is aimed to observe the effect of topoisomerase IIβ overexpression on alpha synuclein formation and detect the mechanism behind it.
Methods: After optimization of KCl concentration, topoisomerase IIβ was overexpressed in SH-SY5Y cell line. Then alpha synuclein aggregation was induced by KCl and investigated the aggregation of alpha synuclein by immunofluorescence. In addition, alpha synuclein and topoisomerase IIβ mRNA levels were detected by RT-qPCR and protein levels of alpha synuclein, phosphorylated-alpha synuclein topo IIβ, ROCK2, ROCK1 and autophagy markers (P62 and LC3) were detected by western blot.
Results: It was found that 50 mM KCl is the less toxic concentration with efficient ability to induce alpha synuclein aggregations. The results illustrated also a reverse relation between topoisomerase IIβ and both mRNA and protein levels of ROCK2. Besides, it was showed that topoisomerase IIβ overexpression prevents alpha synuclein formation and aggregation. An up-regulation of autophagy was detected under topoisomerase IIβ overexpression.
Conclusions: The findings suggest that topoisomerase IIβ, as a novel inhibitor of ROCK2 in Parkinson's disease, could be a worth target for preventing or decreasing alpha synuclein aggregations. This emphasizes topoisomerase IIβ potential to treat Parkinson's Disease and other synucleinopathies by altering the illness. However, further studies must be carried out in vivo to elucidate the precise association topoisomerase IIβ with Parkinson's Disease.

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OD227 / #2026

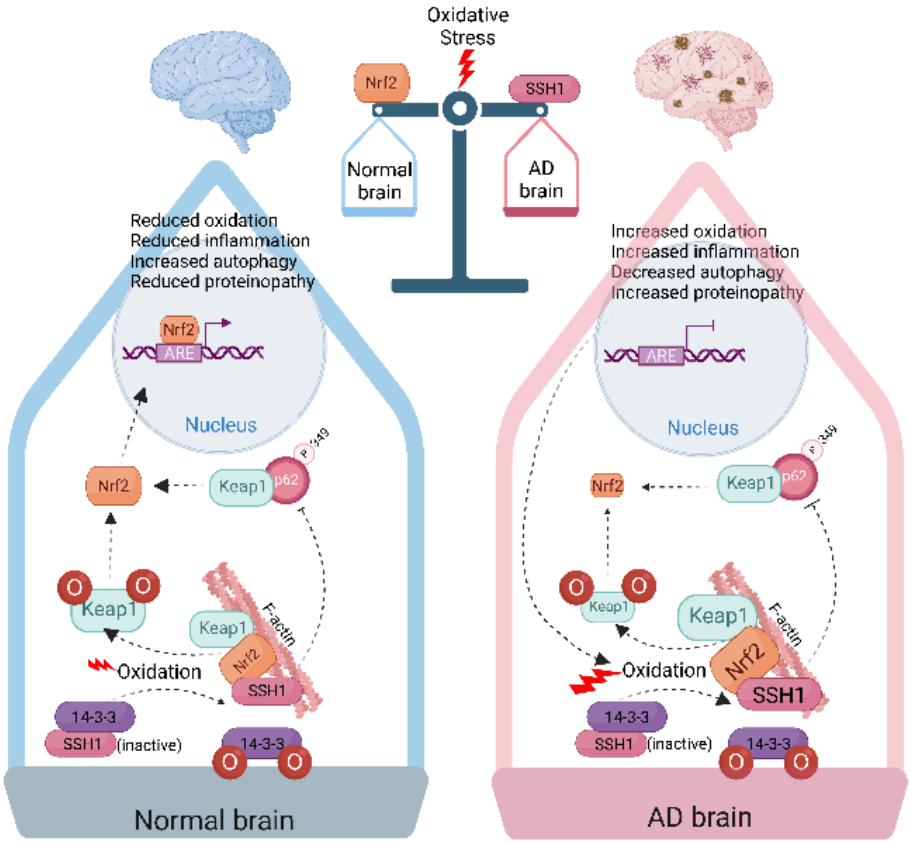
ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

SSH1-NRF2 INTERSECTION TIPS THE BALANCE FROM NEUROPROTECTION TO NEURODEGENERATION IN ALZHEIMER'S DISEASE

Sara Cazzaro[1,2], Jung A 'Alexa' Woo[1], Xinming Wang[1], Tian Liu[1], Teresa Kee[1,2], Shanon Rego[2], David Kang[1,3]
[1]Case Western Reserve University, Pathology, Cleveland, United States of America, [2]University of South Florida, Molecular Medicine, Tampa, United States of America, [3]Louis Stokes Cleveland VA Medical Center, N/a, Cleveland, United States of America

Aims: Loss of Nrf2 replicates transcriptomic changes in Alzheimer's disease (AD) and exacerbates tau and amyloid deposition. Although Nrf2 oxidative stress response declines with age and nuclear Nrf2 is depleted in AD brains, the mechanistic basis is unknown.
Methods: We utilized transfected cells, human postmortem brains, and cohorts of APP/PS1 (WT, APP/PS1, & APP/PS1;*Ssh1*$^{-/-}$) and tau^{P301S} mice (WT, tau^{P301S}, & tau^{P301S};*Ssh1*$^{-/-}$) to evaluate the role of SSH1 in Nrf2 oxidative stress response.
Results: Here, we demonstrate through *in vitro* and *in vivo* models, as well as human AD brain tissue, that slingshot homolog-1 (SSH1) acts as a counterweight to neuroprotective Nrf2-signaling by enhancing Keap1-Nrf2 interaction and sequestering Nrf2 on F-actin filaments, independently of SSH1 phosphatase activity. Human AD brains exhibit excessive inhibitory SSH1-Nrf2 and Keap1-Nrf2 interaction signatures, and elimination of *Ssh1* in AD animal models enhances Nrf2 signaling, which mitigates tau and Ab deposition and protects against oxidative injury and neuroinflammation. Loss of *Ssh1* also prevents synaptic plasticity deficits and normalizes transcriptomic perturbations in tau^{P301S} mice.
Conclusions: As oxidative stress activates Nrf2 and SSH1 while suppressing Keap1, our findings indicate that the intersection between Nrf2 and SSH1 represents a tipping point that impacts the balance between neuroprotection and neurodegeneration during oxidative stress. Due to chronic oxidative and proteotoxic stress weighing on the aging brain, this balance tips toward SSH1 at the expense of Nrf2-mediated neuroprotection in AD and FTLD-tau. Thus, inhibiting SSH1-mediated Nrf2 suppression may provide an effective therapeutic opportunity to protect from

AD.


Oxidative Stress
Nrf2
SSH1
Normal brain
AD brain
Reduced oxidation
Reduced inflammation
Increased autophagy
Reduced proteinopathy
Increased oxidation
Increased inflammation
Decreased autophagy
Increased proteinopathy
ARE
Nucleus
Keap1
p62
P 349
F-actin
Oxidation
14-3-3
SSH1 (inactive)
Normal brain
AD brain

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ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

MECHANISM OF A MULTIFUNCTIONAL METAZOAN AAA+ CHAPERONE

Arpit Gupta[1], Alfred Lentzsch[1], Alex Siegel[1], Chuqi Lu[1], Chun-Shik Shin[2], David Chan[2], Shu-Ou Shan[1]
[1]California Institute of Technology, Chemistry And Chemical Engineering, Pasadena, United States of America, [2]California Institute of Technology, Biology And Biological Engineering, Pasadena, United States of America

Aims: To elucidate the biochemical activities and physiological roles of Skd3, a AAA+ chaperone in the mitochondrial inter membrane space (IMS).
Methods: The assembly and structure of Skd3 were studied using mass photometry and cryo-electron microscopy. Luciferase disaggregation and refolding assays were used to study the chaperone activities of Skd3. Thioflavin T fluorescence and transmission electron microscopy were used to probe the chaperone activity of Skd3 toward Aβ42 and α-Synuclein. shRNA-mediated knockdown of Skd3 and complementation were used to study the effects of Skd3 in cell models.
Results: Skd3 forms both hexamers and cage-like dodecamers. Lucifrease refolding assays show that after aggregated substrates are solubilized, they further undergo protected folding on Skd3. Structure-informed mutations that disrupt dodecamer formation retains Skd3's disaggregase activity but specifically disrupt substrate refolding, indicating that Skd3 hexamers mediate aggregate solubilization whereas dodecamers enable efficient refolding. Skd3 knockdown in HeLa cells causes slower growth and impaired mitochondrial function, as evidenced by reduced mitochondria respiration, reduction in mitochondrial membrane potential, and mitochondria fragmentation. In addition, cytochrome c is destabilized and mislocalized. These results indicate an essential role of Skd3 in mitochondria function and protein quality control. Finally, Skd3 interacts with AD/PD-linked proteins that cause mitochondria dysfunction: it efficiently protects Aβ42 from aggregation and solubilizes pre-formed α-Synuclein aggregates.
Conclusions: Skd3 harbors both disaggregase and protein refolding activities enabled by distinct assembly states. In the absence of Hsp40/60/70 homologs in the mitochondrial IMS, the multiple chaperone activities of Skd3 may be particularly suited to maintain protein homeostasis in this space. The biochemically observed protective effect of Skd3 with α-Synuclein and Aβ42 suggest its potential role in protecting mitochondria from the toxicity of these proteins.

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OD229 / #664

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

PATHOLOGICAL CHARACTERIZATION OF NOVEL MOUSE MODELS EXPRESSING CHCHD2-WT AND PD-ASSOCIATED CHCHD2-T61I

Teresa Kee[1,2], Jessica Wehinger[1], Pamela Espinoza Gonzalez[1], Eric Nguyen[1], Kyle Mcgill Percy[2], Sophia Khan[2], Dale Chaput[3], Xinming Wang[2], Tian Liu[2], Jung A 'Alexa' Woo[2], David Kang[2,4]
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Aims: Coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2) is a multifunctional mitochondrial protein localized to the mitochondrial intermembrane space (IMS). In the IMS, CHCHD2 plays crucial roles in regulating oxidative phosphorylation, cristae structure, and preventing apoptosis. Mutations in CHCHD2 have been associated with familial autosomal dominant Parkinson's disease (PD). Given that previous animal models of CHCHD2-driven PD were limited to non-mammalian models, we created and characterized the first transgenic mouse models neuronally expressing CHCHD2-WT or PD-associated CHCHD2-T61I.
Methods: We utilized immunofluorescence staining, electrophysiological recordings, western blotting, rotarod testing, fear conditioning testing, and mass spectrometry to compare CHCHD2-T61I, CHCHD2-WT, and wild-type littermates.
Results: CHCHD2-WT and CHCHD2-T61I transgenic mice are grossly normal and do not exhibit CNS abnormalities at pup age and 1 year of age. The transgenes are successfully expressed in the brain, and properly localize to the IMS. However, CHCHD2-T61I mice exhibit mitochondrial fragmentation, gliosis, synaptic dysfunction, loss of midbrain dopaminergic neurons, and mislocalization and aggregation of alpha-synuclein at 1 year of age. CHCHD2-T61I mice also develop a motor phenotype without cognitive dysfunction at 1 year of age, and proteomic analysis of 10-month-old cortex indicate the insoluble accumulation of disease-associated proteins. CHCHD2-WT mice are phenotypically normal, and do not show any significant changes in gliosis or synaptic, motor, or cognitive functions compared to wild-type littermates.
Conclusions: We found that CHCHD2-T61I mice exhibit pathological and phenotypic changes consistent with Lewy body disorders, while CHCHD2-WT mice do not exhibit the same changes. These results indicate that CHCHD2-T61I mice recapitulate the pathological and phenotypic changes seen in human PD patients carrying the CHCHD2-T61I mutation, supporting their future use in studying mechanistic basis of T61I instigated pathogenesis in PD.

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OD230 / #1882

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

SMALL MOLECULE PINK1 ACTIVATORS RESCUE MITOCHONDRIA-ASSOCIATED PATHOLOGY IN IDIOPATHIC PARKINSON'S DISEASE MODELS

Nicholas Hertz, Randall Chin
Mitokinin Inc, Discovery Research, SAN FRANCISCO, United States of America

Aims: Impaired mitochondrial homeostasis is believed to be one of the main molecular contributors to cellular dysfunction in Parkinson's disease (PD) as evidenced by the discovery of genetic risk factors within key pathways of mitochondrial function and quality control. Homozygous loss-of-function mutations in the genes PINK1 and Parkin cause familial forms Parkinson's disease (PD).
Methods: We analyzed >1600 blinded plasma samples from two independent cohorts within the LRRK2 consortium cohort (LCC) We found significantly elevated plasma pUb in each cohort (BioRep $p<0.0001$, Tel Aviv $p<0.0001$), combined we found plasma pUb levels are significantly increased by 22.4% in the plasma of PD patients vs healthy controls. Remarkably, plasma pUb also correlates with the UPDRS Part 3 and Modified H&Y clinical progression scores suggesting pUb may be a PD progression biomarker.
Results: We show that pathological a-synuclein deposition impairs mitophagy and induces mitochondrial dysfunction in vitro. Using an ultrasensitive biomarker assay to quantify levels of the PINK1 substrate, pS65-Ub (pUb), we were able to quantify pUb levels in plasma of PD patients suggesting a reduced rate of mitophagy and therefore accumulation of pUb in PD subjects as compared to healthy controls. To test the therapeutic potential of activating the mitochondrial quality control pathway, we developed a brain penetrant, small molecule activator of PINK1, MTK458. MTK458 activates PINK1 by directly binding and stabilizing the PINK1/TOM complex that is rapidly inactivated in unimpaired mitochondria. We demonstrate that MTK458 binds to PINK1, increases level of mitophagy, reduces the amount of pUb and further clears alpha-synuclein pathology in PFF seeding models in vitro and in vivo.
Conclusions: Our data support the clinical development of PINK1 activators as disease-modifying therapeutics for the treatment of idiopathic PD.

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OD231 / #726

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

VUTIGLABRIDIN, AN ANTI-OBESITY DRUG CANDIDATE, MODULATES A NOVEL TARGET PROTEIN PARAOXONASE-2 (PON2) FOR PROTECTION OF DOPAMINERGIC NEURONS AGAINST MITOCHONDRIAL DYSFUNCTION.

Leo Choi[1], Hyung Soon Park[1], Hyeong Min Lee[1], Sang-Ku Yoo[1], Youngmi Kim Pak[2], Sora Kang[2]
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Aims: Vutiglabridin is a clinical phase 2-stage drug candidate for the treatment of obesity (NCT05197556). Parkinson's disease (PD), characterized by dopaminergic neuronal degeneration, share pathogenic features with obesity, including mitochondrial dysfunction and oxidative stress. Paraoxonase 2 (PON2) is an inner mitochondrial membrane protein that is highly expressed in dopaminergic neurons and is involved in the regulation of mitochondrial oxidative stress. However, no drug targeting PON2 has ever been developed for the treatment of PD. Here, we aimed to investigate whether vutiglabridin has therapeutic effects in PD models and whether it modulates mitochondrial PON2.
Methods: Brain penetration was assessed via pharmacokinetics analysis of vutiglabridin in brain of C57BL/6J mice and brain radiography of ^{14}C-vutiglabridin after a single oral administration. PON2 binding and modulation by vutiglabridin were assessed via in silico 3D modeling and in vitro binding assays, and binding interactions and affinity were determined. Neuroprotective effect of vutiglabridin was evaluated in SH-SY5Y neuronal cells and C57BL/6J mice after treating MPP^+ as a mitochondrial complex I inhibitor. Mitochondrial markers and motor behavior were examined. Target validation was performed with PON2 knockout cells and mice.
Results: We found that vutiglabridin penetrates the blood-brain barrier, binds to PON2, increases its protein stability, and alleviates toxin-induced mitochondrial dysfunction in human neuronal cells. Knockdown of PON2 abolished the effects of vutiglabridin on mitochondria. In mice, vutiglabridin significantly alleviated motor impairments and damage to dopaminergic neurons in toxin-induced PD model, and these effects were also abolished in PON2-knockdown mice.
Conclusions: Our results demonstrate that vutiglabridin is neuroprotective via PON2 and provide support for the immediate clinical development of vutiglabridin as a novel PON2 modulator for the treatment of PD.

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OD232 / #1815

ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

MITOCHONDRIAL METABOLIC PROCESSES ASSOCIATED WITH INCREASED APOEE4 EXPRESSION AND AFFECTED BY ANCESTRY AND SEX IN ALZHEIMER DISEASE

Maria Del Mar Muniz Moreno[1], Katrina Celis[1], Farid Rajabli[2], Patrice Whitehead[3], Kara Hamilton-Nelson[4], Derek Dykxhoorn[3], Karen Nuytemans[5], Liyong Wang[5], Eileen Bigio[6], Gary Beecham[3], Olivia Gardner[3], Daniel Dorfsman[2], Marsel Mesulam[7], Sandra Weintraub[8], Changiz Geula[7], Marla Gearing[9], Elisa Mcgrath-Martinez[10], Clifton Dalgard[11], William Scott[3], David Davis[5], Jonathan Haines[12,13], Margaret Pericak-Vance[2], Anthony Griswold[3], Juan Young[3], Jeffery Vance[2]
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Aims: *APOE* allele-dependent mitochondrial dysfunction (MTD) has been reported in Alzheimer Disease (AD). Since APOEε4 confers different risk for AD in African vs European ancestry patients, we sought to understand the role of MTD in driving these ancestry-specific effects.
Methods: Single nuclei RNA sequencing of frontal cortex (Brodmann area 9) in 17 homozygous AD APOEε4/4 carriers with African Local Ancestry (ALA; N=7, 4 females) and European LA (ELA; N=10, 7 females) was performed. Data were analyzed by comparing gene expression differences in ALA vs ELA samples in a sex-stratified manner focusing on mitochondria-related processes (MRP) using MitoXplorer. MTD-centered regulatory networks (MTDNet) were built using REACTOME to identify MTD-genes in close network proximity with APOE.
Results: MTD-related transcriptional alteration was significantly higher in cell types with the highest APOEε4 expression, namely astrocytes, microglia, endothelial cells, and L2/3 layer excitatory neurons. Overall, we identified 657 genes associated with all mitochondrial metabolic function (MTD-genes) significantly altered between the ancestries (adj p-value <0.05, -0.32< log2FC>0.25). Amongst the MRP, Tricarboxylic acid cycle and fatty acids had the stronger ancestry-specific changes, with most MTD-genes expression enriched in ELA. Analyzing sex differences, all cell types showed higher MTD 95 percentile expression index in males APOEε4 ALA carriers compared to ELA. This ratio was reversed in females.
Conclusions: Specific mitochondrial processes were significantly altered in cell types with the highest expression of APOEε4 but differing in direction and degree by both sex and ancestry. Furthermore, we identified possible ancestry-specific genes associated with different risk outcomes in ALA. Thus, deeper studies of APOEε4 effect on mitochondrial dysfunction are warranted and highlight the importance of considering sex and ancestry in the pathological mechanisms of AD

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ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

MULTI-REGIONAL CEREBRAL ALTERATIONS IN GLUCOSE AND PURINE METABOLISM PATHWAYS ARE COMMON TO PARKINSON'S DISEASE DEMENTIA AND ALZHEIMER'S DISEASE

Melissa Scholefield[1], Stephanie Church[1], George Taylor[2], David Knight[2], Jingshu Xu[3], Stefano Patassini[3], Garth Cooper[1]
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Aims: Parkinson's disease (PD) is one of the most common neurodegenerative diseases; it is primarily characterised by motor dysfunction, but also has a high prevalence of cognitive decline in the decades following diagnosis—a condition known as Parkinson's disease dementia (PDD). Although several metabolic disruptions have been identified in PD, this study is the first to perform a multi-regional analysis of multiple metabolites conducted in PDD brains; the findings from this analysis were then compared to observations from Alzheimer's disease (AD) brains obtained using similar methods.
Methods: A semi-targeted liquid chromatography–mass spectrometry analysis of nine PDD cases vs eight controls was performed, looking at nine different brain regions including the cingulate gyrus, cerebellum, hippocampus, motor cortex, medulla, middle temporal gyrus, pons, substantia nigra, and primary visual cortex. Metabolic alterations were then compared to results from previous mass spectrometry analyses of AD.
Results: Of 64 identified analytes, 47 were found to be altered in at least one region of the PDD brain. These included metabolites from several pathways including glucose and purine metabolism and the TCA cycle, with widespread increases in fructose, inosine, and ribose-5-phosphate, as well as decreases in proline, serine, and deoxyguanosine. Higher numbers of alterations were observed in regions of the PDD brain affected during earlier α-synuclein Braak stages—with the exception of the cerebellum, which showed an unexpectedly high number of metabolic changes. The changes observed were similar to those previously seen in AD, including alterations in glucose and purine pathways.
Conclusions: PDD and AD share multi-regional metabolic insults across several metabolic pathways; this suggests a shared dysfunction of glucose and purine metabolism across both of these neurodegenerative conditions, despite their differences in clinical and neuropathological presentation.

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ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

CHANGING THE COURSE OF DISEASE PROGRESSION WITH PARKIN THERAPEUTICS: THE MASTER REGULATOR OF MITOCHONDRIA, AUTOPHAGY AND INFLAMMATION

Jennifer Johnston
NysnoBio, Executive, Mill Valley, United States of America

Aims: Mutations in the Parkin gene are the most common genetic cause of Young Onset PD. Increasingly, mutations are also being identified in previously considered idiopathic patients, making Parkin one of the top three genetic causes of PD. Parkin enzyme activity is established as a master regulator at the nexus of several pathological pathways implicated in PD: Mitochondrial repair, autophagy and ubiquitin, and a multitude of studies have demonstrated neuroprotective activity and restoration of dopaminergic function after delivery of the enzyme. Our team is rapidly advancing Parkin Gene Therapy to the clinic using translational biomarkers based on its established MOA, and as a result have identified several novel markers that translate from Parkin KO animals to human patients. In addition to clinical biomarkers, we are also employing a novel neural network imaging analysis and wearable monitors to improve our ability to measure meaningful clinical improvement. Our goal is to demonstrate first-in-human therapeutic benefit of Parkin gene delivery in genetic parkin patients to alleviate progression of disease and restore dopamine neuron function, followed by expansion into treatment of additional validated subtypes of PD.
Methods: Pre-clinical models of Parkin KO rodents, MitoPark mouse models and alpha-synuclein PFF models are used to evaluate efficacy of Parkin Gene Therapy. Biomarker endpoints based on Parkin-dependent mitophagy are used to determine efficacious dosing and pharmacodynamics.
Results: Data demonstrating reversal of defects in Parkin KO animals, and damage-induced genetic models of PD, provide compelling evidence of efficacy for therapeutic benefit.
Conclusions: Our studies suggest Parkin Gene Replacement is a powerful strategy for potential benefit in Parkin-PD patients. Our efforts to establish efficacious, well-tolerated dosing in humans, while developing novel clinical translational biomarkers will provide a solid foundation for therapeutic testing in humans.

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ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

A-SYNUCLEIN DRIVES MITOCHONDRIAL MIRO1 RETENTION ACROSS PARKINSON'S DISEASE MODEL SYSTEMS

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AcureX Therapeutics, Biology, SAN CARLOS, United States of America

Aims: Mitophagy defects represent a major underlying pathology driving neurodegenerative conditions like Parkinson's disease (PD). The mitochondrial protein Miro1 is the key gatekeeper regulating the initiation of mitophagy and must be released from mitochondria for mitophagy to proceed. Miro1 release fails in sporadic PD (sPD) brain tissues, specifically in regions exhibiting α-synuclein pathology. The aims here were to (1) further test the hypothesis that elevated pathogenic α-synuclein protein levels correlate to elevated Miro1 protein levels across various well-established and widely used PD model systems and (2) demonstrate in human iPSC-derived dopaminergic (DA) neurons from multiple different PD genotypes that the failure to properly release Miro1 delays mitophagy.
Methods: A wide range of distinct models and assays were employed to investigate the deeper relationship between α-synuclein protein levels, Miro1 protein levels, and mitophagy.
Results: In PD subject iPSC-derived DA neurons a failure to release Miro1 lead to a significant delay in the recruitment of mitophagy adaptors LC3 and Optineurin, resulting in TH neuron loss under stress conditions. In primary rat midbrain neuron co-cultures treated with exogenous α-synuclein oligomers, protein levels of phospho-S129 α-synuclein and Miro1 were both significantly elevated while protein levels of TH were significantly reduced. In AAV-A53T α-synuclein mouse Striatum, protein levels of TH and DaT were significantly lowered as compared to the AAV-Null control mice while protein levels of human A53T α-synuclein and Miro1 were significantly elevated.
Conclusions: Our findings support that α-synuclein pathology is linked to the failure of Miro1 release and mitophagy defects. These findings have implications for other synuclein-related pathologies, including Dementia with Lewy Bodies and Alzheimer's disease. Identifying novel therapeutics that enable Miro1 release will have important clinical implications for PD and other Synucleinopathies.

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ON-DEMAND SYMPOSIUM: MITOCHONDRIAL DYSFUNCTION, AUTOPHAGY, MITOPHAGY IN AD, PD
31-03-2023 07:00 - 08:30

VB-08: A SMALL MOLECULE INHIBITOR OF USP30 THAT ENHANCES MITOPHAGY

Bahareh Behrouz[1], Donna Romero[1], Edward Fritzen[1], Mingchong Yang[2], Zhiyuan Li[3], Nuo Sun[2], Ian Ganley[3], Jeremy Yu[1], Andrew Lee[1]
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Aims: Strong genetic evidence from monogenic mutations in PINK1, parkin, and FBXO7, as well as risk factors for idiopathic PD establish a strong causative link between deficits in mitochondrial quality control and the etiology of Parkinson's disease (PD). This data is further supported by transcriptional and pathological abnormalities observed in idiopathic forms of PD.
Methods: USP30 has recently emerged as a key regulator of mitochondrial clearance in opposition to the actions of pink1 and parkin to drive ubiquitination and clearance of depolarized mitochondria. Here, we report a novel USP30 inhibitor, VB-08.
Results: VB-08 is a small molecule with low nanomolar *in vitro* potency and high selectivity for USP30 compared with other deubiquitinating enzymes. Using the Mito-QC system, we demonstrate that mitophagy is increased with VB-08 treatment in APRE-19 cells. VB-08 did not damage or depolarize mitochondria as measured by TMRM assay and did not decrease cell viability. VB-08 penetrates the brain and preliminary data using the Mt-Keima system demonstrates increase in mitophagy in the brains of mice after 5-days of treatment with VB-08. The compound is well tolerated following 5 days of repeated dosing.
Conclusions: VB-08 presents a useful tool to test the effect of increased mitophagy in rodent models of neurodegeneration and sets the stage for translational development of a new and promising class of compounds for PD.

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OD237 / #1007

ON-DEMAND SYMPOSIUM: BRAIN GUT INTERACTIONS – MICROBIOME 02
31-03-2023 07:00 - 08:30

IMAGING PERIPHERAL PATHOLOGY IN ALZHEIMER'S DISEASE: A PILOT STUDY TO DETECT ABERRANT AMYLOID DEPOSITION IN THE GASTROINTESTINAL TRACT

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Aims: Recent studies in Alzheimer's disease (AD) mouse models suggest that amyloid deposition in the gastrointestinal tract may contribute to brain amyloid deposition. In this study, we aimed to compare the uptake of the amyloid imaging agent 18F-Flutemetamol along the gastrointestinal tract in AD and cognitively unimpaired (CU) subjects.
Methods: Forty-eight individuals were recruited at the Memory Center of Geneva and underwent brain and abdominal ^{18}F-Flutemetamol PET. To evaluate the accumulation of tracer over time, two PET images of the whole abdomen were acquired at 40 and 120 minutes after tracer injection. For this preliminary analysis, standardized uptake values (SUVs) in the stomach and sigmoid colon wall of 9 CU and 9 AD patients were quantified using manually drawn regions of Interest. SUVs and the difference between 120 and 40 minutes (delta) were compared in AD and CU using Wilcoxon rank sum tests and associations with Spearman's rank correlation.
Results: CU were younger than AD (mean age 64.0 ± 5.2 years vs 73.2 ± 6.6 years, p= 0.017). AD patients showed an increase in the SUVs at 40 minutes post injection (p= 0.029) and a higher reduction over time (delta, p= 0.019) in the stomach. Both these measures correlated with amyloid deposition in the brain and cognitive impairment measured using mini-mental state examination scores (|rho|>0.63, p<0.012). No differences between AD and CU were identified in the sigmoid colon wall.
Conclusions: These preliminary results suggest that ^{18}F-Flutemetamol PET enables the detection of tracer uptake differences between AD patients and CU in the gastrointestinal tract. However, further analyses are needed to determine whether these differences denote amyloid- or age-related perfusion phenomena.

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ON-DEMAND SYMPOSIUM: BRAIN GUT INTERACTIONS – MICROBIOME 02
31-03-2023 07:00 - 08:30

DESIGNING A NOVEL DROSOPHILA MODEL OF ALZHEIMER'S DISEASE TO STUDY ABETA PROTEOTOXICITY IN THE DIGESTIVE TRACT

Greta Elovsson, Therése Klingstedt, Peter R. Nilsson
Linköpings university, Department Of Physics, Chemistry And Biology, Linköping, Sweden

Aims: *Drosophila melanogaster* (fruit fly) is often used as a model of Alzheimer's disease (AD), where toxic Aβ peptides are expressed in the fly brain. Since drug molecules usually are administrated orally to the fly there is a risk that the compounds will not reach the brain, due their inability to pass the brain barrier. To circumvent this problem, we have designed a novel *Drosophila* model of AD that expresses the Aβ peptides in the digestive tract. In addition, a built-in apoptotic sensor was exploited and provides a fluorescence signal from the green fluorescent protein as a response to caspase activity, thus indicating apoptosis.
Methods: Proteotoxic effects by expression of Aβ peptides in the fly gut were examined by a longevity assay, GFP fluorescence to identify apoptotic cells and by specific staining of Aβ aggregates using an antibody and the amyloid binding luminescent conjugated oligothiophene (LCO) h-FTAA.
Results: The fly genotypes that we utilized in our study expressed either two copies of the Aβ1-42 peptide, one copy of a tandem Aβ1-42 dimeric construct (TandemAβ), or one copy of the Arctic mutation of the Aβ1-42 peptide in the fly gut. Aβ-expressing genotypes displayed disease-related phenotypes, such as decreased survival and presence of aggregates and apoptotic cells, because of the toxic effects. Expression of TandemAβ in the fly gut resulted in a great amount of aggregates, but even so, this genotype did not appear to be too toxic and thus being suitable for drug screens and for studying the proteotoxicity caused by Aβ aggregation.
Conclusions: Taken together, this gut-based Aβ-expressing fly model can be used to study the mechanism of Aβ proteotoxicity and to screen for novel therapeutic candidates to combat AD.

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ON-DEMAND SYMPOSIUM: BRAIN GUT INTERACTIONS – MICROBIOME 02
31-03-2023 07:00 - 08:30

SEEDING COMPATIBLE ALPHA-SYNUCLEIN SPECIES IN STOOL SAMPLES OF PARKINSON'S DISEASE PATIENTS

Livia Civitelli[1], Selene Lee[1], Stefano Romano[2], Filip Scheperjans[3], Laura Parkkinen[1]
[1]University of Oxford, Nuffield Department Of Clinical Neurosciences, Oxford, United Kingdom, [2]Quadram Institute Bioscience, Norwich Research Park, Norwich, United Kingdom, [3]Helsinki University Hospital, Department Of Neurology, Helsinki, Finland

Aims: Parkinson´s disease (PD) is a progressive, neurodegenerative disease, pathologically confirmed by intracellular alpha-synuclein (aSyn) inclusions in certain vulnerable neurons and glial cells. aSyn can misfold and aggregate into fibrillar species with a propensity to progressively and sequentially spread from affected to unaffected brain regions. However, in PD patients, aSyn-positive aggregates are also found in the enteric nervous systems (ENS), possibly contributing to the occurrence of gastrointestinal symptoms. PD-associated aSyn aggregates can act as proteinaceous nuclei ("seeds") able of self-templated propagation from the gut into the brain via the vagal nerve. This has led us to investigate what the initial insult for aSyn aggregation could be in the ENS and what role different bacteria can have in this process.
Methods: To extract the proteins, stool homogenate of 45 PD samples and 10 healthy controls (HC) was homogenized and analyzed with biochemical techniques. Stools were subjected to the seeding amplification assay (SAA) and immunogold-labeling coupled to transmission electron microscopy (TEM) was used to investigate the structure of the SAA end-point fibrils. Human-extracted bacteria (genera Lactobacillus and Bifidobacterium) were also tested in the SAA.
Results: 20 out of 35 PD samples displayed the presence of aSyn species in western and slot blots, but with different immunoreactivity to aSyn antibodies. The SAA reaction showed that PD stools could act as seeds and immunogold-TEM revealed that SAA end-point samples were immunocaptured by aSyn antibodies. The different bacteria showed that they could seed aSyn aggregation in the SAA, with different seeding capacities.
Conclusions: Our data demonstrate that aSyn species detected in stools from PD patients as well as different PD-related bacteria show seeding activity These results will have an impact on both developments of biomarkers and possible therapies.

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ON-DEMAND SYMPOSIUM: BRAIN GUT INTERACTIONS – MICROBIOME 02
31-03-2023 07:00 - 08:30

RELATIONSHIP OF COGNITION AND ALZHEIMER'S DISEASE WITH GASTROINTESTINAL TRACT DISORDERS: A LARGE-SCALE GENETIC OVERLAP AND MENDELIAN RANDOMISATION ANALYSIS

Emmanuel Adewuyi, Eleanor O'Brien, Tenielle Porter, Simon Laws
Centre for Precision Health/Edith Cowan University, School Of Medical And Health Sciences, Perth, Australia

Aims: Studies suggest links between Alzheimer's disease (AD) and gastrointestinal tract (GIT) disorders; however, the relationship between cognition and GIT traits remains unclear. Given AD is characterised primarily by cognitive deterioration, this study comprehensively assesses genetic overlap and potential causality of cognitive traits and AD with GIT disorders.
Methods: We assessed global and local genetic correlation of ten cognitive traits (N = 68,065 – 766,345) and AD (N = 455,258) with six GIT disorders (N = 332,601 – 456,327) using the linkage disequilibrium score regression (LDSC) and the Local Analysis of [co]Variant Association (LAVA) methods, respectively. We also utilised the bidirectional Mendelian randomisation analysis method in investigating potential causality between cognitive traits and GIT disorders.
Results: LDSC reveals a strong and highly significant inverse global genetic correlation of cognitive traits and AD with GIT disorders—peptic ulcer disease (PUD), gastritis-duodenitis, diverticulosis, irritable bowel syndrome, gastroesophageal reflux disease (GERD), but not inflammatory bowel disease (IBD). LAVA detects 35 significant ($P < 4.37 \times 10^{-5}$) bivariate local genetic correlations across 14 loci, of cognitive traits and AD with GIT disorders (IBD inclusive). MR analysis suggests a risk-decreasing causality of cognitive traits on the risk of PUD and GERD but not IBD. The causality of GERD with some cognitive traits was bidirectional, suggesting a putative risk of decreased cognitive function in GERD.
Conclusions: Our study provides new insights into the relationship of cognitive traits and AD with GIT disorders, identifying highly significant global and local genetic correlations between the traits. Findings support the protective causality of cognitive traits on GIT disorders and the potential risk of cognitive deficit with GERD. The shared loci identified provide important targets for further translational investigation in AD, cognition and GIT disorders.

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ON-DEMAND SYMPOSIUM: BRAIN GUT INTERACTIONS – MICROBIOME 02
31-03-2023 07:00 - 08:30

FECAL MICROBIOTA TRANSPLANTATION FROM AN INDIVIDUAL GENETICALLY PROTECTED AGAINST ALZHEIMER'S DISEASE TO 3XTG MICE COUNTERACTS COGNITIVE IMPAIRMENT AND ALZHEIMER'S PATHOLOGY

Claire Chevalier[1], Benjamin Tournier[2], Moira Marizzoni[3], Rahel Park[1], Kelly Ceyzériat[2], Arthur Paquis[1], Emma Troesch[1], Philippe Millet[2], Giovanni Frisoni[1]
[1]HUG-memory clinic, Lanvie, Geneve, Switzerland, [2]University of Geneva, Psychiatry Department, Geneve, Switzerland, [3]IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Laboratory Of Biological Psychiatry And Laboratory Of Neuroimaging And Alzheimer's Epidemiology, Brescia, Italy

Aims: Humanizing the gut microbiota of a mouse by fecal microbiota transplantation (FMT) is a method developed to study the relation between the human gut microbiota and diseases. In this study we evaluate the effect of the transplantation of gut bacteria isolated from donors "resistant" to Alzheimer's disease (AD) pathology (i.e. amyloid and p-Tau), to AD transgenic (Tg) mice.
Methods: 3xTgAD mice (APP_{SWE}, $PS1_{M146V}$ and Tau_{P301L}) received antibiotic treatment (for 14 days) followed by microbiota transplantation (twice a week for 2 months). The transplanted microbiota was isolated from donors pertaining to two different profiles: amyloid negative cognitively healthy subject with protective APOEε2 genotype or young healthy donor. Controls were mice receiving water or microbiota of untreated 3xTgAD mice.
Results: FMT from the donor genetically protected improved memory (object recognition test), reduced hippocampal load of p-Tau (-76%), and Amyloidβ40 (-65%) and increased the TSPO (18kDa translocator protein) neuroinflammation marker (+76%). FMT from the young donor did not show effect on behaviour or pathology. 16SrRNA sequencing of the cecum indicates that few bacterial species (on average 4.8%) grafted in the recipient mice from the genetically protected donor FMT. Among them, several belonging to the Parabacteroidetes genera.
Conclusions: Despite the low FMT efficiency, our results suggest that i) microbiota transplantation could be a therapeutic strategy in AD and, ii) the choice of donor is a critical issue in the success of the treatment. Deeper ongoing gut microbiota sequencing from the mice, but also from a large human cohort will help us understand the interaction of the APOE genotype and the gut microbiota.

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ON-DEMAND SYMPOSIUM: BRAIN GUT INTERACTIONS – MICROBIOME 02
31-03-2023 07:00 - 08:30

GUT-TO-BRAIN PROGRESSION OF SYNUCLEINOPATHY IN THE C-REL-/- MOUSE MODEL OF PARKINSON'S DISEASE.

Edoardo Parrella, Michele Gennari, Marina Benarese, Giulia Abate, Mariachiara Pucci, Daniela Uberti, Marina Pizzi, Vanessa Porrini
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. Braak and colleagues proposed that PD pathology starts from the intestine and end 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: Intestinal pathology as well as hemivagotomy effect on AS spreading were evaluated by immunohistochemistry and biochemistry methods in c-rel$^{-/-}$ and wt mice from 2 to 12 months of age.
Results: At intestinal level, accumulation of phosphorylated AS was present in the myenteric plexus of c-rel$^{-/-}$ mice proximal colon at 2 months and increased at 10 months. Gut synucleinopathy was paralleled by increasing oxidative stress and inflammation markers in 10-month-old c-rel$^{-/-}$mice. 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.
Conclusions: These results indicate that the c-rel$^{-/-}$ mice develop a progressive PD pathology at intestinal levels. Furthermore, the vagal nerve can partecipate to the gut-to brain spreading of AS in this PD mouse model.

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ON-DEMAND SYMPOSIUM: BRAIN GUT INTERACTIONS – MICROBIOME 02
31-03-2023 07:00 - 08:30

RT-QUICR A-SYNUCLEIN DETECTION IN ANTE-MORTEM INTESTINAL BIOPSIES FROM PARKINSON'S DISEASE PATIENTS

Christina Groveman (Orru)
NIH, Lnii, Hamilton, United States of America

Aims: Aggregates of α-synuclein (α-Syn) are promising biomarkers for Parkinson's disease (PD). The concept that misfolded α-Syn can spread in a prion-like fashion has gained interest. Reports show that PD can be experimentally transmitted in cellular and animal models. Such findings have encouraged the development of ultrasensitive assays for pathological α-Syn aggregates that harness the seeds' prion-like amplification properties *in vitro*. The real-time quaking-induced conversion (RT-QuICR) assay is one such approach which detects α-Syn seeds in different PD biospecimens. Since the gastrointestinal (GI) tract has been proposed as an initial site of α-Syn aggregation, detection of GI α-Syn seeds could be used for early diagnosis. We evaluated the ability of α-Syn RT-QuICR to detect seeding activity in intestinal mucosa biopsies from clinically diagnosed PD patients.
Methods: A total of 24 participants were recruited for this study: 20 PD and 4 non-neurodegenerative healthy patients. All patients underwent upper GI endoscopy for placement of a jejunal extension tube (PEG-J) for continuous levodopa enteral infusion. For each patient, two GI biopsies were taken. Based on the rostrocaudal distribution of α-Syn in the GI tract, the proximal small intestine (duodenum) was chosen as the part most likely to contain seeds. Sample collection/analysis is still ongoing, we expect to test additional samples before this conference.
Results: So far α-Syn RT-QuICR analysis gave positive reactions for 17/20 patients with PD and negative reactions for all non-neurodegenerative healthy subjects, giving a diagnostic sensitivity of 85% and a specificity of 100%.
Conclusions: These findings indicate that α-Syn RT-QuIC allows sensitive detection of α-Syn seeds in intestinal biopsies from live PD patients and suggest a new approach to the *intra vitam* diagnosis of clinical and prodromal PD.

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OD244 / #2240

ON-DEMAND SYMPOSIUM: BRAIN GUT INTERACTIONS – MICROBIOME 02
31-03-2023 07:00 - 08:30

EXPLORATION OF FAECAL FUNGAL LOAD AND MARKERS OF INTESTINAL BARRIER DYSFUNCTION WITH AGE, CONSTIPATION AND PARKINSON'S DISEASE

Chianna Umamahesan[1], Aleksandra Pilcicka[2], Shervin Dokht Sadeghi Nasab[2], David Moyes[2], Yun Ma[3], David Taylor[1], Bu' Hussain Hayee[4], Sylvia M Dobbs[1], Richard John Dobbs[1], André Charlett[5]
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Aims: Constipation is prodromal to Parkinson's disease (PD), worsening thereafter: we explore relationship of faecal microbiota (here, fungal) and intestinal barrier-dysfunction to age, constipation- and PD-status.
Methods: A fungal-load PCR was developed using ITS1F-ITS2 primer-set, run, in triplicate, on microbial DNA-extract from stool, stored at -80ºC from 4 h of defaecation, in 43 participants with PD, 72 without. Barrier-dysfunction markers, faecal zonulin and alpha-1 antitrypsin (AAT) and serum fatty-acid-binding-protein (I-FABP) antibody, were assayed in duplicate using commercial ELISAs. Intraclass correlation indicated excellent reliability for all assays.
Results: Fungal-load increased by 4.1 (95% C.I. 1.5, 11.2) times per decade after age 60, with no PD-status interaction with age. It was 116 (-14, 447)% higher, after age-adjustment, in presence of functional constipation (Rome III Classification Functional Bowel Disorders), a large effect, reaching significance only at 0.1 level. Fungal-load was not associated with antimicrobial consumption (last three years or time since last course). AAT and zonulin concentrations were not age-related, but higher by 121 (50, 225) and 57 (-2, 151)%, respectively (p=0.001 & 0.06), with constipation. Moreover, they were (30 (13, 47) and 22 (6, 40)% higher per 10/60 transit-pellets retained (p=0.001 & 0.009) on colonic-transit x-ray. I-FABP was higher by 6.8 (1.2, 12.5)% per decade, p=0.02), with no PD-status interaction with age, but not associated with constipation-status. Fungal-load and barrier-dysfunction were not associated.
Conclusions: Neither fungal-load nor barrier-dysfunction were associated with PD-status, but were with age and constipation. Sequencing of mycobiome and exploration of discriminant fungal-taxa in relation to PD-facets are indicated.

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OD245 / #1792

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

COVID-19 IMPACT ON DEPRESSIVE SYMPTOMATOLOGY AND PARKINSON'S DISEASE SEVERITY IN HAWAII

Ana Tavares[1], Zoeann Kon[2], Brennan Lee[2], Richard "kainalu" Rista[3], Jason Viereck[4,5], Kore Liow[4,6], Enrique Carrazana[4,6]
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Aims: In the first year of the COVID-19 pandemic, Hawaii was one of the least affected states. Our study aimed to identify the prevalence of depression in the Parkinson's Disease (PD) population at Hawaii Pacific Neuroscience (HPN), to determine if depression is positively correlated with PD severity, and to clarify the impact the COVID-19 pandemic has had on the depressive symptomatology of the PD population of Hawaii.
Methods: We conducted a retrospective review of patient records from the Hawai'i Pacific Neuroscience (HPN) eClinicalWorks 11e software with a diagnosis of PD from June 18th, 2017, to June 18th, 2022, via International Classification of Diseases 10th Revisions, Clinical Modification (ICD-10) codes for PD: G20. To be included in this study, PD patients had to have PHQ-2 scores recorded before 2020 and during/after 2020, and taking medication to treat PD. Depression was defined as a recorded PHQ-2 score of 3 or more during or after the year 2020 or having a diagnosis of depression. ≥800 mg/day of a Levodopa and/or a Levodopa Equivalent Dosage (LED), ≥ 5 doses of an LED per day, and/or an ICD-10 code for Dementia was necessary for Advanced PD (APD) classification.
Results: Our results suggested that there were no significant differences in PHQ-2 scores from pre 2020 to current. We also found that the proportion of those who are depressed and have APD is not significantly different from those without depression and APD, suggesting that there appears to be no association between depression and APD in our population at HPN.
Conclusions: Our results were different than that of other studies. This difference may be due to the differential effects of COVID-19 in Hawaii compared to the continental states.

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OD246 / #2627

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

NOT JUST A MISSING NUMBER: GENDER DIVERSITY AND LGBTQ+ INCLUSIVITY IN DEMENTIA CARE AND RESEARCH

Sarah Bauermeister
University of Oxford, Department Of Psychiatry, Oxford, United Kingdom

Aims: Over 20% of LGBTQ+ older adults are living with dementia and concurrently, the number of adults openly living as LBGTQ+ is expected to double by 2030. However, this community continues to lack adequate research profiling due to poor categorisation of gender identity. Particularly in the trans community where little/no provision is made for gender identification in cohorts, clinical trials or biographical profiling. The aims of this project are to highlight inadequacies in current research and clinical environments for the LGBTQ+ community and to establish a research programme within the community for the community.
Methods: An LGBTQ+ public interest group forms core of this programme of work. The group works closely with the scientific team to decide on the objectives, outcomes and implications of the programme of work. The public interest group is led by a steering group within the LGBTQ+ community representing ethnic and economic diversities. 1. The public interest and steering group form core of the programme 2. The longitudinal LGBTQ+ population cohort will be focused on the trans community collecting biopsychosocial data approved by the LGBTQ+ steering group 3. Data will be accessible for researchers on the Dementias Platform UK (DPUK) Data Great Minds platform and a member of the LGBTQ+ steering group will sit on the Great Minds access committee.
Results: The results of 'Not just a missing number' will have multiple positive effects on both the LGBTQ+ community and understanding neurodegenerative disease in a population that is often recoded as 'missing' simply because the gender option of choice is not available.
Conclusions: Many legacy cohorts and medical institutions have not taken into account a non-binary gender world so the LGBTQ+ community is losing out due to miss and non-classification.

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OD247 / #1246

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

TRAUMATIC EXPOSURE, POST-TRAUMATIC STRESS, AND COGNITIVE IMPAIRMENT: A LONGITUDINAL MEDIATION ANALYSIS IN WORLD TRADE CENTER (WTC) RESPONDERS

Frank Mann[1], Sean Clouston[1], Adolfo Cuevas[2], Monika Waszczuk[3], Benjamin Luft[1]
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Aims: The present study aimed to clarify the mediating role of post-traumatic stress disorder (PTSD) in accounting for the effects of exposure severity on cognitive impairment in World Trade Center responders. Pathways that help explain, at least in part, *why* traumatic exposures are related to an increased incidence of cognitive impairment might help clinicians to better understand where to intervene to bring about change. If symptoms of PTSD partially or fully account for the effects of exposure severity on cognitive impairment, then this finding would be consistent with PTSD being a cause of cognitive impairment, and one might expect treatment of PTSD to help ameliorate the onset or progression of cognitive impairments that resemble symptoms of Alzheimer's Disease and related dementia (ADRD).
Methods: The present study conducted a longitudinal mediation analysis of trauma exposure, post-traumatic stress, and incidence of cognitive impairment in a large sample of WTC responders (n = 3992). Specifically, a continuous time-survival model was embedded within a path analytic framework to estimate the direct and indirect effects of exposure severity mediated by symptoms of PTSD. The precision of indirect effects was evaluated using 95% bootstrapped confidence intervals based on 500 random draws.
Results: indicate that PTSD symptoms partially mediate the effects of different indicators of exposure severity on the hazard rate of cognitive impairment. Exposure to human remains had no direct effect on cognitive impairment, only an indirect effect mediated by symptoms of PTSD, further strengthening causal inference.
Conclusions: Although cause and effect relations cannot be established conclusively in the absence of a randomized experiment, results are consistent with PTSD being a cause of cognitive impairments among WTC responders at midlife, which present phenotypically as symptoms of ADRD.

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OD248 / #2216

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

CLINICAL , INVESTIGATIONAL PROFILE OF DEMENTIA AND MCI IN TERITARY CARE CENTRE IN NORTH INDIA AND ASSESS FOR CARE GIVER BURDEN AMONG THE CARE GIVERS

Sai Teja, Karthik Vm, Dr Sameer Vyas, Manish Modi, Dr Sandeep Grover
PGIMER, Neurology, chandigarh, India

Aims: To study the clinical , investigational profile in patients with dementia and Mci in teritary care centre in north India setting and assess care giver burden among the care givers
Methods: study design - observational , descriptive study meathodology- All confirmed cases of dementia and mci based on DSM 5 criteria attending neurology outpatient department or admitted inpatients and fulfilling inclusion criteria would be included instudy
• Written informed consent would beobtained
• Detailed history as well as neurological examination will be carried out in all patients eligible forstudy
• All hematological, biochemical , optional investigation if required(whole body/ brain PET, S.ammonia, EEG
• Neuroimaging including Brian MRI and FDG BrainPET Daily activity is assessed by Lawton instrumental activity of dailyindex.
• Care giver burden is assessed by family burden interview Pai andKapoor
Results: 30 patients of Mci (amnestic variant) and patients including AD, CBS, FTDBv ,primary progressive aphasic varinat ,vascular dementia has been assesed. Neuro cognitive assesement was done with Mini mental status examination, montreal cognitive assesement , neuropsychaitric symptoms was assesed by neuropsychiatric inventory questionnare.Care giver burdern was assesed by family burdern interview scale (shaila pai and R L kapoor 1981) mean care giver burden was 11.15 with maximum of 30 and minimum of 0. maximum burden was seen in FTDBv with minimum in Amnestic Mci and CBS.
Conclusions: care giver burden was maximum in FTDbv with minimum in amnestic mci and CBS

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OD249 / #704

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

NEURAL CORRELATES OF NEUROPSYCHIATRIC SYMPTOMS IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT

Natascia De Lucia[1], Giovanni Carbone[2], Benedetta Muzii[1], Nicola Ferrara[2], Giuseppe Rengo[2], Nelson Mauro Maldonato[1], Grazia Daniela Femminella[2]
[1]University of Naples Federico II, Department Of Neurosciences, Reproductive And Odontostomatological Sciences, Napoli, Italy, [2]University of Naples Federico II, Department Of Translational Medical Sciences, Napoli, Italy

Aims: Neuropsychiatric symptoms are prevalent in individuals with MCI and are correlated with an increased risk of progression to AD. The cognitive and neuroanatomical underpinnings of neuropsychiatric symptoms in MCI remain partially understood. In this study, we aimed to examine the relationship between neuropsychiatric symptoms, cognitive function, regional tau deposition, and brain volume in individuals with MCI.
Methods: 233 individuals with MCI and 305 healthy controls were identified from the ADNI 3 cohort. Each individual received a comprehensive neuropsychological evaluation, a volumetric MR brain scan, and Flortaucupir PET for in vivo evaluation of regional tau accumulation. Using the NPI questionnaire, the frequency of neuropsychiatric symptoms was assessed. Using multivariate analyses of variance (MANOVA), variations in cognitive and imaging markers between MCI patients with and without neuropsychiatric symptoms were identified.
Results: 61.4% of MCI individuals exhibited at least one neuropsychiatric symptom, with depression (26.1%), irritability (23.6%), and sleep difficulties (23.6%) being the most prominent. Neuropsychiatric conditions had a considerable impact on cognitive tests of frontal and executive functioning. MCI patients with neuropsychiatric symptoms exhibited decreased brain volumes in the orbitofrontal and posterior cingulate cortices, although regional tau accumulation was unaffected.
Conclusions: Neuropsychiatric symptoms appear early in the progression of Alzheimer's disease and are mostly associated with deficits in executive control abilities and a reduction in grey matter volume in the orbitofrontal and posterior cingulate cortices. A greater understanding of the cognitive and neuroanatomical mechanisms underlying neuropsychiatric symptoms in MCI may facilitate the development of more targeted and effective treatment options.

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OD250 / #2469

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

THE IMPACT OF SOCIOECONOMIC STATUS IN THE ASSOCIATION BETWEEN ALZHEIMER'S DISEASE AND MORTALITY

Sri Banerjee
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Aims: Cognitive dysfunction continues to be one of the top ten causes of mortality. While there have been treatment efforts for 20 years, there have been no new medications for this condition. In this research we investigated if socioeconomic status modifies the effect of cognitive dysfunction in association with overall mortality.
Methods: In the National Health and Nutrition Survey, we used population-based cohort study of 1999-2002 National Health and Nutrition Examination Surveys with mortality data obtained through 2015. Adults aged 60 years or older were assessed for cognitive skills using Digit Symbol Substitution Test (DSST). Outcomes of all-cause mortality were evaluated using Cox regression.
Results: We had a mean follow-up of 11.2 years. Percent of deaths from low cognitive function among the population (N=29,799) were higher among Hispanic Americans (38.4%) than Caucasians (29.9%). The mean follow-up was 13.1 years. For all-cause mortality, the overall unadjusted hazard ratio (HR) of low Cognitive dysfunction had a hazard ratio of 2.74 (95% confidence interval [CI], 2.23-3.38, $p = 0.002$). Adjusted HR was elevated, 3.08 (CI 1.54-6.03, $p < 0.001$), among high Poverty-Income-Ratio with low cognitive function but closer to 1.0 (1.92 CI 1.28-6.13, $p < 0.25$) among low poverty-income-ratio with low cognitive function, after controlling for medical (stroke, congestive heart failure, and chronic kidney disease) and demographic risk factors (age, gender, food insecurity, and education).
Conclusions: Our research shows that low cognitive function leads to higher mortality. In addition, individuals in low socioconomic status experience poorer outcomes from low cognitive function than than those in higher SES. Improved identification of dementia, increased surveillance efforts, and addressing issues with health equity are needed to improve survival.

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OD251 / #946

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

EMOTIONAL PATTERN IN PRODROMAL ALZHEIMER'S DISEASE. A MOOD INDUCTION PROCEDURE USING FILM CLIPS

Raquel Sahuquillo[1], Beatriz Navarro[1], Ignacio Párraga[2], Elena Martín[3], José Latorre[1], Luz Fernández-Aguilar[1]
[1]Universidad de Castilla-La Mancha, Psicología, Albacete, Spain, [2]Gerencia de Atención Integrada de Albacete, Centro De Salud Zona Viii, Albacete, Spain, [3]Gerencia de Atención Integrada de Albacete, Geriatría, Albacete, Spain

Aims: Alzheimer's disease (AD) is the most common form of dementia in older adults. This disease involves loss of memory, but also of other key functions, such as emotion. The literature on emotions in AD is, however, scant. The main aim of this research was to explore the emotional response in persons with prodromal AD by means of an induction procedure using film clips
Methods: We compared emotional responses in healthy older adults (n=17) and older adults with prodromal AD (n=9) to 5 pleasant and unpleasant targets; of high and low arousal: amusement, tenderness, fear, sadness and anger. Additionally, AD was the main topic in one of the clips. Emotional response was measured using the Self Assessment Manikin (SAM) for valence and arousal, and the Discrete Emotional Scale (DES) for the basic emotions.
Results: Differences were found between the two groups for high arousal emotional stimuli. The older adults experienced more positive valence in amusement (healthy MD=5.50, AD MD= 1.00, p= .006) and more negative valence in fear (healthy MD=1.00, AD MD= 4.00, p= .027) compared to the older adults with AD. Regarding the basic emotions, in response to the anger film clip, the healthy older adults showed higher levels of anger compared to their counterparts with AD to the anger clip (healthy MD=7.00, AD MD=4.00; p= .036) and more sadness than those with AD after exposure to the AD clip (healthy MD= 6.00, AD MD= 4.00, p= .049).
Conclusions: The emotional pattern of older persons with AD shows less emotional discrimination than that observed in healthy older individuals.

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OD252 / #2435

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

COGNITIVE IMPAIRMENT IN VASCULAR PARKINSONISM: UNRAVELLING BEHAVIOURAL AND PSYCHIATRIC SYMPTOMS

Raquel Manso Calderón, María Dolores Sevillano García
Complejo Asistencial de Salamanca, Neurology, Salamanca, Spain

Aims: The clinical profile of cognitive impairment in vascular parkinsonism (VP) is not well established in the literature, especially with regard to behavioural and psychiatric symptoms (BPS). Our goal is to evaluate the frequency of BPS in this subtype of VP.
Methods: This is an observational descriptive study that prospectively recorded data of 48 consecutive patients, who met vascular parkinsonism criteria proposed by Zijlmans plus cognitive impairment, in two outpatient neurological consultations in Salamanca, Spain. Mean age at onset was 74.3 ± 7.9 years, 45.8% were women, education 10.1 ± 3.9 years, mean duration of cognitive impairment 4.3 ± 2.8 years, MMSE score 15.9 ± 6.3, 31.3% living in nursing homes. 85.4% exhibit hypertension, 41.7% diabetes, 66.7% dyslipidaemia, 41.7% cigarettes and 25% alcohol consumption. 17.1% reported previous transient ischemic attack, 75% ischemic stroke, 4.2% haemorrhagic stroke and 55.1% recurrent cerebrovascular events. The Neuropsychiatric Inventory (NPI) was used to assess BPS.
Results: At least one BPS occurred in 97.9% of VP participants with cognitive impairment; the median NPI score was 46 (range:0-132), with a median number of 5 symptoms per patient. The most frequent symptoms were depression (70.8%) apathy (70.8%), sleep disturbances (64.6%) and irritability (64.6%), followed by agitation (54.2%), anxiety (54.2%), delusions (52.1%), hallucinations (41.7%), appetite/eating abnormalities (33.3%), disinhibition (27.1%), aberrant motor behaviour (18.8%) and euphoria (8.3%). 52.1% received antidepressants, 43.8% antipsychotics, 35.4% anxiolytics and 25% hypnotics. It is remarkable that 8 of 16 patients with appetite/eating abnormalities showed hyperphagia.
Conclusions: BPS are frequent in cognitive impairment related to VP. New investigations are required to better evaluate the relationship between neuroimaging evidence of cerebrovascular disease in this subtype of VP and different BPS profiles.

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OD253 / #778

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

BUILDING CARE ECOSYSTEM WITH SUPPORTIVE MONITORING TOOLS TOGETHER WITH PEOPLE

Špela Glišović Krivec[1], David Krivec[1], Danaja Fabčič Povše[2], Panagiotis Karkazis[3], Nicholas Vretos[4], Vassilis Solachidis[4], Martina Steinböck[5], Jennifer Jiménez Ramos[6], Javier Serrano[7], Federico Alvarez[7]
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Aims: TeNDER is a multi-sectoral project funded by European Union's Horizon 2020 research and innovation programme where we are developing an integrated care ecosystem with supportive monitoring tools. The system includes several resources of data gathering, addresses the combination of wellbeing parameters and importantly, it is developed according to the participants` lived experiences. The project involves 13 partners: universities, health care organizations, patients' associations, industry and SMEs from 7 European countries, sharing the common aim to improve the quality of life of patients with dementia, Parkinson's disease or after stroke, carers and their care professionals.
Methods: We have firstly conducted an observational study where diverse users provided views on care availability, needs, functionalities` usability, and how would they prefer to interact with such tools. Next, the researchers provided their experiences and views on system testing with people in real-life scenarios.
Results: The personal needs differ regarding the tools that are recognized and known, are preferred to be used, digital competences and views on usefulness. The researchers` feedback opened some well-known questions as privacy, usage, critical assessment, implementation barriers and affordability, but also reflected on monitoring-related challenges.
Conclusions: There is still a question if technology has a true potential to enable people with dementia and movement disorders to continue living in their own homes and assist them in daily challenges. Only the diverse users` engagement, person-centred and professionals` driven approach, will allow the development of a solution that would be adopted in wider community.

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OD253a / #1589

ON-DEMAND SYMPOSIUM: AD, MCI, PD: PSYCHIATRIC & NEUROPHSYOLOGICAL MANIFESTATIONS, ECONOMIC STATUS, CARE & SUPPORT
31-03-2023 07:00 - 08:30

PSYCHIATRIC SYMPTOM PROFILE OF AD, DLB AND FTD: PRELIMINARY FINDINGS FROM THE NATIONAL ALZHEIMER'S COORDINATING CENTER UNIFORM DATA SET

Mary Sano[1], Carolyn Zhu[2], Hillel Grossman[1]
[1]Icahn School of Medicine at Mount Sinai, and JJP VA Medical Center, Psychiatry, Bronx, United States of America, [2]Icahn School of Medicine, Geritiatrics, NYC, United States of America

Aims: Neuropsychiatric ymptoms are well-recognized as key features in the clinical profile of neurodegenerative diseases. Here we use common data collection tools to describe unique patterns of these symptoms in AD, DLB and FTLD individuals who were assessed by clinical dementia experts.
Methods: Participants from the National Alzheimer's Coordinating Center Uniform Data Set (NACC-UDS, 9/2005-5/2019) with baseline cognitive status of mild cognitive impairment (MCI) or dementia and ≥ one follow-up were included. Baseline etiologic diagnosis of AD, FTLD with suspected underlying etiology of behavioral variant of FTLD (bvFTD), and DLB were included. Behavioral symptoms were reported using clinician judgment items within the NACC-UDS protocol, included apathy, depressed mood, hallucinations, disinhibition, irritability, agitation, and anxiety. We categorized participants into four groups: (1) never symptomatic across all visits, (2) intermittently symptomatic (<50% visits), *(3)* persistently symptomatic (≥50% visits), and (4) always symptomatic.
Results: The sample included 9445 participants with AD, 868 with bvFTD, and 725 with DLB. Among the symptoms assessed, apathy was the most prevalently reported symptom across all groups (AD: 62%; DLB: 78%; bvFTD: 88%) and it was persistently observed (i.e. persistent or always symptomatic) in all diagnostic groups with the highest persistence experience in bvFTD (78.5%), followed by DLB (64.6%) and then AD (44.0%). Depression was also relatively prevalent and comparable across all conditions (AD: 51.3%; DLB: 66%; bvFTD: 50.2%). Uniquely highly prevalent symptom profiles include visual hallucinations (63%) in DLB and disinhibition (79%) in FTLD.
Conclusions: Neuropsychiatric symptoms organize in disease-specific patterns that are important in clinical characterization as well as in designing treatment and management algorithms.

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OD255 / #1824

ON-DEMAND SYMPOSIUM: BACE-1, BACE-2, PRESENILIN, GAMMA-SECRETASE, TACE, APP
31-03-2023 07:00 - 08:30

THE SIGNAL PEPTIDE PEPTIDASE-LIKE 2B AFFECTS APP CLEAVAGE AND EXHIBITS A BIPHASIC AB-MEDIATED EXPRESSION IN ALZHEIMER´S DISEASE.

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Aims: One of the characteristic hallmarks of Alzheimer's disease (AD) is the aggregation of amyloid β-peptide (Aβ) into amyloid plaques. To identify new druggable pathways involved in the Aβ cascade we here investigated the AD pathophysiological role of the presenilin-like protease signal peptide peptidase-like 2b (SPPL2b). SPPL2b is involved in the proteolysis of a key AD-related protein, BRI2, which colocalizes with APP in neurons and modulates its processing. Here we have explored the pathophysiological role of SPPL2b in the APP cleavage and its expression levels in the AppNL-G-F knock-in AD mouse model.
Methods: To verify the potential role of SPPL2b in the APP cleavage process we have established a primary cell culture derived from WT and SPPL2b-deficient mice. To investigate how Aβ pathology affects SPPL2b levels in vivo, SPPL2b brain expression was evaluated in the *App*$^{NL-G-F}$ mice. The samples were analyzed by western blot, ELISA, and immunofluorescence staining.
Results: BRI2 staining, in primary neuronal cell culture derived from the SPPL2b KO mice, was significantly higher as compared with the control WT neurons. Most importantly, in the neuronal media from SPPL2b KO cells, the soluble fraction of APP (sAPP) was strongly reduced, consistently, with a significant decrease in both Aβ40 and Aβ42 levels. In *App*$^{NL-G-F}$mice, SPPL2b expression is increased at an early stage of the pathology (3 months of age). This is followed by a downregulation in the late stage of the Aβ pathology (22 months).
Conclusions: SPPL2b genetic deletion affects the BRI2 levels and significantly reduced APP cleavage and Aβ production. On the other hand, an early Aβ-induced SPPL2b upregulation may enhance Aβ production in a vicious cycle further aggravating the Aβ pathology suggesting SPPL2b as a potential anti-Aβ target.

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OD256 / #341

ON-DEMAND SYMPOSIUM: BACE-1, BACE-2, PRESENILIN, GAMMA-SECRETASE, TACE, APP
31-03-2023 07:00 - 08:30

EARLY DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE BY TARGETING TOXIC SOLUBLE AB OLIGOMERS

Shai Rahimipour[1], Maram Habashi[1], Suresh Vutla[2], Kuldeep Tripathi[1], Sudipta Senapati[1], Pradeep Chauhan[2], Anat Haviv-Chesner[1], Michal Richman[1], Samia-Ait Mohand[3], Véronique Dumulon-Perreault[4], Ramakotaiah Mulamreddy[2], Jordan Chill[1], Brigitte Guérin[4], William Lubell[2]
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Aims: The main aim of this study was to develop novel self-assembled cyclic D,L-α-peptide nanotubes as theranostic agents to diagnose early Aβ oligomers in pre-symptomatic stage of AD and diminish memory and cognition decline.
Methods: Kinetic Thioflavin T, electron microscopy, NMR and CD spectroscopy as well as immunochemical and biochemical methods were used to study the effect of aza-glycine insertion on cyclic D,L-α-peptide self-assembly, Aβ oligomer disruption, and toxicity. The *In vivo* PET imaging studies and therapeutic activity were performed in AD transgenic mice and *Caenorhabditis elegans.*
Results: Introducing an aza-glycine residue with extra hydrogen-bond donor to tune nanotube assembly and amyloid engagement, cyclic azapeptide **1** interacted with early Aβ oligomers (1-3 mers) and inhibited Aβ aggregation and toxicity at sub-stoichiometric concentrations. NMR studies revealed dynamic interactions between **1** and Aβ42 residues F19 and F20, which are pivotal for early dimerization and aggregation. In an AD mouse model, brain PET imaging using stable ^{64}Cu-labeled azapeptide **1** gave unprecedented early amyloid detection in 44-day pre-symptomatic 5xFAD mice better than^{11}C-PIB. No tracer accumulation was detected in the cortex and hippocampus of treated AD mice; instead, intense PET signal was observed in the thalamus, from where Aβ oligomers may spread to other brain parts with disease progression. Effectively crossing the BBB, the cyclic (aza)peptides reduced Ab oligomer levels, prolonged lifespan of AD transgenic*Caenorhabditis elegans*, and abated memory and behavioral deficits in AD mice.
Conclusions: Cyclic (aza)peptides offer novel promise for early AD diagnosis and therapy by targeting the soluble oligomers.

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OD257 / #1032

ON-DEMAND SYMPOSIUM: BACE-1, BACE-2, PRESENILIN, GAMMA-SECRETASE, TACE, APP
31-03-2023 07:00 - 08:30

SOMATOSTATIN SLOWS AB PLAQUE DEPOSITION IN AGED APPNL-F/NL-F MICE BY BLOCKING AB AGGREGATION IN A NEPRILYSIN-INDEPENDENT MANNER

Gerold Schmitt-Ulms[1], Declan Williams[1], Bei Qi Yan[1], Hansen Wang[1], Logine Negm[1], Christopher Sackmann[1], Claire Verkuyl[1], Vanessa Rezai-Stevens[1], Shehab Eid[1], Christine Sato[1], Joel Watts[2], Holger Wille[3]
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Aims: The molecular underpinnings that govern the endoproteolytic release of the amyloid beta peptide (Aβ) from the amyloid precursor protein (APP) are now quite well understood. The same cannot be said for events that precipitate the aggregation and amyloid deposition of Aβ in Alzheimer's disease (AD). The 14-amino-acid cyclic neuroendocrine peptide somatostatin (SST-14) has long been thought of as playing a role, foremost by controlling the expression of the Aβ clearing enzyme neprilysin, and more recently by directly interacting with Aβ oligomers. Missing have been *in vivo* data in a relevant Aβ amyloidosis model.
Methods: Here we addressed this shortcoming by crossing $App^{NL\text{-}F/NL\text{-}F}$ mice with *Sst*-deficient mice of identical genetic background to assess if and how the presence of Sst influences key pathological hallmarks of Aβ amyloidosis that develop in $App^{NL\text{-}F/NL\text{-}F}$mice after 10 months of age.
Results: Surprisingly, we found that Sst had no influence on whole brain neprilysin transcript, protein or activity levels, an observation that cannot be accounted for by a compensatory upregulation of the Sst paralog, cortistatin (Cort), that we observed in 15-month-old Sst-deficient mice. The absence of Sst did lead to a subtle but significant increase in the density of cortical Aβ amyloid plaques. Follow-on western blot analyses of whole brain extracts indicated that Sst interferes with early steps of Aβ assembly that manifest in *Sst* null brains through the appearance of SDS-stable smears of 55-150 kDa. As expected, no effect of Sst on tau steady-state levels or its phosphorylation were observed.
Conclusions: Results from this study are easier reconciled with an emerging body of data that point toward Sst affecting Aβ amyloid plaque formation through direct interference with Aβ aggregation rather than through its effects on neprilysin expression.

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OD258 / #1071

ON-DEMAND SYMPOSIUM: BACE-1, BACE-2, PRESENILIN, GAMMA-SECRETASE, TACE, APP
31-03-2023 07:00 - 08:30

PHYSIOLOGICAL PRODUCTION AND CLEARANCE RATES OF HUMAN SOLUBLE AMYLOID PRECURSOR PROTEIN ISOFORMS AND PATHOPHYSIOLOGICAL CHANGES IN ALZHEIMER'S DISEASE

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Aims: We hypothesize that a subgroup of the AD and non-demented Amyloid [+] populations overproduce Aβ because of increased BACE1 activity. Our objective is to measure CSF sAPPβ and sAPPα production and clearance rates, as surrogate markers of BACE1 activity, to determine if, and by how much, BACE1 activity is increased.
Methods: Using stable isotope labeling kinetics/immunoprecipitation/liquid chromatography-tandem mass spectrometry methods, we quantified sAPPβ and sAPPα turnover rates in CSF from 96 Amyloid [+] and Amyloid [-] subjects who had undergone [U-$^{13}C_6$]-leucine labeling and hourly CSF collection. Utilizing internal standards, absolute concentrations of sAPPβ and sAPPα were also measured by MS to quantify production. The fraction of metabolite derived from de novo synthesis was measured by calculating metabolites' hourly mole fraction labeled, over 36 hours. An APP kinetics model was derived, including subjects' historical Aβ measurements, to study parameters of APP metabolism in the living human.
Results: Clearance rates of sAPPα and sAPPβ are highly positively correlated, as are their delay times, regardless of Amyloid status. sAPPβ is cleared significantly slower than sAPPα regardless of Amyloid status. Both metabolites' clearance rates were slower in Amyloid [+] than Amyloid [-] group. Amyloid status did not have an effect on sAPPβ and sAPPα Delay Times. However, sAPPβ Delay Time was significantly higher than sAPPα Delay Time in both groups. We will also present model-derived grouped production rates, analyses of which are pending.
Conclusions: Our final model of the complete cohort of 95 subjects will be presented. We will address potential implications for the use of these APP metabolites as biomarkers of AD in clinical trials, to both successfully select individuals for specific trials and to assess therapeutic interventions once an individual is enrolled in a trial.

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OD259 / #1173

ON-DEMAND SYMPOSIUM: BACE-1, BACE-2, PRESENILIN, GAMMA-SECRETASE, TACE, APP
31-03-2023 07:00 - 08:30

INCREASED AGE IN SYMPTOMATIC PSEN1 MUTATION CARRIERS IS ASSOCIATED WITH HIGHER CONCENTRATIONS OF AMYLOID-FORMING AMYLIN WITHIN PLASMA LDL

Florin Despa[1], Nirmal Verma[1], Deepak Kotiya[1], Emily Abel[1], Tammaryn Lashley[2], Henrik Zetterberg[3,4], John Hardy[5], Nick Fox[6], Natalie Ryan[4]
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Aims: This study assessed relationships between age, disease duration and accumulation of islet amyloid polypeptide (amylin) within plasma low-density lipoprotein (LDL) fraction in autosomal dominant familial Alzheimer disease (ADAD).
Methods: Plasma samples were collected from symptomatic *PSEN1* mutation carriers not participating in a disease-modifying therapy trial at the time of plasma sampling (n=10) and age-matched cognitively unaffected individuals (n=10). Frozen plasma samples were thawed for 15 minutes at 37^{o}C water bath and transferred to ultracentrifuge tubes containing potassium bromide to a final volume density of 1.066 g/ml followed by centrifugation at 65000 rpm at 4^{o}C for 24 hours. Top layer (VLDL and LDL) and the bottom layer (HDL and Lipoprotein a) were collected in separate tubes and analyzed for amylin concentrations using the enzyme-linked immunosorbent assay (ELISA) for amylin (EIA-AMY; RayBiotech). The association between age at plasma collection and amylin concentration in VLDL/LDL fractions was examined using multiple linear regression.
Results: Older age at plasma collection was associated with higher levels of amylin in VLDL/LDL fractions. After adjusting for disease duration, each one year increase at the plasma collection was associated with an average increase in plasma VLDL/LDL of 4.89 ng/g total protein ($P<0.05$).
Conclusions: Increased age in *PSEN1* mutation carriers was associated with elevated amyloid-forming amylin in plasma VLDL/LDL, providing a potential mechanism underlying the development of cerebrovascular amylin deposits. Given that cerebrovascular amylin-β amyloid (Aβ) deposits are often detected in both sporadic AD and ADAD, further studies in a larger sample size are needed to delineate the influence of circulating amylin-LDL fractions in disease progression and potentially in disease-modifying therapy trials in ADAD.

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OD260 / #2436

ON-DEMAND SYMPOSIUM: BACE-1, BACE-2, PRESENILIN, GAMMA-SECRETASE, TACE, APP
31-03-2023 07:00 - 08:30

ELUCIDATING THE MOLECULAR BASIS OF ALTERED PRESENILIN 2 EXPRESSION ON ALZHEIMER'S DISEASE PATHOLOGY

Anika Perdok[1], Zoë Van Acker[1], Zsuzsanna Callaerts-Végh[2], Suresh Poovathingal[3], Kristofer Davie[4], Lutgarde Serneels[3], Renzo Mancuso[5], Wim Annaert[1]
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Aims: Background: γ-Secretase is an intramembrane protease which plays a pivotal role in the onset and progression of Alzheimer's disease (AD). Presenilin provides the catalytic activity of which two homologues exist, Presenilin-1 and Presenilin-2 (Psen1/2). Psen2/γ-secretase complexes are restricted in their localization to the late endosomes and lysosomes, as opposed to the broader distribution of Psen1/ γ-secretase, making it the main generator of intracellular abeta (Aβ). Although the focus has been on the extracellular pool, this toxic intracellular pool has been shown to precede plaque and tangle formation and correlates well with synaptic dysfunction highlighting its importance. This project aims to unravel the effects of altered Psen2 expression and this intracellular pool on AD pathogenesis.
Methods: Methods: We generated novel mouse models by crossing the well characterized APP NL-G-F model with a Psen2 knock out (KO) mouse and an in-house generated Psen2 knock in (KI) model carrying the familial AD-linked N141I mutation (FAD-Psen2).
Results: Results: Curiously, opposed to expectations, we found an identical accelerated plaque pathology coinciding with the presence of dystrophic neurites and amyloid precursor protein c-terminal fragment (APP-CTF) accumulation in genotypes with altered Psen2 expression. This acceleration translated to an earlier deficit in working memory for both APPxPsen2KO and APPxFADPsen2 and corresponding deficiencies in LTP. In contrast, gliosis was markedly different with increased and earlier microglia recruitment in the case of APPxPsen2KO whereas APPxFAD-Psen2 displayed a delayed recruitment. Herein, distinct microglia transcriptional signatures are also detected in both models.
Conclusions: Conclusion: These surprising differential effects on distinct pathological features suggest both a protective role for Psen2 as well as specific, yet unexplored, roles in neurons as well as glial cells. We are currently examining primary neurons and microglia to explore underlying molecular mechanisms.

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OD262 / #693

ON-DEMAND SYMPOSIUM: BACE-1, BACE-2, PRESENILIN, GAMMA-SECRETASE, TACE, APP
31-03-2023 07:00 - 08:30

UNRAVELLING THE ROLE OF BACE2 IN A HUMAN CEREBRAL ORGANOID MODEL OF ALZHEIMER'S DISEASE

Yee Jie Yeap[1], Kah Leong Lim[1], Dean Nizetic[2], Anne Rovelet-Lecrux[3]
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Aims: The purpose of this study is to understand the contribution of BACE2 to the pathogenesis of Alzheimer's Disease (AD) by using a cerebral organoid model to compare the extent of amyloid and tau pathology between an individual with Early Onset Alzheimer's Disease (EOAD) harbouring a *de novo* 12kb deletion in intron 1 of BACE2 with his asymptomatic parental control. There is no AD history in his first-and second-degree relatives.
Methods: Induced pluripotent stem cells (iPSCs) were generated from fibroblasts derived from an EOAD individual with a BACE2 intronic mutation and his parental control using non-integrational Sendai reprogramming. Cerebral organoids were generated from these iPSCs and maintained beyond 200 days in culture. Subsequently, these organoids underwent immunohistochemical staining for the quantification of phosphorylated tau, amyloid plaques, and neuronal death – the three hallmarks synonymous with AD.
Results: Amyloid plaques were observed in both patient and control organoids by day 70. An age-related increase in the number of amyloid plaques was observed at day 100, where the patient demonstrated a significant exacerbation in amyloid plaque deposition as compared to the control. Phosphorylated tau started to appear in the patient by day 150, and by day 200, a significant increase in phosphorylated tau accompanied by cell death was observed in the patient as compared to the control. More importantly, in our model, the appearance of amyloid plaques preceded that of phosphorylated tau, which aligns with the order of pathology proposed by the amyloid cascade hypothesis.
Conclusions: We found that BACE2 intronic mutation promotes AD-related pathologies in patient-derived brain organoids, suggesting that BACE2 normally functions as a neuroprotective factor. We propose that targeting BACE2 for therapeutic purposes in AD presents a viable alternative strategy that merits consideration.

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OD263 / #2757

ON-DEMAND SYMPOSIUM: BACE-1, BACE-2, PRESENILIN, GAMMA-SECRETASE, TACE, APP
31-03-2023 07:00 - 08:30

ENDOLYSOSOMAL DYSFUNCTION IN PRESENILIN/GAMMA-SECRETASE DEFICIENT CELLS ORIGINATES FROM DEFECTIVE INTER-ORGANELLAR COMMUNICATION

Wim Annaert[1], Ragna Sannerud[1], Marine Bretou[1], Céline Vrancx[1], Tom Leroy[1], Zoë Van Acker[1], Eeva-Liisa Eskelinen[2]
[1]VIB Center for Brain & Disease Research, Ku Leuven, Department Of Neurosciences, Leuven, Belgium, [2]University of Turku, Institute Of Biomedicine, Turku, Finland

Aims: Endolysosomal abnormalities are early cytopathological changes observed in Alzheimer's disease, well before amyloid plaques appear. Several of these defects are recapitulated in presenilin (PSEN) deficient cells and neurons of which the underlying derailed mechanism(s) remain debated. In this study, we aimed to determine (i) the chronology of events leading to endolysosomal dysfunction and (ii) the contribution of a derailed APP proteolysis.
Methods: We used CRISPR/Cas9 to generate cell lines deficient for both PSENs and PSENs/APP triple KO lines. This allowed us to re-introduce APP fragments using lentiviral technology and explore their contribution to endolysosomal dysfunctions. We used functional endolysosomal readouts and combined this with advanced imaging, including super-resolution (live) imaging and EM to evaluate endolysosomal dyshomeostasis, including their communication through membrane contact sites (MCSs).
Results: When γ-secretase activity is chronically inhibited, the earliest defects include a lysosomal calcium imbalance and cholesterol accumulation, causing a subsequent collapse of endolysosomal compartments that affected normal endosome recycling and maturation as well as cargo sorting and turnover, including of APP. The decrease in lysosomal calcium content in PSEN deficient cells originated from defective calcium re-filling from the endoplasmic reticulum (ER). A concomitant accretion of cholesterol instigated a cascade leading to endolysosomal demise. Furthermore, transmission EM and live super-resolution imaging demonstrated that MCSs between lysosomes and ER are morphologically altered leading to decreased lysosomal motility and prolonged lingering at the ER. Whereas KO of APP significantly contributed to the restoration of endolysosomal homeostasis, reversely, defects re-appeared when introducing APP fragments.
Conclusions: Collectively, γ-secretase-dependent cytopathogenic changes suggest a surveillance role for presenilin/γ-secretase activity in lysosomal function. Herein we reveal a novel role for APP in the homeostatic regulation of inter-organellar communication.

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OD264 / #905

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

GENETIC VARIANTS WITHIN THE HPA-AXIS ARE ASSOCIATED WITH DIFFERENCES IN THE RATE OF LONGITUDINAL HIPPOCAMPAL ATROPHY.

Ayeisha Milligan Armstrong[1,2], Tenielle Porter[2,3,4], Simon Laws[2,3,4], Giuseppe Verdile[1,2,5], David Groth[1,2]
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Aims: Chronic psychological stress is associated with an increased risk for Alzheimer's disease, however the underlying mechanisms are not fully understood. The major stress pathway, the hypothalamic pituitary adrenal (HPA) axis and the stress hormone cortisol, are thought to be implicated. Studies have shown that increased levels of cortisol are associated with an accelerated rate of cognitive decline and decreased hippocampal volumes. HPA-axis gene variants exist that alter an individuals' sensitivity to cortisol. Therefore, the aim of this study was to determine whether genetic variants within this pathway alter the rate of neurodegeneration.
Methods: Longitudinal data from the Australian, Imaging and Biomarker study of ageing (AIBL) was used to investigate the association of single nucleotide polymorphisms (SNPs) within HPA-axis genes with neurodegeneration. The R package '*lmer'* was used to perform linear mixed models to determine the effect of the SNP by time interaction on longitudinal brain volumes taken by magnetic resonance imaging (MRI).
Results: We found that numerous SNPs within HPA-axis genes are associated with differences in the rate of neurodegeneration. In particular, we found that SNPs that have been previously associated with altering cortisol sensitivity, located within the cortisol receptor genes *NR3C1* and *NR3C2*, were associated with increased rates of hippocampal atrophy. We are currently validating these findings in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort study.
Conclusions: Our results imply a role for SNPs within the HPA-axis genes in influencing the rate of neurodegeneration. This work has implications for those at most risk of neurodegeneration associated with increased cortisol and who may benefit the most from interventions targeting this pathway to slow down its progression.

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OD265 / #1746

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

MULTI-ANCESTRY GENOME-WIDE ASSOCIATION ANALYSIS OF LATE-ONSET ALZHEIMER'S DISEASE (LOAD) IN 60,941 INDIVIDUALS IDENTIFIES A NOVEL CROSS-ANCESTRY ASSOCIATION IN LRRC4C

Adam Naj[1,2], Christiane Reitz[3], Farid Rajabli[4], Gyungah Jun[5], Penelope Benchek[6], Giuseppe Tosto[7], Jin Sha[2], Congcong Zhu[5], Nicholas Kushch[4], Wan-Ping Lee[1], Jacob Haut[2], Kara Hamilton-Nelson[8], Nicholas Wheeler[6], Yi Zhao[1], John Farrell[5], Jaeyoon Chung[9], Michelle Grunin[6], Yuk Yee Leung[1], Donghe Li[5], Eder Lucio Da Fonseca[8], Jesse Mez[9], Ellen Palmer[6], Jagan Pillai[10], Richard Sherva[5], Yeunjoo Song[11], Xiaoling Zhang[5], Taha Iqbal[2], Omkar Pathak[1], Otto Valladares[1], Amanda Kuzma[1], Brian Kunkle[8], William Bush[12], Li-San Wang[13], Lindsay Farrer[14], Jonathan Haines[11], Richard Mayeux[15], Margaret Pericak-Vance[8], Gerard Schellenberg[13]
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Aims: Increasing ancestral diversity in genomic studies is critical for defining the genetic architecture of LOAD by improving power to identify variants more prevalent in or specific to a given ancestry. We constructed and analyzed multi-ancestry GWAS datasets in the Alzheimer's Disease Genetics Consortium (ADGC) to identify novel LOAD loci and characterize shared and unique features of LOAD genomic risk profiles.
Methods: The ADGC multi-ancestry dataset includes GWAS genotype and phenotype data on 37,382 non-Hispanic White, 6,728 African American, 11,436 Hispanic, and 3,232 East Asian subjects, all imputed to the TOPMed v5 reference panel. We performed a two-stage analysis: (1) single-variant association using score-based logistic regression for unrelated subjects and generalized linear mix-model for family datasets with adjustment for onset/exam age, sex, principal components for population substructure, and *APOE* ε2/ε3/ε4 genotype, followed by within-ancestry fixed-effects meta-analysis using METAL; and (2) cross-ancestry meta-analysis of within-ancestry summary statistics using the random-effects model (RE2) in METASOFT.
Results: In addition to *APOE* region associations, we identified twelve loci with cross-ancestry genome-wide significant associations ($P \leq 5\times10^{-8}$) including 10 previously known: *CR1, BIN1, TREM2, CD2AP, PTK2B, CLU, SHARPIN, MS4A6A, PICALM,* and *ABCA7.* Two novel loci were identified: *LRRC4C* ($P=2.2\times10^{-8}$) and *LHX5-AS1* ($P=3.0\times10^{-8}$). Follow-up analyses including cross-ancestry fine-mapping, gene-based analyses, eQTL (expression) analyses, and functional analyses are in progress.
Conclusions: Cross-ancestry GWAS meta-analyses identified two novel LOAD susceptibility loci. *LRRC4C* (MIM: 608817) has been shown to regulate the development and function of thalamocortical axons while *LHX5-AS1* (MIM: 605992) is known to control neuronal differentiation and migration during hippocampal development. Our data validate that multi-ancestry analyses are a powerful and necessary approach. Multi-ancestry studies with even larger sample sizes will prove even more powerful for further elucidating the genomic underpinnings of LOAD.

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OD266 / #2728

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

THE EFFECT OF SPLICE EVENTS IN ABCA7 MUTATION CARRIERS ON EXPRESSION AND DISEASE SEVERITY

Lena Duchateau[1], Fahri Küçükali[1], Jasper Van Dongen[1], Elisabeth Hendrickx Van De Craen[2,3], Arne De Roeck[1], Christine Van Broeckhoven[3], Kristel Sleegers[1]
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Aims: Premature termination codon (PTC) mutations in *ABCA7* have been found to increase risk for Alzheimer's disease (AD), and lead to decreased *ABCA7* expression due to nonsense-mediated decay (NMD). Carriers however vary in phenotype and age at onset (AAO). We hypothesized that the presence of NMD escape and 'rescue' alternative splicing might influence *ABCA7* expression and disease severity. Here we leveraged long-read sequencing and qPCR to study these events.
Methods: We characterized the *ABCA7* transcript, derived from lymphoblastoid cell lines or brain, in a group of 28 AD patients (24 PTC carriers), 17 controls (11 carriers) and 5 mild cognitive impairment patients using Oxford Nanopore sequencing. Using the FLAIR pipeline and an in-house R script, alternative splicing events, NMD escape and rescue events were quantified. In a subset of 19 samples (17 carriers), qPCR was used to determine *ABCA7* expression.
Results: All PTC mutations displayed varying degrees of NMD escape (ranging from 1.3% up to NMD at all). Rescue events were found in 17 carriers (0.45%-80%). We did not find any significant associations of rescue with diagnosis ($p=0.15$) or AAO ($p=0.98$). We did however see a significant increase in *ABCA7* RNA expression with increasing amounts of rescue ($p=0.0003$) and observed a similar, albeit not significant, effect with increasing amounts of NMD escape ($p=0.18$). We also observed 199 previously undescribed splice events, which is a 4-fold increase of the known junctions. Further evaluation of the effect of rescue and NMD escape on protein level are ongoing, as well as targeted nanopore sequencing to further study the *ABCA7* transcriptome.
Conclusions: Our results show varying amounts of NMD escape and rescue splicing in PTC carriers, which can influence *ABCA7* RNA expression but have no clear impact on disease endophenotype.

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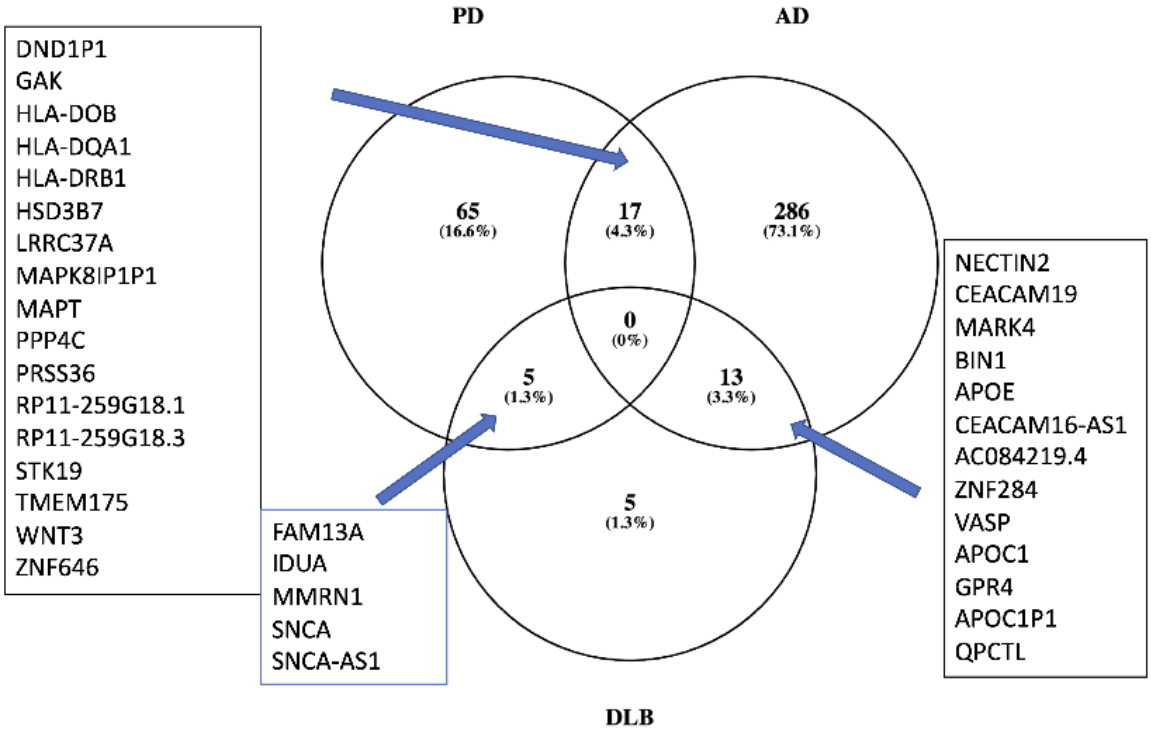
OD267 / #1992

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

MULTI-OMIC INFERENCE OF SHARED AND DISTINCT NON-CODING GENETIC MECHANISMS FOR ALZHEIMER'S DISEASE, LEWY BODY DEMENTIA AND PARKINSON'S DISEASE

Yuk Yee Leung, Pavel Kuksa, Jeffrey Cifello, Gerard Schellenberg, Li-San Wang
University of Pennsylvania Perelman School of Medicine, Department Of Pathology And Laboratory Medicine, Philadelphia, United States of America

Aims: Diagnosing Alzheimer's Disease (AD), Dementia with Lewy bodies (DLB) and Parkinson's disease (PD) early in disease trajectory is challenging due to overlapping symptoms. We hypothesize that the molecular mechanisms driven by the understudied non-coding genetic variations could contribute to understanding these diseases' pathophysiology. By integrating seven GWASs for AD [(Lambert, 2013; Kunkle 2019; Wightman, 2021; Swartzentruber, 2021; Bellenguez, 2022), N cases=25,580; 35,274; 90,338; 53,042; 111,326], DLB [(Chia, 2021), N=2,591] and PD [(Nalls, 2019), N=56,306], our goal is to identify the shared and distinct genes and mechanisms across AD, DLB and PD.
Methods: For each GWAS, using the INFERNO pipeline, we first identified genome-wide significant variants (*p*<5e-8) with brain-specific enhancers and active epigenetic marks. We then performed colocalization analyses of expression quantitative trait loci across 78 cell types to confirm the brain-specific effects of these regulatory variants. Finally, we determined whether the expression levels of the identified target genes were associated with disease status in humans.
Results: 19,189 independent variants (*p*<5e-8) were uncovered in these GWASs. 1,338 overlapped with brain-specific enhancers, of which 52% disrupted transcription factor binding (delta-PWM<-4) and 32% overlapped brain-specific active H3K27ac/H3K4me1/H3K4me3/H3K36me3 marks. We linked 738, 24 and 74 AD/DLB/PD loci to 705, 44 and 170 causal genes with at least 80% posterior colocalization probability. 13 and 5 target genes are common between AD+DLB, and DLB+PD (Figure 1). Common AD+DLB genes, including *APOE*, *BIN1*, and *APOC1*, are all found to have changing RNA expression in AD brains. Common DLB+PD genes include *SNCA*, *IDUA*, *MMRN1*, and *FAM13A;* known to be related to DLB/PD via mechanisms such as GTPase-mediated signal transduction, alpha-synuclein, and lysosomal activity.



Conclusions: We successfully identified common and distinct loci across AD, DLB and PD via integrative multi-layer genomics approach.

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OD268 / #2120

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

GENETIC INFLUENCES ON A JOINT AFFECTIVE-PSYCHOTIC NEUROPSYCHIATRIC SYMPTOM (NPS) PHENOTYPE IN ALZHEIMER'S DISEASE

Inga Antonsdottir[1,2], Mary Ann Sweet[3], Lambertus Klei[3], Byron Creese[4], Clive Ballard[4], Bernie Devlin[3], Constantine Lyketsos[1], Robert Sweet[3]
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Aims: Neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) such as psychotic (delusions or hallucinations) and affective symptoms (depression, anxiety, and/or irritability) are common and can negatively influence patient outcomes.
Methods: Participants with AD in one of six source studies were included in a Genome-wide association (GWAS) analysis of each pure phenotype and a joint phenotype, along with genetic correlation and heritability analyses conducted using GenomicSEM.
Results: Data from 8,714 participants (60.2% female) were analyzed with 32% having neither NPS phenotype, equal groups (28% each) exhibiting the affective phenotype (AD+A) or the joint affective + psychotic phenotype (AD+A+P), and a smaller group (12%) exhibiting the psychotic phenotype (AD+P). All three NPS phenotypes were heritable. For the AD+A+P (joint) phenotype the estimated h^2 on the liability scale was **0.16 ± 0.07** (95%CI: 0.02-0.30). While no SNPs achieved genome-wide significance, three SNPs approached significance, including a locus at 9q31 spanning RAD23B, a single SNP at 1q42, and a third at 15q22 spanning GTF2A2 and the 3' portion of BNIP2. Notably, the genetic correlation of the joint phenotype with AD+P was **0.95 ± 0.31** and with AD+A was **0.78 ± 0.64.** Different SNPs were associated with the pure AD+P or AD+A NPS phenotypes.
Conclusions: The AD+A+P (joint) phenotype affects over a quarter of patients with AD and is associated with common genetic variation. SNPs most strongly associated with each phenotype were different, a finding that stresses the importance of a distinct phenotype involving both affective and psychotic symptoms which may require specific treatment.

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OD269 / #661

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

QUANTIFYING THE TRANSFERABILITY OF POLYGENIC RISK SCORES FOR ALZHEIMER'S DISEASE ACROSS POPULATIONS

Michael Osterman[1,2], Yeunjoo Song[1], Nicholas Wheeler[1], Audrey Lynn[1], Kristy Miskimen[1], Jacquelaine Bartlett[1], William Bush[1,2], Jonathan Haines[1,2]
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Aims: Alzheimer's disease (AD) has a complex etiology with a strong genetic component. Despite mounting evidence that genetic risk effect sizes vary by population, most research on the genetics of AD has examined only populations of individuals with European ancestry. Here, we investigate the variable performance and transferability of polygenic risk scores (PRSs) by deriving a PRS from analyses of AD within each race/ethnicity group and applying these to other groups using a *k*-fold cross-validation approach.
Methods: We analyzed 15,745 individuals from the Alzheimer's Disease Sequencing Project r3 with three predominant self-identified race/ethnicity groups: African American (AA; n=2,937), Hispanic (n=3,047), and non-Hispanic White (NHW; n=9,708). For each group, a 5-fold cross-validation approach was used to perform genome-wide association study (GWAS; training) and construct PRS estimates (test). Due to its strong effect, *APOE* was excluded from PRS construction and considered as a separate covariate. AUC and other goodness-of-fit measures were calculated for each race/ethnicity-specific PRS within each cross-validation iteration. Minor allele frequency thresholds and sample size were also considered.
Results: Across all groups, the PRS trained in the same race/ethnicity group as the test group outperformed the other PRSs with a mean AUC improvement of 0.06. This was primarily driven by large improvements in the Hispanic group. Range of AUCs across iterations were also greater when applying PRSs from other groups. These findings were robust after inclusion of *APOE*, sex, and age covariates.
Conclusions: We quantified the variable performance of PRSs for AD and improvements in their predictive value when using a race/ethnicity-aware training sample. Further research into cross-ancestry variant, gene, and pathway-level effects influencing AD risk will improve understanding of the biological mechanism of AD and aid in identification of individuals at increased risk.

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OD270 / #1550

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

WHOLE GENOME SEQUENCING OF UNEXPLAINED EARLY-ONSET ALZHEIMER DISEASE

Christiane Reitz[1], Nicholas Ray[2], Jiji Kurup[1], Eder Lucio Da Fonseca[3], Margaret Pericak-Vance[4], Eden Martin[1], Gerard Schellenberg[1], Victoria Fernandez[1], Carlos Cruchaga[1], Gary Beecham[1]
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Aims: Genome sequencing efforts to identify causative genes and mechanistic molecular pathways have nearly exclusively focused on the late-onset form of the disease occurring in seniors. However, early-onset AD occurring before the age of 65 accounts for up to 10% of cases, shows a more aggressive course, and has a particularly detrimental medical, emotional, social and financial impact on patients and their families. Over 90% of these EOAD cases are unexplained by known mutations in *APP, PSEN1* and *PSEN2*, resulting in an extensive lack of understanding of the molecular etiology of this disastrous form of AD.
Methods: To begin closing this gap, we collated and whole-genome sequenced over 5,000 EOAD and early-onset MCI cases of diverse ancestry employing bioinformatics protocols and pipelines developed for the Alzheimer's Disease Sequencing Project (ADSP).
Results: This EOAD whole-genome sequencing dataset will be integrated with over 30,000 whole genomes of late-onset AD cases and cognitively healthy controls of diverse ancestry processed with similar protocols through the ADSP, the ADSP-follow-up study (FUS), and related efforts. This allows the comprehensive analysis of genetic factors underlying EOAD, as well as comparison to LOAD, and modulation of age of onset.
Conclusions: Primary goals are to (1) create a publicly available large-scale genomics resource for EOAD with WGS data generated and processed using ADSP protocols and pipelines and extensive harmonized phenotype data; (2) identify novel genomic EOAD risk and protective loci and loci modulating age at onset and decline in specific cognitive domains; (3) assess the role of polygenic and local-ancestry effects in EOAD etiology; (4) create EOAD-specific prediction models; (5) assess genetic overlap with cardiovascular and other potentially associated traits; and (6) identify druggable targets.

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OD271 / #1205

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

A LRRK2-SPECIFIC POLYGENIC RISK SCORE IDENTIFIES A NOVEL COHORT OF PATIENTS WITH LRRK2-DRIVEN PARKINSON'S DISEASE

Sam Jackson, Michael Nalls, Sahar Esmaeeli, Burke Lawlor, Adam Knight, Luc Desnoyers, Marcel Van Der Brug
Neuron23, Clinical Development, South San Francisco, United States of America

Aims: To develop a polygenic risk score (PRS) to identify a novel cohort of patients with LRRK2-driven Parkinson's Disease.
Methods: To build the LRRK2-PRS we analyzed data on patients with PD from publicly available cohorts (PPMI, PDBP, HBS, LCC, total *n*=3222) comprised of LRRK2 G2019S carriers and non-carriers. We employed several algorithmic approaches to identify genetic features in idiopathic PD patients that were also present in G2019S carriers. Associations between the LRRK2-PRS and disease progression were tested using an independent cohort (Quebec Parkinson's Network, *n*=515).
Results: 43 SNPs tagging the LRRK2 region, flanks and interaction network were selected for the LRRK2-PRS. Approximately 34% of idiopathic PD patients could be classified as diagnostically positive for LRRK2-driven disease. Pathway analysis of the 43 SNPs highlighted potential biological mechanisms for LRRK2-pathway altering alleles that could enhance or reduce the effects of LRRK2-driven PD.
Conclusions: This study represents a novel assessment of heritable genetic variation that expands the number of patients that may be considered as having LRRK2-driven disease. Our results suggest that alterations of function in the LRRK2 pathway are important in a larger population with Parkinson's disease than previously believed. This finding has important implications for the development of diagnostics and for the selection of patients in clinical trials testing LRRK2 inhibition in Parkinson's disease. We are currently investigating the ability of fluid biomarkers to characterize LRRK2-pathway function in this group of patients.

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OD272 / #748

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

PRELIMINARY FINDINGS OF WHOLE EXOME SEQUENCING IN A CROATIAN COHORT OF PARKINSON'S DISEASE PATIENTS

Valentino Racki[1,2], Eliša Papić[1], Mario Hero[1], Gloria Rožmarić[2], Anja Kovanda[3], Aleš Maver[3], Nada Starčević-Čizmarević[4], Borut Peterlin[3], Vladimira Vuletić[1]
[1]Faculty of Medicine, University of Rijeka, Department Of Neurology, Rijeka, Croatia, [2]Clinical Hospital Center Rijeka, Department Of Neurology, Rijeka, Croatia, [3]University Medical Center Ljubljana, Clinical Institute Of Genomic Medicine, Ljubljana, Slovenia, [4]Faculty of Medicine, University of Rijeka, Department Of Medical Genetics And Biology, Rijeka, Croatia

Aims: Parkinson's disease is a multifactorial disease, and an estimated 5-10% can be contributed to monogenic causes, and identifying those patients remains a diagnostic challenge. Whole-exome sequencing enables us to simultaneously analyse a large number of genes, although a lack of clear criteria for genetic evaluation and testing leads to reduced genetic testing in routine clinical practice. Our aim was to assess the clinical application of whole-exome sequencing Parkinson's disease patients.
Methods: Our study cohort includes patients from the Clinic of Neurology at the Clinical Hospital Centre Rijeka, referred to genetic testing during 2021 and 2022. Exome sequencing was performed at Clinical Instutite of Medical Genomics at the University Medical Center Ljubljana using standardized protocols in use. Identified variants were classified according to the ACMG and AMP 2015 joint consensus recommendation, along with ACGS recommendations where applicable.
Results: We have performed exome sequencing in 74 patients. Causative pathogenic mutations have been confirmed in 9 patients (12,16%, GBA n=8, PRKN n=1), while variants of uncertain significance were found in 17 patients (22,97%, ATP13A2 n=2, EIF4G1 n=2, PSEN1 n=1, SORL1 n=1, LRRK2 n=1, SNCA n=1,, GCDH n=1, ATP7B n=1, THAP1 n=1, TBK1 n=1, ERBB4 n=1, ITM2B n=1, NOTCH 3 n=1, SETX n=1, NR4A2 n=1). Additonally, 3 patients have confirmed carriership of classically recessive genes (GCHD n=1, FIG4 n=1, RNF216 n=1).
Conclusions: Pathogenic mutation yield of 12,16% is comparable to current findings for european populations, with GBA as the most common pathogenic risk factor, similar to earlier reports in Czech and German population. Our findings show that whole-exome sequencing can be considered in the clinical evaluation of Parkinson's disease, as it can lead to the findings of causative pathogenic mutations and expand our knowledge by discovering novel variants of target genes.

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OD273 / #423

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

CNTN5 AND APOLIPOPROTEINS INTERPLAY IN THE PRE-SYMPTOMATIC PHASE OF ALZHEIMER'S DISEASE

Marina Tedeschi Dauar[1,2,3], Cynthia Picard[2,3], Anne Labonte[2,3], Pedro Rosa-Neto[1,4], John Breitner[1,2,3], Sylvia Villeneuve[1,2,3], Judes Poirier[1,2,3]
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Aims: To examine the relationship between disease-associated *CNTN5* gene and apolipoproteins homeostasis in the central nervous system
Methods: Data for this work was obtained from the PREVENT-AD longitudinal cohort which recruited cognitively unaffected individuals over the age of 55 who have a first degree relative with Alzheimer's disease. Participants are followed annually with multiple biochemical and imaging biomarkers and cognitive assessments. Contactin 5 levels in the plasma and CSF were measured using Olink's proximity extension assay, apolipoproteins in the CSF were measured using Luminex multiplex assay, and plasma cholesterol was measured in a comercial service.
Results: Contactin 5 in the CSF was found to positively associate with CSF apolipoproteins D, E, J and B ($p<0.001$), and with CSF cholesterol ($p=0.0096$). In the plasma, Contactin 5 levels were positively associated with levels of total cholesterol ($p=0.02$), LDL ($p=0.012$) and HDL ($p=0.014$). Participants who carry at least one copy of the *CNTN5* risk-variant had significantly lower levels of CSF ApoD ($p=0.029$).
Conclusions: *CNTN5* is a neurodevelopmentally-regulated gene implicated in the specification of dendritic arbors and central nervous system plastic response in neurons. Its extensive interactions with key regulators of lipid homeostasis in cognitivelly unaffected subjects at high risk for AD is consistent with a role during the compensatory brain response associated to neurodegeneration and synaptic damage.

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OD274 / #273

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

USING EPIGENOMIC PROFILING TO ELUCIDATE THE MOLECULAR MECHANISMS UNDERLYING LEWY BODY DEMENTIAS

Jennifer Imm[1], Joshua Harvey[1], Ehsan Pishva[1,2], Byron Creese[1], Leonidas Chouliaras[3], Emma Dempster[1], Clive Ballard[1], John O'Brien[3], Dag Aarsland[4,5], Jonathon Mill[1], Katie Lunnon[1]
[1]University of Exeter, Clinical And Biomedical Sciences, Exeter, United Kingdom, [2]Maastricht University, Psychiatry And Neuropsychiatry, Maastricht, Netherlands, [3]University of Cambridge, Department Of Psychiatry, Cambridge, United Kingdom, [4]Kings College London, Department Of Old Age Psychiatry, London, United Kingdom, [5]Stavanger University Hospital, Centre For Age-related Medicine, Stavanger, Norway

Aims: The Lewy body diseases (LBDs) (Dementia with Lewy bodies (DLB), Parkinson's disease (PD) and Parkinson's disease dementia (PDD)) are all neurodegenerative diseases classified by the accumulation of alpha-synuclein in neurons, forming Lewy bodies (LB). We hypothesise that these LBs cause epigenetic changes within neurons and surrounding cells and that these changes can be used to distinguish the different diseases from one another.
Methods: DNA and RNA has been extracted from 921 bulk tissue samples from 474 unique donors and, where possible, we have tried to obtain both the cingulate gyrus and prefrontal cortex from the same individual. We have profiled all 921 DNA samples on the Illumina EPIC array, which generates a quantitative measure of DNA methylation for over 850,000 CpG sites. Linear regression and groupwise comparisons were then used to identify loci that are significantly associated with neuropathology or clinical diagnosis, with downstream network and pathway analyses.
Results: Study groups have been sourced consisting of cases with PD, PDD and DLB based on LB deposition and clinical symptom staging. Control cases have been selected for matched age and levels of concomitant AD pathology. We have identified significant changes in DNA methylation associated with both clinical diagnosis and neuropathology. These loci include genes that have been previously associated with synucleinopathies, including *PTPRN2, DGKI and SYN3.*
Conclusions: We have interrogated the epigenetic basis of neuropathological progression and clinical staging of LB disease, controlling for levels of concomitant AD pathology. We have completed bulk methylation analysis for two disease relevant brain regions and identified both phenotypic and neuropathologic changes within these regions. Processing of samples for fluorescence activated nuclei sorting and laser capture microdissection has begun (n=15/group) to assess the cell-type specificity of the methylation changes.

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ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

GWAS OF ALZHEIMER'S DISEASE ACROSS AGE AND APOE*4 STRATA IMPLICATES THE ELL/LRRC25 LOCUS

Michael Belloy[1], Pablo García-González[2], Atahualpa Castillo Morales[3], Yann Le Guen[1], Nandita Kasireddy[1], Sarah Eger[1], Rebecca Sims[3], Julie Williams[3], Agustín Ruiz[4], Maria Saez[5], Valerio Napolioni[6], Zihuai He[1], Michael Greicius[1]
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Aims: We sought to identify how the interaction of *APOE**4 and age affects genome-wide genetic risk for AD.
Methods: Case and control participants (European ancestry) were split into four strata across age (60-80y/80y+) and *APOE**4 (positive/negative). Genetic data were available from whole-genome-sequencing (WGS) or SNP arrays imputed to TOPMed. Genome-wide association studies (GWAS) were performed per data type, followed by fixed-effects meta-analysis within strata (LMM-BOLT v2.4; GWAMA v2.2.2). GWAS performed case-control logistic regressions or multiple linear regressions on an AD-age score (outcomes combined). Models adjusted for sex, *APOE**4/*APOE**2 dosage, the first five genetic principal components, and array/sequencing center. GWAS hits were evaluated for SNP-by-*APOE**4-by-age interactions. Significant hits/loci were followed up with external replications, Quantitative Trait Locus (QTL) colocalization analyses (R coloc package), and *APOE**4-stratified QTL analyses in AMP-AD brain RNAseq data.
Results: We found a novel genome-wide AD locus specific to *APOE**4 positive individuals ages 60-80y (**Figure-1**). The top variant rs10405479 was risk-increasing and showed concordant effects in two replication cohorts (**Figure-2**). The locus showed good colocalization with non-stratified brain/blood expression (e)QTLs for *ELL* and brain prefrontal cortex eQTLs for *LRRC25* (**Table-1, Figure-3**). The top variant was a more pronounced brain eQTL for *ELL* in *APOE**4 positive individuals (**Figure-4**). *ELL* has been associated with leukemia and is an Elongation factor component of the super elongation complex (SEC), which affects the catalytic rate of RNA polymerase II transcription. *LRRC25* saw recent support for colocalization of microglial eQTLs with non-stratified subthreshold AD GWAS

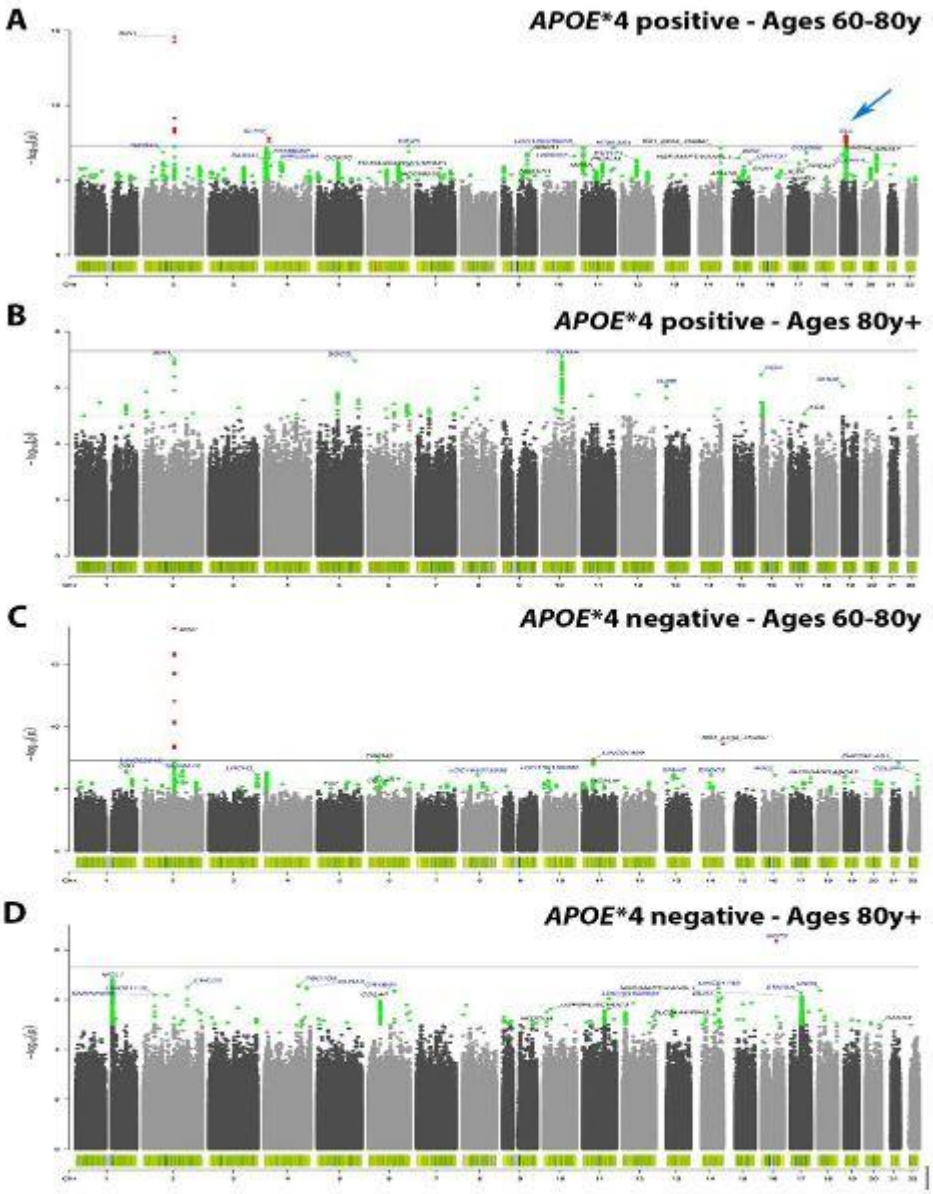

Figure-1. Manhattan plots of Discovery GWAS stratified across *APOE4 and age status.** Green and red dots respectively indicate suggestive and genome-wide significance. Top variants passing below a P-value of 10^{-5} within 500Kb of known AD loci were annotated in black. Top variants passing below a P-value of 10^{-6} in novel loci were annotated with the nearest gene from the NCBI RefSeq curated gene set in blue. The blue arrow indicates the GWAS hit/locus (p<5e-8) that also passed Bonferroni significance for the three-way SNP-by-*APOE**4-by-age interaction effect in the full discovery sample (accounting for the number of independent GWAS-significant loci across strata).

signal.

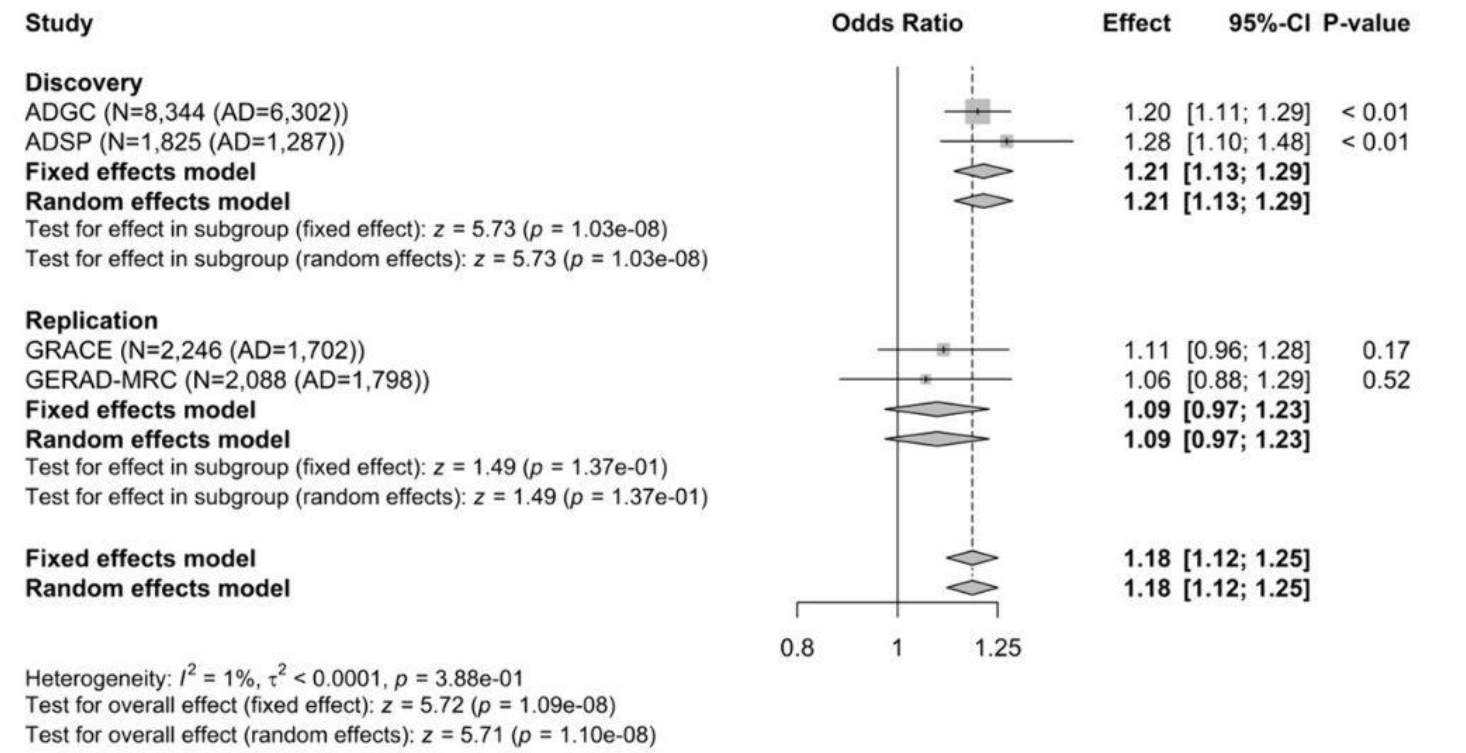

Figure-2. Discovery and replication findings for the top variant rs10405479 in the *ELL/LRRC25* locus in the *APOE4 positive ages 60-80y AD GWAS.** Replications showed concordant effect directions and are trending toward significance; additional replication efforts are being pursued. *Abbreviations: Alzheimer's disease Genetics Consortium, ADGC; Alzheimer's disease Sequencing Project, ADSP.*

Dataset	N. Subjects	Tissue	QTL type	Gene	nsnps	PP.H0.abf	PP.H1.abf	PP.H2.abf	PP.H3.abf	PP.H4.abf
xQTLServe	**534**	**Brain - DLPFC**	**eQTL**	**LRRC25**	4677	1.03E-07	1.66E-04	2.59E-05	0.0408	**0.9590**
eQTLGen	**10826**	**Blood**	**eQTL**	**ELL**	2705	0.00E+00	2.96E-305	5.54E-05	0.0889	**0.9110**
xQTLServe	**534**	**Brain - DLPFC**	**eQTL**	**ELL**	4514	2.07E-50	3.34E-47	7.11E-05	0.1138	**0.8862**
MetaBrain	**2897**	**Brain - multiple regions**	**eQTL**	**ELL**	5284	2.97E-12	4.82E-09	1.11E-04	0.1796	**0.8202**
ROSMAP_DLPFC_Sieberts_et_al_2020	570	Brain - DLPFC	eQTL	ISYNA1	3420	8.55E-05	0.1377	5.14E-05	0.0820	0.7802
eQTLGen	10612	Blood	eQTL	ISYNA1	2705	5.45E-07	8.85E-04	1.66E-04	0.2684	0.7306
MetaBrain	2897	Brain - multiple regions	eQTL	LRRC25	5442	1.18E-31	1.91E-28	2.18E-04	0.3524	0.6474
microglia_eQTL	400	microglia - scRNAseq	eQTL	SSBP4	1681	1.47E-04	0.2381	9.02E-05	0.1456	0.6160
eQTLGen	10826	Blood	eQTL	CRTC1	2705	1.10E-06	0.0018	2.99E-04	0.4845	0.5134
xQTLServe	534	Brain - DLPFC	eQTL	ISYNA1	4596	2.28E-04	0.3680	1.33E-04	0.2137	0.4179
microglia_eQTL	400	microglia - scRNAseq	eQTL	LRRC25	1658	1.16E-09	1.89E-06	3.95E-04	0.6395	0.3601
MetaBrain	2897	Brain - multiple regions	eQTL	SSBP4	5384	2.53E-04	0.4109	1.71E-04	0.2777	0.3115
ARIC	7213	Blood	pQTL	ELL	2322	3.73E-04	0.6036	6.88E-05	0.1110	0.2849
eQTLGen	10612	Blood	eQTL	LRRC25	2705	6.16E-307	1.00E-303	4.83E-04	0.7838	0.2157
ROSMAP_DLPFC_Sieberts_et_al_2020	570	Brain - DLPFC	eQTL	ELL	3495	3.71E-04	0.5984	1.15E-04	0.1857	0.2154
ROSMAP_DLPFC_Sieberts_et_al_2020	570	Brain - DLPFC	eQTL	CRTC1	3297	3.51E-04	0.5655	1.57E-04	0.2528	0.1812
ROSMAP_DLPFC_Sieberts_et_al_2020	570	Brain - DLPFC	eQTL	SSBP4	3439	4.14E-04	0.6677	1.51E-04	0.2438	0.0880
MetaBrain	2897	Brain - multiple regions	eQTL	ISYNA1	5355	2.99E-04	0.4856	2.77E-04	0.4489	0.0649
microglia_eQTL	400	microglia - scRNAseq	eQTL	GDF15	1627	4.97E-04	0.8052	8.96E-05	0.1452	0.0490
microglia_eQTL	400	microglia - scRNAseq	eQTL	CRTC1	1263	5.19E-04	0.8419	7.13E-05	0.1155	0.0420
eQTLGen	7973	Blood	eQTL	SSBP4	2534	3.90E-47	6.34E-44	5.95E-04	0.9655	0.0339
microglia_eQTL	400	microglia - scRNAseq	eQTL	ELL	1621	3.51E-04	0.5689	2.48E-04	0.4018	0.0287
microglia_eQTL	400	microglia - scRNAseq	eQTL	PGPEP1	1597	3.78E-04	0.6122	2.21E-04	0.3587	0.0285
xQTLServe	534	Brain - DLPFC	eQTL	SSBP4	4623	4.26E-04	0.6866	1.77E-04	0.2853	0.0275
microglia_eQTL	400	microglia - scRNAseq	eQTL	ISYNA1	1707	3.32E-04	0.5382	2.70E-04	0.4384	0.0228
MetaBrain	2897	Brain - multiple regions	eQTL	CRTC1	5035	3.96E-04	0.6422	2.12E-04	0.3446	0.0126
MetaBrain	2897	Brain - multiple regions	eQTL	GDF15	5500	1.41E-04	0.2294	4.69E-04	0.7610	0.0090
ARIC	7213	Blood	pQTL	LRRC25	2234	4.55E-04	0.7357	1.58E-04	0.2549	0.0088
DECODE	35354	Blood	pQTL	ELL	3641	4.25E-04	0.7788	1.18E-04	0.2154	0.0052
DECODE	35354	Blood	pQTL	LRRC25	3641	4.53E-04	0.8296	9.03E-05	0.1653	0.0046
eQTLGen	10612	Blood	eQTL	GDF15	2702	1.04E-91	1.68E-88	6.16E-04	0.9994	1.68E-05
MetaBrain	2897	Brain - multiple regions	eQTL	PGPEP1	5529	3.42E-72	5.55E-69	6.16E-04	0.9994	1.25E-05
ROSMAP_DLPFC_Sieberts_et_al_2020	570	Brain - DLPFC	eQTL	PGPEP1	3549	9.80E-29	1.58E-25	6.20E-04	0.9994	1.19E-05
eQTLGen	5537	Blood	eQTL	PGPEP1	2699	2.61E-68	4.23E-65	6.16E-04	0.9994	1.17E-05
ARIC	7213	Blood	pQTL	GDF15	2192	0.00E+00	0.00E+00	6.18E-04	0.9994	6.58E-06
DECODE	35354	Blood	pQTL	GDF15	3641	0.00E+00	0.00E+00	5.46E-04	0.9994	5.80E-06

Table-1. Colocalization findings with public non-stratified eQTL/pQTL summary statistics resources. The AD GWAS signal for the *ELL/LRRC25* locus in *APOE**4 positive subjects ages 60-80y was evaluated for colocalization with expression (e)QTL and protein (p)QTL summary statistics from a vast range of publicly available resources across variable tissues. We focused on 7 genes for which FDR-significant QTLs were observed in any dataset for the top hit in the AD GWAS. The current table is non-exhaustive and lists results for high-interest datasets. The PP.H4.abf column reports the posterior probability that the respective two evaluated traits share a common causal variant; a probability higher than 0.8 is considered good colocalization (green shading in cells). *Abbreviations: dorsolateral prefrontal cortex, DLPFC; single cell RNA sequencing, scRNAseq.*

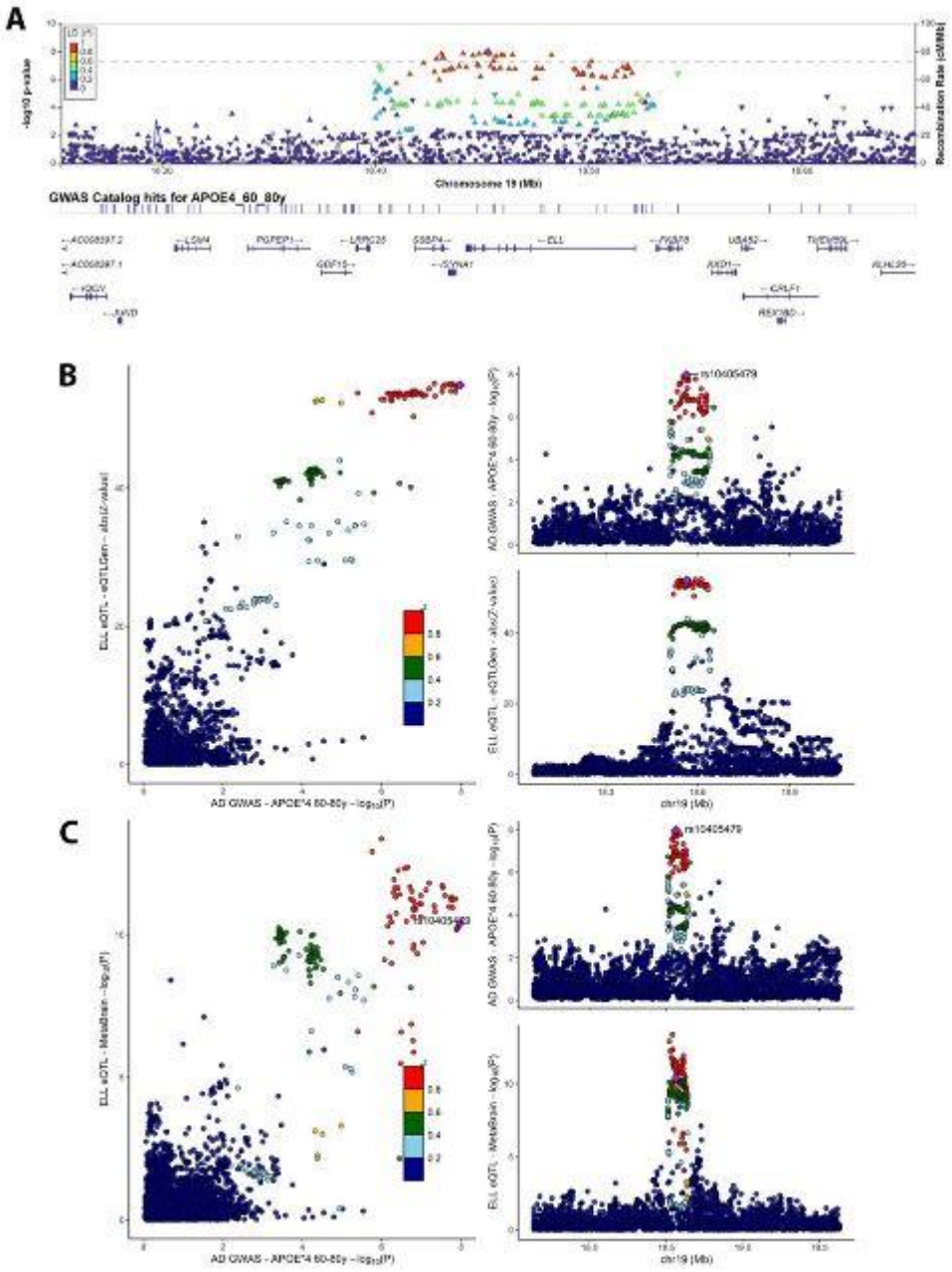

Figure-3. Locus Zoom and Locus Compare plots for the *ELL/LRRC25* locus in the *APOE*4* positive ages 60-80y AD GWAS. A) Locus zoom plot. **B)** Locus Compare plot for blood eQTL signal in the eQTLGen dataset and **C)** brain eQTL signal in the MetaBrain dataset (see Table-1), showing good colocalization. Note that in (B), the eQTL signal is shown with absolute Z-values rather than P-values due to the numerical lower cap of 1e-300 in the R software environment. Plots were set to indicate the rs10405479 variant.

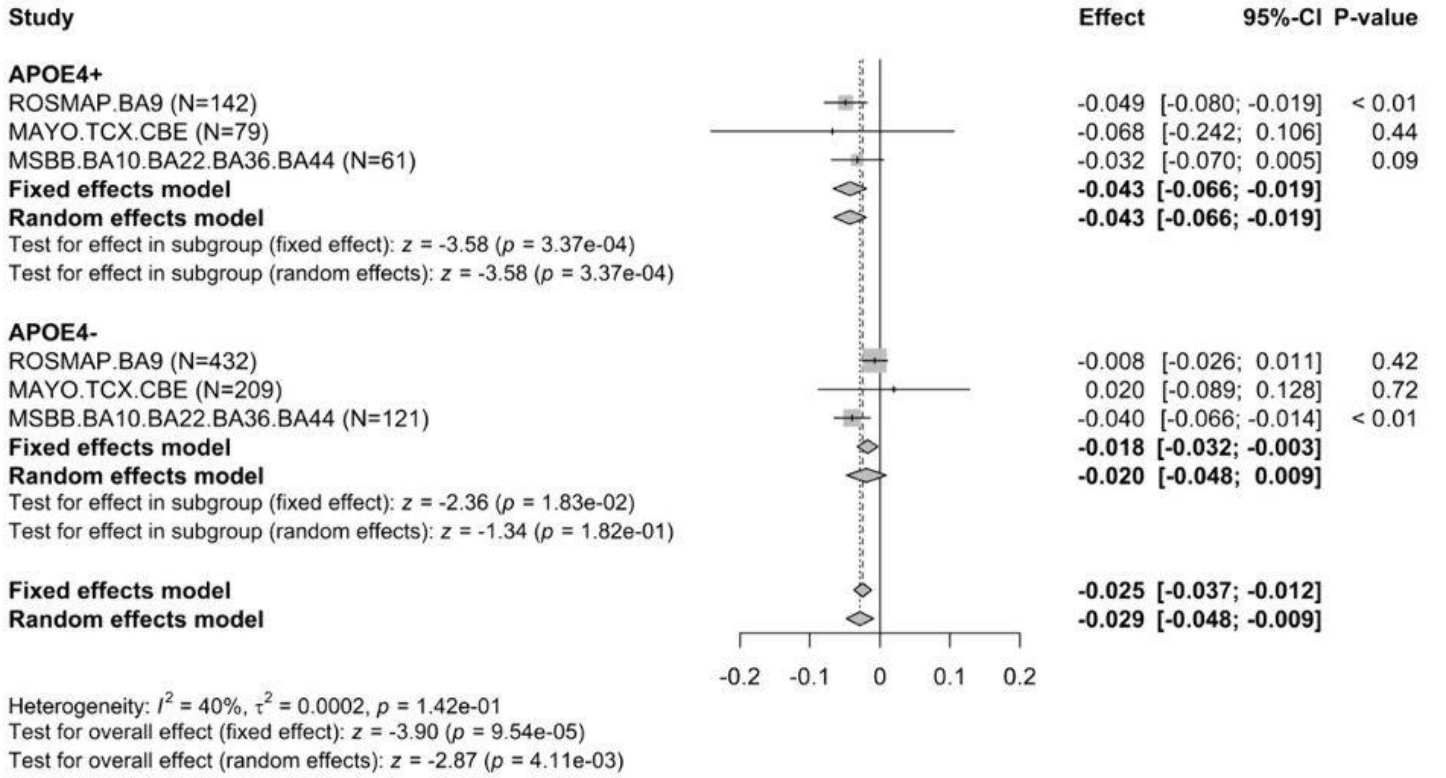

Figure-4. Evaluation of the *ELL/LRRC25* locus top variant rs10405479 for *APOE4-stratified eQTL effects on *ELL* in brain RNAseq data from AMP-AD (N=1,044).** Note the stronger eQTL effect in *APOE**4 carriers, consistent with the primary AD GWAS Findings where the effect of this variant is specific to *APOE**4 carriers. Analyses were restricted to ROSMAP/MAYO/MSBB individuals with matching joint-called WGS data available from AMP-AD. In MAYO and MSBB, eQTL effects were evaluated through random effects analyses to account for expression level data being available across multiple brain regions for individuals.

Conclusions: We identified a novel genome-wide significant AD risk locus that is modulated by *APOE**4 status and age. This contributes to personalized genetic medicine and paves the way towards new potential AD drug targets. Additional replication efforts are being pursued.

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OD276 / #736

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

GENETIC VARIATION IN THE MELANOPSIN GENE OPN4 MODERATES THE RELATIONSHIP OF SLEEP WITH COGNITIVE PERFORMANCE

Eleanor O'Brien[1,2], Stephanie Rainey-Smith[3], Tenielle Porter[1,2], Pierrick Bourgeat[4], Vincent Dore[5,6], Paul Maruff[7,8], Christopher Rowe[6,8], Victor Villemagne[9,10], Simon Laws[1,2]
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Aims: We test (1) whether genetic variation in the melanopsin gene *OPN4* is associated with risk of Alzheimer's disease (AD), and with variation in other AD-related traits (amyloid burden, cognition, brain volumetrics) and sleep measures, and (2) whether genetic variation in *OPN4* moderates the association of sleep with AD-related traits.
Methods: For 827 older adults (aged ≥ 60 years) enrolled in the Australian Imaging, Biomarker and Lifestyle (AIBL) Study of Ageing, we used linear models to test for associations of six SNPs within the *OPN4* gene with incidence of AD, cortical amyloid burden, scores for six cognitive composites, and volumes of four brain regions, as well as with six sleep measures derived from the Pittsburgh Sleep Quality Index (PSQI) questionnaire. We then used linear models to test for interactions of *OPN4* SNPs and sleep measures in predicting outcomes for AD and related traits.
Results: *OPN4* SNPs were associated with significant variation in the cognitive traits language and attention processing, and with ventricular volume, but not with incidence of AD, amyloid burden or sleep measures. Further, two *OPN4* SNPs (*rs1079610* and *rs3740334*) moderated the association of several sleep measures (duration, disturbances, daytime dysfunction and global PSQI) with language among cognitively unimpaired participants. For each SNP, one genotype showed a positive association between sleep quality and language score, while the other showed no association.
Conclusions: Our findings suggest that the cognitive benefits of improving sleep quality vary significantly depending on genetic variation in the *OPN4* gene. Understanding how genetic variation moderates the effect of modifiable lifestyle factors such as sleep on the onset, progression and severity of AD symptoms is important for ensuring treatment recommendations can be optimally tailored for individuals.

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OD277 / #762

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

RAPID PROGRESSION OF EARLY-ONSET PARKINSON'S DISEASE WITH DEMENTIA CAUSED BY A LARGE DE NOVO TRIPLICATION OF THE SNCA LOCUS

Katrin Beyer[1], Mireia Gea[2], Mar Mallo[3], Lourdes Ispierto[2], Dolores Vilas[2], Cynthia Caceres[2], Silvia Martínez[2], Pau Pastor[2], Ramiro Alvarez[2]
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Aims: To identify the genetic cause of early-onset fast-progressing motor symptoms with fluctuations accompanied by a fast-progressing cognitive decline that appeared less than three years after the onset of motor symptoms, in a 41-year-old female patient.
Methods: Genetic testing was carried out by targeted NGS using the in-house Park-Dyst v3 panel. The copy number of 6 PD genes including *SNCA* was determined by MLPA. The size of the amplified region was determined by the Cytoscan HD Array. Expression of *SNCA, MMRN1, GPRIN3, HERC6, PPM1K* and *SPP1* was determined by real-time PCR on a Rotor-Gene 3000 using Luna Universal qPCR in 3 independently purified RNA samples of the patient compared to 17 age-matched controls (age 48.2 years, age range 42-58) and 14 age-matched idiopathic PD patients (age 47.6 years, age range 32-59).
Results: Neither known disease-causing nor other rare variants were identified. De novo mono-allelic triplication of *SNCA* was found by MLPA, since neither the mother nor the father carried the multiplication. CytoScan HD array analysis showed that the triplicated region had a size of 2,412 kb and included 21 genes. The triplicated region is the largest described so far and contains in addition to *SNCA* five other PD-associated genes: *MMRN1, GPRIN3, HERC6, PPM1K* and *SPP1*. Expression analysis of the six genes revealed that these were overexpressed in blood compared to controls and early-onset idiopathic PD. The highest relative expression was found for *SNCA* (3.5-fold increase), *MMRN1* (3.2-fold increase) and *SPP1* (2.9-fold increase).
Conclusions: The 2,412 kb-triplication of the *SNCA* gene region, accompanied by the over-expression of *SNCA* and 5 PD-related genes causes early-onset PD with fast progressing motor symptoms in need of early levodopa treatment and early onset and fast progression of cognitive decline.

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OD278 / #835

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

ALZHEIMER'S DISEASE BIOMARKER STATUS IS ASSOCIATED WITH KLOTHO GENOTYPE BUT NOT KLOTHO PROTEIN LEVELS IN AN AT-RISK COHORT

Ira Driscoll[1,2], Noah Cook[1], Julian Gaitan[1], Catherine Gallagher[3], Sterling Johnson[1], Sanjay Asthana[1], Bruce Hermann[1], Mark Sager[1], Kaj Blennow[4], Henrik Zetterberg[4], Cynthia Carlsson[1], Gwendlyn Kollmorgen[5], Margherita Carboni[6], Dan Wang[7], Dena Dubal[7], Ozioma Okonkwo[1]
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Aims: Klotho is an anti-aging, neuroprotective hormone encoded by the *KLOTHO* gene. *KLOTHO* KL-VS heterozygosity (KL-VS$_{HET}$) is protective against beta-amyloid (Aβ) and tau, the two neuropathological hallmarks of Alzheimer's disease (AD; Erickson et al., 2019; Driscoll et al., 2021). We examined whether KL-VS$_{HET}$ frequency varies based on Aβ (A) and tau (T) status – Aβ positive (A+T-), tau positive (A-T+), or both (A+T+) – in a cohort enriched for AD risk.
Methods: The sample included non-demented adults (N=310; Mean$_{AGE}$[SD]=63.9 [6.7]) from Wisconsin Registry for Alzheimer's Prevention and Wisconsin Alzheimer's Disease Research Center who were genotyped and underwent venipuncture or lumbar puncture for sampling of circulating serum (Immuno-Biological Laboratories) or cerebrospinal fluid (CSF; Roche NeuroToolKit) klotho respectively. Fisher's exact and logistic regression models, controlling for age at data collection and sex, were used to determine whether A/T status covaried with KL-VS$_{HET}$ frequency. Linear regression models controlling for sex, age at collection, and time between sample collections were used to determine whether A/T status predicted circulating klotho levels in serum or cerebrospinal fluid (CSF).
Results: A/T status was associated with KL-VS$_{HET}$ frequency (p=0.04). KL-VS$_{HET}$ frequency was lower in those who were A+ vs. A- (p=0.01), and in those with A+/T- compared with A-T- (p=0.03). KL-VS$_{HET}$ frequencies did not differ in A-T+ or A+T+ participants compared with A-T-, nor between those T+ and T- (p=0.53). A/T status did not significantly predict CSF or serum klotho levels (all p's>0.06).
Conclusions: The neuroprotective KL-VS$_{HET}$ variant is less frequent in A+ than A- cognitively unimpaired individuals. A/T status does not predict circulating klotho levels in CSF or serum. Our results add to the growing *KLOTHO* literature and suggest the need for further research focusing on understanding the underlying mechanisms.

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ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

GENETIC ASSOCIATION BETWEEN ALZHEIMER'S DISEASE AND CARDIO-CEREBROVASCULAR RISK FACTORS

Annie Lee[1], Dolly Reyes-Dumeyer[1], Philip De Jager[2], David Bennett[3], Julie Schneider[3], Vilas Menon[4], Yanling Wang[3], Rafael Lantigua[5], Martin Medrano[6], Diones Rivera Mejia[7], Ivonne Jiménez-Velázquez[8], Walter Kukull[9], Adam Brickman[10], Jennifer Manly[10], Giuseppe Tosto[1], Caghan Kizil[1], Lindsay Farrer[11], Jesse Mez[12], Jaeyoon Chung[12], Badri Vardarajan[1], Richard Mayeux[13]
[1]Columbia University Irving Medical Center, Department Of Neurology, New York, United States of America, [2]Columbia University Medical Center, Center For Computational & Translational Neuroimmunology, Department Of Neurology, New York, United States of America, [3]Rush University Medical Center, Rush Alzheimer's Disease Center, Chicago, United States of America, [4]Columbia University, Center For Translational And Computational Neuroimmunology, New York City, United States of America, [5]Columbia University, Department Of Medicine, New York, United States of America, [6]Corominas, Geriatrics, Santiago, Dominican Republic, [7]CEDIMAT, Neurosurgery, Santo Domingo, Dominican Republic, [8]University of Puerto Rico, Medicine, San Juan, Puerto Rico, [9]University of Washington, Epidemiology, WA, United States of America, [10]Columbia University, Neurology, New York, United States of America, [11]Boston University School of Medicine, Medicine, Boston, United States of America, [12]Boston University School of Medicine, Neurology, Boston, United States of America, [13]Columbia University, Department Of Neurology, New York, United States of America

Aims: Alzheimer's disease (AD) has been associated with cardiovascular and cerebrovascular risk factors (CVRFs) during middle age and later and is frequently accompanied by cerebrovascular pathology at death. We previously observed an interaction between CVRFs and *MNL2* ($p= 6.6x10^{-7}$). The aim here was to increase sample size to identify additional variants contributing to pathogenesis.
Methods: Genome-wide, gene by CVRF interaction analyses for AD, in 6,927 patients and 9,195 controls identified. Clinical AD was defined using NINCDS-ADRDA criteria and controls were found to lack cognitive impairment. A cardiovascular risk score was developed using self-reported history of heart disease, hypertension, and diabetes, and by measured body mass index (BMI). A dimensionality reduction approach was used to capture the amount of variance accounted for by the CVRFs resulting in individual principal component scores. Gene-based tests were performed using the adaptive gene-environment interaction (aGE) test and validated using an alternative method implemented in the gene-environment set association test (GESAT). Statistical significance was set at $p=5x10^{-6}$.
Results: The previous association with *FMNL2* was strengthened and several additional genes were identified as significantly associated including *SLC22A14, RFC2, IGFN1,* and *CFAP99*. FMNL2 encodes a formin-related protein important in regulating actin and microtubules. Other genes are involved in maintenance of the extracellular matrix, plasma membrane adhesion, and transmembrane transport. *RFC2* is one of several genes deleted in Williams Syndrome.
Conclusions: *FMNL2* regulates pathology-dependent plasticity of the blood-brain-barrier by controlling gliovascular interactions and stimulating the clearance of extracellular aggregates. Several other genes are likely to be involved in the complex interaction between Alzheimer's disease pathology and cerebrovascular pathology. Understanding how these genes interfere with the normal mechanisms underlying the clearance of amyloid and tau increasing their deposition in brain will be essential.

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ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

FINE-MAPPING OF ALZHEIMER'S DISEASE SUSCEPTIBILITY LOCI PRIORITIZES FUNCTIONAL VARIANTS WITHIN MYELOID CELL ENHANCERS

Ashvin Ravi[1], Joy Lee[2], Jack Humphrey[1], David Knowles[3], Kristen Brennand[4], Towfique Raj[1]
[1]Icahn School of Medicine at Mount Sinai, Neuroscience, New York, United States of America, [2]Yale University, Genetics, New Haven, United States of America, [3]New York Genome Center, Genetics, New York, United States of America, [4]Yale University, Neuroscience, New Haven, United States of America

Aims: Genome-wide association studies (GWAS) and quantitative trait locus (QTL) analysis have identified many common variants and genes associated with Alzheimer's Disease (AD) and highlighted the role of myeloid cells (microglia, monocytes, and macrophages) in the pathogenesis of AD. Our aims are to (i) prioritize common genetic variants that may indicate a causal effect; (ii) understand the role of these variants in myeloid cells; and (iii) perform functional validation of these variants.
Methods: We perform statistical and functional fine mapping of 75 risk loci from the largest AD GWAS to date (Bellenguez et al. 2022), using PolyFun and SuSiE, to identify putative functional variants. We used deep learning models of gene regulation in AD-relevant cell types to empower functional fine-mapping. We perform a random-effects meta-analysis of 10 myeloid-cell expression-QTL (eQTL) datasets (**meta-myeloid:** 1,763 samples, 1,187 unique donors), followed by colocalization analysis to identify significant myeloid-cell variants and genes in AD.
Results: Our fine mapping results reveal 60/75 AD risk loci have at least one significant SNP (PIP > 0.1). While several loci contain missense variants, particularly in the *TREM2*, *SHARPIN*, *ABI3*, *PLCG2,* and *MME* loci, most SNPs identified lie in noncoding regions, requiring further validation. We found significant enrichment of putative functional variants in myeloid cell enhancers identified by the ABC model, with the strongest enrichment seen in microglia ($p = 2x10^{-12}$). Colocalization analysis with the meta-myeloid eQTL identifies 43 significant AD GWAS loci-eQTL gene pairs. We are currently conducting a massively-parallel reporter assay (MPRA) of 11,550 fine-mapped and eQTL variants in iPSC microglia.
Conclusions: Overall, these results illustrate the significance of myeloid cells in AD risk and provide a comprehensive list of regulatory variants and genes that may serve as therapeutic targets.

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OD281 / #1360

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

RECRUITMENT AND RETENTION FOR ALZHEIMER'S DISEASE DIVERSITY GENETIC COHORTS IN THE ADSP (READD-ADSP): A GLOBAL EFFORT TO IDENTIFY GENETIC FACTORS IN ALZHEIMER DISEASE

Rufus Akinyemi[1,2], Michael Cuccaro[3], Brian Kunkle[3], Giuseppe Tosto[4], Joshua Akinyemi[5], Azizi Seixas[6], Farid Rajabli[7], Anthony Griswold[3], Christiane Reitz[8], William Bush[9], Jeffery Vance[7], Jonathan Haines[10], Oyedunni Arulogun[11], Albert Akpalu[12], Fred Sarfo[13], Biniyam Ayele[14], Albertino Damasceno[15], Lwere Kamada[16], Richard Walker[17], Thierry Adoukonou[18], Alfred Njamnshi[19], Judith Boshe[20], Njideka Okubadejo[21], Mayowa Owolabi[1,2], Olusegun Bayeiwu[22], Scott Williams[9], Rajesh Kalaria[23], Sudha Seshadri[24], Goldie Byrd[25], Adesola Ogunniyi[1,2], Margaret Pericak-Vance[7]
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Aims: This study will increase the global resource of the Alzheimer's Disease Sequencing Project (ADSP) by including underrepresented African ancestry (Black Americans (BA), African (AF)) and Hispanic/Latinx (HL) individuals in AD genetic studies to deepen understanding of the effects of ancestral genetic variations on AD biology.
Methods: READD-ADSP is a case/control study that will recruit, retain, evaluate 13,000 participants of diverse race/ethnicity, including 5,000 AF, 4,000 BA, and 4,000 US HL. The study in Africa involves multiple sites in 9 African countries operating under the African Dementia Consortium (AfDC).
Sociodemographic, clinical, and neurocognitive data will be obtained on all participants using protocol-guided evaluation procedures that have been developed to accommodate different cultures and to support phenotype harmonization, and for joint studies of biological and social risks of AD. The inclusion of overlapping clinical measures will facilitate harmonized phenotypes that are inferentially equivalent across the different cohorts.
A clinical adjudication committee from US and AfDC sites will develop and apply culturally informed algorithms for AD to adjudicate multi-domain data from the cohorts. Biological samples include whole blood for DNA, plasma for AD biomarkers, and PAXGene for future gene expression studies.
Results: All phenotype, genomic and biomarker data are housed in a centralized database to facilitate hypothesis driven genomic and phenotypic analyses within cohorts and ancestry-based hypotheses across populations. We will present this integrated approach as a prototype for global ascertainment of this complex phenotype.
Conclusions: Outcomes from this study will enhance focused, precision medicine approaches for AD and reduce health disparities across ancestries.

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OD282 / #1776

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

ASSOCIATION OF SHORT TANDEM REPEATS WITH NEUROPATHOLOGICAL FEATURES IN LATE-ONSET OF ALZHEIMER'S DISEASE BRAINS

Jinfeng Lu[1], Annie Lee[1,2], Hans Ulrich-Klein[3,4], Julie Schneider[5,6,7], David Bennett[5,6], Philip De Jager[1,2,3,4], Giuseppe Narzisi[8], Michael Zody[8], Badri Vardarajan[1,2,3]
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Aims: Short tandem repeats (STRs), which are hyper-mutable sequences in the human genome could explain some of the missing heritability in Alzheimer's Disease. We systematically evaluated the impact of genome-wide STRs on neuropathological LOAD features.
Methods: Using whole-genome sequencing in 1,134 unrelated individuals from Religious Orders Study (ROS) and Rush Memory and Aging project (MAP) cohorts, we identified over 80,000 STRs genome-wide using GangSTR and LuSTR, a novel algorithm that we developed for accurate identification of repeat sequences. We tested the association of STRs with a) clinical and neuropathological LOAD status, b) beta-amyloid levels, c) neurofibrillary tangle (NFT) burden, and d) global measure of AD pathology. Subsequently, we examined if STRs influenced gene and protein expression in dorsolateral prefrontal cortex (DLPFC), posterior cingulate cortex (PCC) and the anterior cingulate (AC) and tested if the association of STRs with neuropathological traits were mediated by altered gene expression.
Results: Repeats in *NCK2* was associated with pathological AD diagnosis (p=1.4e-05), beta-amyloid level (p=5.5e-05) and tangle load (p=8e-03). Amongst known, pathogenic neurological STRs, TGC repeat in *ATXN1* was associated with cognitive decline (p=0.014) and risk of clinical AD (p=0.03). Variations in CAG repeats in *ATN1* was associated with cognition (p=0.022) and risk of pathological AD (p=0.035). Longer Repeats *ATXN1* increased gene expression in DLPFC (p=0.049) and PCC (p=0.006) and repeats in *ATN1* altered DLPFC (p=0.016) and PCC (p=0.026) expression. Mediation analysis determined that the effect of the CAG repeats in *ATN1* on tau was mediated by gene expression in PCC (p=0.004).
Conclusions: STRs could explain some of the missing heritability in LOAD and influence gene and protein expression in clinical AD and AD pathology.

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OD283 / #1813

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

AGE AT ONSET OF IDIOPATHIC AND LRRK2-RELATED PARKINSON'S DISEASE IS LINKED TO EPIGENETIC CLOCK ACCELERATION

Ekaterina Rogaeva[1], Xuelin Tang[2], Paulina Gonzalez-Latapi[3], Connie Marras[3], Naomi Visanji[3], Wanli Yang[2], Anthony Lang[3], Ming Zhang[2]
[1]University of Toronto, Tanz Centre For Research In Neurodegenerative Disease, Toronto, Canada, [2]The First Rehabilitation Hospital of Shanghai, Medical Genetics, Shanghai, China, [3]Toronto Western Hospital, Movement Disorders Clinic, Toronto, Canada

Aims: The aim was to evaluate whether age at onset of Parkinson's disease (PD) is associated with DNA methylation age (DNAm age) acceleration, which is the difference between DNAm age and chronological age.
Methods: We used the genome-wide Infinium MethylationEPIC array to assess DNAm age in discovery (n = 96) and replication (n = 182) idiopathic PD cohorts and a unique longitudinal LRRK2 cohort (n = 220) at four time points over a 3-year period, comprising 91 manifesting and 129 nonmanifesting G2019S carriers at baseline. Cox proportional hazard regression and multivariate linear regression were used to evaluate the relation between DNAm-age acceleration and PD age at onset, which was highly variable in manifesting G2019S carriers (36–75 years) and both idiopathic PD cohorts (26–77 and 35–81 years).
Results: DNAm-age acceleration remained steady over the 3-year period in most G2019S carriers. It was strongly associated with age at onset in the LRRK2 cohort ($P = 2.25 \times 10^{-15}$) and discovery idiopathic PD cohort ($P = 5.39 \times 10^{-9}$), suggesting that every 5-year increase in DNAm age acceleration is related to about a 6-year earlier onset. This link was replicated in an independent idiopathic PD cohort ($P = 1.91 \times 10^{-10}$). In each cohort, the faster-aging group has an increased hazard for an earlier onset (up to 255%).
Conclusions: DNAm-age acceleration is linked to PD age at onset, which could be considered in disease-modifying clinical trials. Future studies should evaluate the stability of DNAm-age acceleration over longer time periods, especially for phenoconverters from nonmanifesting to manifesting individuals.

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ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

MULTI-ETHNIC META-ANALYSIS OF EARLIER ONSET ALZHEIMER'S DISEASE IDENTIFIES NOVEL RISK LOCI

Joseph Bradley[1], Eder Lucio Da Fonseca[2], Jiji Kurup[3], Christiane Reitz[3], Gary Beecham[2], Carlos Cruchaga[4], Victoria Fernandez[4]
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Aims: Alzheimer's disease (AD) is a highly polygenic disease that presents with relatively earlier onset (EOAD) in about 5% of cases (≤70yo). It is sometimes equated with dominantly inherited AD; however, 90% of EOAD cases remain unexplained by these variants. This project aims to identify novel EOAD-associated loci through a large-scale, multi-ethnic genome-wide association study (GWAS).
Methods: We leveraged GWAS data from the Alzheimer Disease Genetics Consortium and the Knight-ADRC mapped to GRCh38 and imputed with TOPMed. After selecting cases with age at onset ≤ 70 and controls older than 70 at last assessment, our dataset consisted of 6,282 cases (CA) and 13,386 controls (CO) for non-Hispanic Whites (NHW); 782 CA and 3,663 CO for African American (AA); and 608 CA and 1,714 CO Asian. We performed single-variant analysis (SVA) to identify variants that confer a higher risk for EOAD, followed by meta-analysis to identify variants contributing to the earlier onset across ethnicities.
Results: SVA (using sex, PC1-PC10 as covariates) identified 19 and four loci associated with EOAD in NHW and AA respectively. Seven of the NHW loci are novel and not reported in large GWAS for late-onset AD. Two EOAD loci for AA near ATXN7L3B and POTED, are novel and specific to AA. No genome-wide significant signals were detected for Asian. Subsequent meta-analysis of NHW, AA, and Asian identified 24 EOAD loci, including eight novel loci.
Conclusions: This is the largest GWAS of EOAD and will be instrumental to identifying novel variants and pathways implicated in unexplained EOAD. We confirmed 13 previous AD risk loci and identified nine novel EOAD loci. Analyses to assess overlap with LOAD and identify functional gene targets —including LDSC regression, PRS, colocalization, and mendelian randomization— are ongoing.

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OD285 / #2753

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

IDENTIFYING SECONDARY GENETIC RISK FACTORS IN GAUCHER SIBLING PAIRS DISCORDANT FOR PARKINSONISM USING VARIANT ANALYSIS

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NIH/NHGRI, Medical Genetics, Bethesda, United States of America

Aims: Parkinson disease (PD), caused by interactions between genes and/or environmental factors, a milestone genetic finding was that variants in *GBA1,* the mutated gene cause Gaucher disease (GD), encoding lysosomal glucocerebrosidase (GCase) confer an increased risk for PD. However, implicates additional risk factors including other genetic variants, aging genes, genetic background, environment, and epigenetics.
Methods: To identify secondary genetic risk variants, we performed exome sequencing on DNA samples from nine sibling pairs with GD discordant for PD, six with Ashkenazi Jewish, and three with European backgrounds. Quality variants (MPG Score ≥ 10, Score/Coverage ≥ 5) of Annovar annotated exome data were filtered to include those with a gnomAD v2.11 exome allele frequency ≤ 0.05 and predicted to be damaging by at least two in silico predictors. To identify variants, genes, and pathways serving as potential secondary risk factors for parkinsonism, variants were compared within each family to identify those found only in the GD sibling with PD.
Results: Six variants were shared by the GD/PD and not GD in three families and seventy variants were shared by the GD/PD siblings in two families. Shared compound heterozygous variants in two genes were found: *PCDHB8*, in the GD/PD sibling in two families with European backgrounds, and *ZNF737*, in two Ashkenazi Jewish families., The further variant analysis uncovered two additional genes of interest only in the PD sibling. Network analysis demonstrated the links between the identified genes *SNCA* and *GBA1*.
Conclusions: A larger GD/PD cohort will be used to validate the genes. This data confirms the utility of sib-pairs and nuclear families in identifying risk factors including genetic background, predisposition of gene variants, and even epigenetics provides advantages over pooled heterogeneous samples in complex diseases.

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OD285a / #2271

ON-DEMAND SYMPOSIUM: GENETICS OF NEURODEGENERATION 04
01-04-2023 07:00 - 08:30

A GENOME-WIDE ASSOCIATION STUDY IN CARIBBEAN HISPANICS SUGGESTS NEW RISK LOCI FOR ALZHEIMER'S DISEASE

Basilio Cieza Huaman[1], Zikun Yang[1], Caghan Kizil[2], Dolly Reyes-Dumeyer[3], Diones Rivera[4], Martin Medrano[5], Ivonne Jiménez-Velázquez[6], Rafael Lantigua[2], Richard Mayeux[3], Giuseppe Tosto[2,7]
[1]Columbia University, Taub Institute, New York, United States of America, [2]Columbia University Irving Medical Center, Department Of Neurology, New York, United States of America, [3]Columbia University, Department Of Neurology, New York, United States of America, [4]School of Medicine, Universidad Pedro Henriquez Urena, Santo Domingo, Dominican Republic, [5]Corominas, Geriatrics, Santiago, Dominican Republic, [6]University of Puerto Rico, Medicine, San Juan, Puerto Rico, [7]Coll. of Physicians and Surgeons, Columbia Univ., Taub Inst. For Res. On Alzheimer's Disease And The Aging Brain, New York, United States of America

Aims: Alzheimer's disease (AD) is significantly more frequent in Hispanics than in non-Hispanic Whites. Ancestry may explain these differences across ethnic groups. To this end, we conducted a genome-wide association study in a large cohort of Caribbean Hispanics to identify novel AD susceptibility loci.
Methods: 7,967 individuals (2,599 cases; 5,098 controls) were imputed to the NHLBI TOPMed haplotype reference panel. We performed genome-wide association analyses with a generalized linear mixed-model using the GMMAT software for single- and gene-based tests, adjusting for sex, age, and principal components (fixed effects) and genetic relationship matrix (random effect).
Results: Beyond the *APOE* locus ($p=4.6x10^{-36}$), we confirmed a known AD locus (*TPCN1* on chromosome 12; $p=1.7x10^{-8}$) and identified two novel significant loci: rs74439126 ($p=4.7x10^{-10}$) on chromosome 2, and *CORO2B* ($p=3.3x10^{-8}$) on chromosome 15. In the *APOE*-adjusted model, we identified an additional locus, *PTPRK* on chr 6 ($p=2.7x10^{-8}$).
Conclusions: This new GWAS confirmed previously AD-associated loci in NHW individuals (e.g. *APOE, TPCN1*) and identified three novel susceptibility loci. *CORO2B* and *PTPRK* genes are promising candidates that play key roles in cellular processes in AD risk.

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OD286 / #2144

ON-DEMAND SYMPOSIUM: CLINICAL TRIALS DESIGN, DIAGNOSTIC CRITERIA
01-04-2023 07:00 - 08:30

INNOVATING THE PROMISING ZONE - APPLICATIONS & INNOVATIONS OF PROMISING ZONE IN ALZHEIMER'S PHASE II TRIAL

Mitchell Wassom, Samuel Dickson, Suzanne Hendrix
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Aims: A failed study is devastating – and more devastating yet is a failed study where the treatment is effective. Unfortunately, this is a reality in clinical trials everywhere, and one of the leading causes is low power – that is, having a lower success probability than originally planned. While there are a handful of methods to provide *better* power initially, Mehta and Pocock (2000) provide a technique that uses an interim analysis to adjust the sample size to increase power. We demonstrate how this method is used and present several innovations.
Methods: Recent applications and innovations to the methods laid forth in Mehta and Pocock are discussed, including: maintaining the blind through a "stair-stepping approach" to sample size adjustment, expanding this approach to multiple primary outcomes, and using an interim analysis on an earlier time point to predict conditional power on a later time point analyzed in the final analysis.
Results: Using a simulation with the "stair-stepping" promising zone approach for two primary endpoints, the power increased by about 3-5% while maintaining the one-sided overall type one error rate below 2.5%. This was consistent across various correlations of the primary endpoints. Similarly, when using an interim analysis on an earlier time points to predict conditional power on a later time point analyzed in the final analysis, power increases by about 1-2%.
Conclusions: When the study design allows for a useful interim analysis, using a promising zone analysis to adjust sample size better ensures study success by raising the power of the study while maintaining type one error. The promising zone approach can be adapted to a variety of clinical trial scenarios.

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OD287 / #2748

ON-DEMAND SYMPOSIUM: CLINICAL TRIALS DESIGN, DIAGNOSTIC CRITERIA
01-04-2023 07:00 - 08:30

REAL AD: A REALISTIC SCREENING APPROACH FOR PRECLINICAL ALZHEIMER'S DISEASE

Kaj Blennow[1,2], Henrik Zetterberg[1], Silke Kern[1], Michael Schöll[1,3,4]
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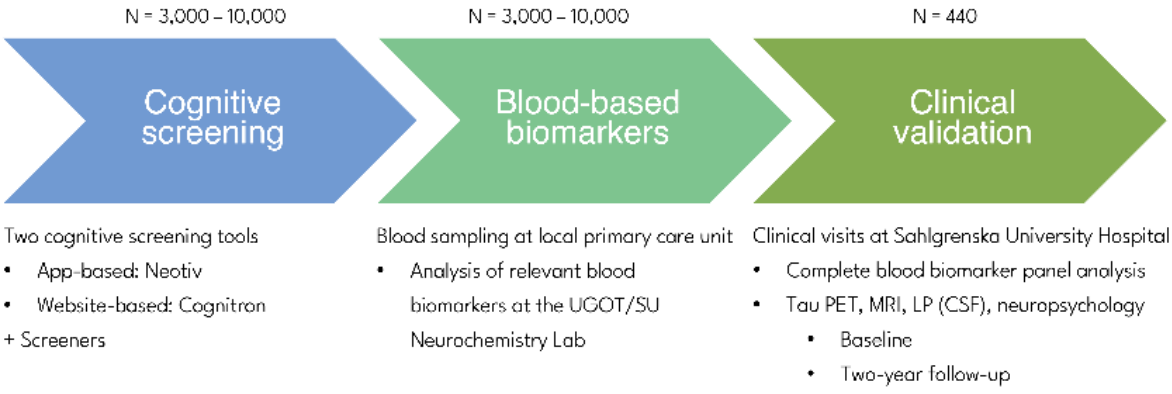
Aims: For disease-modifying treatments to be successful, early diagnosis is crucial. This is especially relevant for Alzheimer's disease (AD) with its protracted preclinical phase. Healthcare is not equipped for preventive measures such as large-scale AD screening in middle-aged individuals for which imminent AD treatment options are likely to be most effective. Ground-breaking recent developments, however, such as remotely administered cognitive tests to detect early cognitive impairment in everyday environments and blood-based biomarkers for early AD pathophysiology offer novel, scalable and cost-effective ways to screen for cognitive and biomarker changes that indicate preclinical AD. Highly promising results in dedicated research cohorts have hitherto not been validated in a realistic population-based setting. The goal of REAL AD is to inform a concrete, individualised diagnostic framework that can significantly improve the prognosis for AD patients.
Methods: In close collaboration with the Swedish Västra Götaland County Council (VGR), relevant resources at the Sahlgrenska University Hospital and pharmaceutical industry partners, this large prospective study plans to establish the practical feasibility and to validate the diagnostic and prognostic properties of a screening approach for preclinical AD. A diverse VGR-based population sample of at least 3,000 50-80-year-olds will be examined for preclinical AD using remote cognitive testing and blood biomarker analyses. The results will be used to stratify a representative subsample that will subsequently undergo longitudinal state-of-the-art clinical, fluid biomarker and neuroimaging assessments to validate the initial screening
results.

REAL AD

- Recruitment of 50-80-year-olds from the entire Västra Götaland County (exluding dementia dx)
- Broad PR campaign to ensure recruitment from different socio-cultural backgrounds (through PR agency)
  - All content in four languages: Swedish, English, Finnish, Arabic
  - Central website as information and recruitment platform using digitalised informed consent



Results: The study design and developments to date close to the launch of the study will be presented in order to open for discussions with the research community.
Conclusions: There is a great need to prepare healthcare for the challenge of implementing recent biomarker developments in the light of forthcoming treatment options.

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OD288 / #2014

ON-DEMAND SYMPOSIUM: CLINICAL TRIALS DESIGN, DIAGNOSTIC CRITERIA
01-04-2023 07:00 - 08:30

THE INCIDENCE RATE OF DEMENTIA IN PATIENTS WITH SUBJECTIVE COGNITIVE DECLINE VARIES ACCORDING TO THE TYPE OF DIAGNOSTIC CRITERIA USED TO EXCLUDE MILD COGNITIVE IMPAIRMENT

Tim Whitfield[1], Leonidas Chouliaras[2], Natalie Marchant[1], Zuzana Walker[1,3]
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Aims: The subjective cognitive decline (SCD) diagnostic criteria require the alternative diagnoses of mild cognitive impairment (MCI) and dementia to be 'ruled out'. However, various approaches are used to diagnose MCI, yet little work has investigated how the use of different MCI diagnostic criteria may impact the SCD 'phenotype', including rates of incident dementia in SCD patients. There is a need to determine this empirically, as it has implications for both research and clinical practice.
Methods: This longitudinal study included an unselected sample of patients from the Essex Memory Clinic database (*n*=2,262), a routine NHS service. All patients underwent a standardised psychiatric and neuropsychological assessment, following which a consensus diagnosis was assigned. Individuals without dementia were followed up at 1-2-year intervals, and the diagnosis updated as appropriate. For analyses, we 'retrospectively' diagnosed SCD with reference to either the 'Petersen' or 'Jak and Bondi' MCI criteria. Incidence rates of all-cause dementia were then calculated for each 'type' of SCD separately.
Results: The SCD sample size varied depending on whether Jak and Bondi (*n*=365; median 3-years follow-up) or Petersen (*n*=192; median 6-years follow-up) criteria were used to exclude MCI. The incidence rate [95% CI] of dementia (per 1,000 years of person-time-at-risk) in SCD was greater using Jak and Bondi (91.5 [75.6-109.6]) compared to Petersen (36.7 [24.4-53.1]) MCI criteria.
Conclusions: These analyses revealed that the rate of progression to dementia in SCD was substantially greater for a population where MCI was excluded according to Jak and Bondi, versus Petersen, MCI criteria. We recommend that future studies/reviews examining SCD prognosis explicitly identify the approach(es) used for the exclusion of MCI, in order to improve the accuracy of prognostic counselling for patients with SCD and to inform ongoing treatment/prevention studies.

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ON-DEMAND SYMPOSIUM: CLINICAL TRIALS DESIGN, DIAGNOSTIC CRITERIA
01-04-2023 07:00 - 08:30

MOLECULAR INTEGRATION IN NEUROLOGICAL DIAGNOSIS (MIND) INITIATIVE AT THE UNIVERSITY OF PENNSYLVANIA

Thomas Tropea[1], Noah Han[1], Whitney Hartstone[1], Rachel Paul[1], Eunran Suh[2], George Kannarkat[3], Eliza Brody[1], Hanwen Zhang[1], Justin James[1], Isabela Albuja[1], Vivianna Van Deerlin[2], Alice Chen-Plotkin[1]
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Aims: The objectives are 1) to describe the clinical characteristics of the entire Parkinson's disease (PD) patient population at the University of Pennsylvania Parkinson's Disease and Movement Disorders Center (PDMDC), and 2) to determine the frequency of *GBA* and *LRRK2* variant carriers. PD research studies that focus on small numbers of participants fall short in capturing the molecular and genetic variability across the PD spectrum. The MIND Initiative seeks to characterize the genetic and molecular features of PD by approaching every patient in a large academic movement disorders center at the University of Pennsylvania.
Methods: The MIND Initiative is an inception cohort study of participants with a clinical diagnosis of PD. At their office visit, participants complete a questionnaire and DNA is isolated from a blood or a saliva sample. Targeted genotyping for eight *LRRK2* and fourteen *GBA* variants is performed for all participants. Plasma and DNA are banked for future research.
Results: Between September 2018, and September 2022, 1593 subjects were enrolled. Among 1786 screened and approached to participate, 193 patients (10.9%) declined participation. Clinical questionnaires were collected for 99% of participants and common motor and non-motor complications of PD are described. *GBA* variants were identified in 152 participants (10.0% of whole cohort), *LRRK2* variants in 39 participants (2.6% of whole cohort). Four participants were found to be co-carriers of both a *GBA* and *LRRK2* variant (0.3% of whole cohort).
Conclusions: This is the first report to demonstrate the clinical and genetic characteristics of a whole-clinic PD population at an academic center. A separate study including genetic counseling, clinical confirmation, and disclosure of *GBA* and *LRRK2* results is ongoing.

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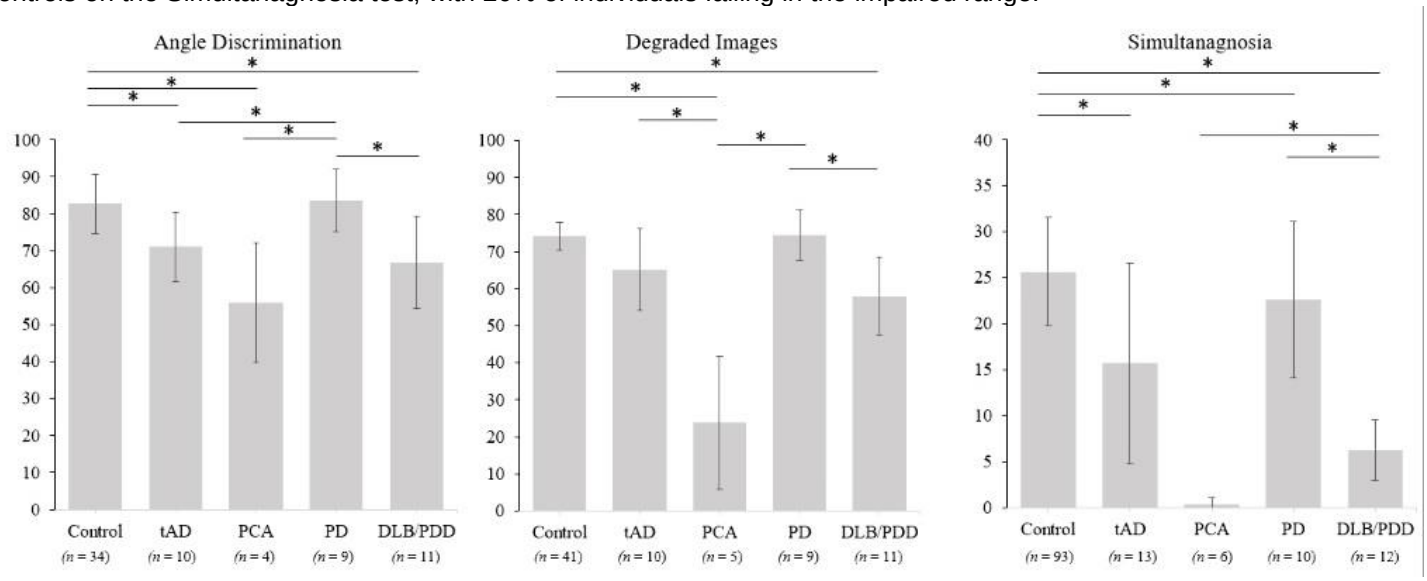
OD290 / #1368

ON-DEMAND SYMPOSIUM: CLINICAL TRIALS DESIGN, DIAGNOSTIC CRITERIA
01-04-2023 07:00 - 08:30

EXPLORING VISUOPERCEPTION IN LEWY BODY DISEASES

Emily Mccann[1], Soohyun Lee[1], Felicia Coleman[1], Peter Nestor[1,2]
[1]The University of Queensland, Queensland Brain Institute, Brisbane, Australia, [2]Mater Hospital, Mater Hospital, Brisbane, Australia

Aims: Occipital and posterior parieto-temporal hypometabolism is a hallmark of dementia in Lewy Body diseases (LBD). These regions are known to process visual information. There has been little research, however, into visuoperceptual dysfunction in LBDs using tests that are not contaminated by motor ability. We developed a novel suite of pure visuoperceptual tests that target the dorsal (Simultanagnosia Test and Angle Discrimination Test) and ventral (Degraded Images Test) visual pathways. The tests have inbuilt graded difficulty that parallels the insidious nature of dementia and allows for the tracking of cognitive change over disease course.
Methods: Test development and calibration involved extensive piloting with healthy controls. It was then applied to LBDs: Parkinson's Disease (PD), PD with Dementia (PDD) and Dementia with Lewy Bodies (DLB). For comparison, patients with typical Alzheimer's disease (tAD) and the posterior cortical atrophy (PCA) variant of Alzheimer's were also examined.
Results: Preliminary results from all three novel tasks identified significant impairments in the PDD/DLB group (Fig.). In the PDD/DLB group, 100% of individuals were impaired on the Simultanagnosia Test and 91% of individuals were impaired on the Degraded Images Test. Non-demented PD were also significantly impaired as a group compared to controls on the Simultanagnosia test, with 20% of individuals falling in the impaired range.



Conclusions: Visuoperceptual impairment is a hallmark of cognitive impairment in LBDs. The novel tests – not confounded by motor abilities or executive function – identified prominent visuoperceptual deficits in LBDs. The tests will enable better understanding of the evolution of visuoperceptual deficits in LBDs.

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OD291 / #183

ON-DEMAND SYMPOSIUM: CLINICAL TRIALS DESIGN, DIAGNOSTIC CRITERIA
01-04-2023 07:00 - 08:30

BARRIERS TO ALZHEIMER'S DISEASE CLINICAL TRIAL PARTICIPATION IN HAWAII'S MINORITY-MAJORITY POPULATION

Anson Lee[1,2], Julia Jahansooz[1,2], Darrell Guittu[2,3], Rexton Suzuki[2,4], Lauren Pak[2,5], Kyle Ishikawa[1,6], Connor Goo[1,2], John Chen[1,6], Enrique Carrazana[1,2], Jason Viereck[2,6], Kore Liow[1,2,6]
[1]University of Hawaii at Manoa, John A. Burns School Of Medicine, Honolulu, United States of America, [2]Hawaii Pacific Neuroscience, Memory Disorders Center & Alzheimer's Research Unit, Honolulu, United States of America, [3]University of Hawaii at Mānoa, Department Of Biology, Honolulu, United States of America, [4]Creighton University, College Of Arts And Sciences, Omaha, United States of America, [5]University of Oregon, Department Of Biology, Eugene, United States of America, [6]University of Hawaii John A. Burns School of Medicine, Department Of Quantitative Health Sciences, Honolulu, United States of America

Aims: Understanding barriers to Alzheimer's Disease (AD) clinical trial participation in underrepresented Asian and Native Hawaiian (NH) patients diagnosed with AD or mild cognitive impairment (MCI) in a minority-majority population.
Methods: This retrospective study included 187 (134 AD, 53 MCI) patients with a Mini-Mental State (MMSE) score ≥14 seen at a Memory Disorders Center between 01/2022-06/2022. Patients and caregivers completed a 15-question telephone survey that assessed demographics, barriers, and improvement methods. Descriptive statistics were performed using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Incomplete surveys were included for analysis.
Results: Forty-nine patients responded (29 AD, 20 MCI). The mean patient age was 77 years, 51% were male, and the mean MMSE score was 23.2. Compared to the clinic population (20.0% Asian, 30.7% NH, 39.7% White), 5.6% Asian, 22% NH, and 32% White patients were in an active trial. More NH and White patients participated in trials than Asian patients. The decision to participate in trials to help others significantly differed by race (91% White, 80% NH, 29% Asian; p=0.023), with other reasons being statistically insignificant. Asian (30%) and NH (80%) patients reported the main barrier to participation was a lack of information about trials, with psychosocial conflicts and financial burdens as the least important barrier. Additional trial information given to family members (64% Asian, 88% NH, 62% White) and patients (64% Asian, 88% NH, 46% White) were listed as the most popular trial improvements.
Conclusions: Asian and NH patients were less likely to participate in AD trials compared to White patients. A deficiency in information was the primary barrier amongst minority patients. To overcome this barrier, increased outreach and education to patients and their families should be pursued.

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OD292 / #477

ON-DEMAND SYMPOSIUM: CLINICAL TRIALS DESIGN, DIAGNOSTIC CRITERIA
01-04-2023 07:00 - 08:30

MODELING PHARMACODYNAMIC EFFECTS OF PUBLISHED CLINICALLY TESTED ANTI-TAU AND ANTI-SYNUCLEIN ANTIBODIES TO IMPROVE CLINICAL TRIAL DESIGN

Hugo Geerts[1], Silke Bergeler[1], Mike Walker[1], Piet Van Der Graaf[1], Jean-Philippe Courade[2]
[1]Certara, Quantitative Systems Pharmacology, Sheffield, United Kingdom, [2]Discoveric Bio Alpha, Clin Development, Pfaffikon, Switzerland

Aims: OBJECTIVE: Several anti-tau and anti-synuclein antibodies have been tested in the clinic without clinical benefit despite substantial target occupancy in Cerebro-Spinal Fluid (CSF). Our aim was to generate hypotheses for the lack of clinical efficacy.
Methods: Quantitative Systems Pharmacology and Physiologically-Based Pharmacokinetic models were used to assess the spatio-temporal progression of monomeric and seed-competent proteins. We simulated clinical trials of gosuranemab, tilavonemab, semorinemab, cinpanemab and prasinezumab using published clinical profiles. The model quantitatively describes protein secretion, diffusion, antibody capture, postsynaptic membrane binding and protein internalization.
Results: Uptake parameters were fitted from preclinical studies. Secretion parameters were adjusted versus clinically observed levels of these proteins in CSF and Interstitial Fluid (ISF). The dynamics of seed-competent protein uptake in the afferent neuron was a proxy for disease progression. The model reproduced the Phase 1 changes in CSF or plasma biomarkers. The antibodies' impact on the biomarkers decreased from CSF to ISF to intrasynaptic cleft to neuronal uptake. Key drivers for the antibody effect on neuronal uptake of seed-competent protein were: (1) Steric hindrance of antibody diffusion from the ISF into the synaptic cleft, (2) Dose of the antibody, (3) Lower degradation rate of seed-competent vs monomeric protein, (4) Antibody selectivity for seed-competent vs monomeric protein, (5) Uptake kinetics at the afferent neuronal membrane.
Conclusions: The current model suggests that the antibodies' effect on accessible biomarkers in CSF is quite different from changes in other brain compartments, notably in the synaptic cleft and neuronal uptake which are proxies for disease progression.

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OD293 / #2624

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

QUANTIFICATION OF SNAP-25 AND VAMP-2 IN PLASMA AND CSF FROM PATIENTS WITH EARLY ALZHEIMER'S DISEASE USING TWO NOVEL DIGITAL IMMUNOASSAYS

Julie Goossens[1], Charlotte De Rocker[1], Shreyasee Das[1], Daniel Alcolea[2], Elizabeth Herries[3], Jack Ladenson[3], Alberto Lleó[2], Olivia Belbin[2], Eugeen Vanmechelen[1]
[1]ADx NeuroSciences NV, Research And Development, Ghent, Belgium, [2]Institut d'Investigació Biomèdica Sant Pau, Memory Unit, Barcelona, Spain, [3]Washington University School of Medicine, Departments Of Pathology And Immunology And Neurology, St. Louis, United States of America

Aims: Development of sensitive immunoassays to detect SNAP-25 and VAMP-2 in plasma and investigate if these synaptic biomarkers hold diagnostic potential for Alzheimer's disease (AD) in blood.
Methods: Prototype Simoa assays for SNAP-25 and VAMP-2 were established as more sensitive versions of previously validated in-house CSF assays using high affinity detector antibodies and diluent suited for both plasma and CSF. The SNARE proteins were quantified in 333 paired samples from the SPIN cohort (96 AD dementia [dAD], 193 prodromal AD [pAD] and 44 cognitively unimpaired controls) using the same assay conditions for each fluid type, except for the dilution factor.
Results: All samples were detected within the measuring range of VAMP-2 (500 – 0,5 pg/mL) and SNAP-25 (25 – 0,02 pg/mL). Plasma inter-run variability was 9,1% (SNAP-25) and 13,5% (VAMP-2). The mean intra-assay variability on the clinical measurements was below 10% for both SNAP-25 (CSF: 2,8%, plasma: 5,8%) and VAMP-2 (CSF: 2,6%, plasma: 4,2%). SNAP-25 increased significantly in plasma and CSF of pAD and dAD patients compared to controls (all p-values<0.0001). VAMP-2 was significantly elevated in CSF at the pAD stage (p=0,018) versus controls, but no changes were observed in plasma. An overall strong correlation between VAMP-2 and SNAP-25 levels was present in CSF (Spearman rho=0,825, p<0.0001), but this correlation was lost in plasma. Plasma SNAP-25 (AUC=0,755, p<0,0001) performed equally well as CSF SNAP-25 (AUC=0,737, p<0,0001) to discriminate AD patients from controls.
Conclusions: Two novel sensitive digital immunoassays can measure SNAP-25 and VAMP-2 robustly in plasma. SNAP-25 is a promising novel synaptic blood biomarker for AD that requires validation in independent cohorts. Exploration of the relationship with *in vivo* PET imaging of synaptic density could inform on the physiological basis of plasma SNAP-25 changes in AD.

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OD294 / #789

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

DECIPHERING PROTEIN SECRETION FROM BRAIN TO CSF FOR BIOMARKER DISCOVERY

Katharina Waury[1], Renske De Wit[1], Charlotte E. Teunissen[2], Sanne Abeln[1]
[1]Vrije Universiteit Amsterdam, Department Of Computer Science, Amsterdam, Netherlands, [2]VU University Medical Centers, Amsterdam UMC, Neurochemistry Laboratory, Clinical Chemistry Department, Amsterdam Neuroscience, Amsterdam, Netherlands

Aims: To identify novel CSF biomarker candidates of neurodegenerative diseases, it is beneficial to gain a deeper understanding of the processes within the brain that lead to the release of proteins to CSF. Here, we aimed to explore if protein transport from brain to CSF can be predicted from protein sequence and which factors determine this process.
Methods: Six previously published mass spectrometry studies were combined to create a large human healthy CSF proteome of 5297 proteins. This dataset was overlapped with the Human Protein Atlas elevated brain proteome to identify CSF-secreted and retained brain proteins. A logistic classifier was trained to differentiate between the two protein classes utilizing sequence-based features.
Results: Prediction of CSF protein secretion achieved a balanced accuracy of 72.44%. The model accuracy increased further to 80.70% if only including CSF proteins that have been found in at least half of the included mass spectrometry studies. Features most important for correct classification include signal peptides and the subcellular localization. We provide an illustrative example for the model's application to biomarker candidate identification within Alzheimer's Disease proteomics studies. Known Alzheimer's Disease biomarkers are correctly predicted as secreted to CSF by the model.
Conclusions: A comprehensive CSF proteome was collected, however, a minimum study criterion is necessary to exclude likely false positives. The trained classifier performs well, and feature analysis elucidates the underlying mechanisms of brain protein secretion processes. The model can be utilized to identify potential CSF biomarkers difficult to detect in discovery studies and guide candidate selection.

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OD295 / #1856

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

PTAU181 PLASMA BIOMARKER PERFORMANCE AS AN INCLUSION CRITERION IN THE RETHINK-ALZ AND REFOCUS-ALZ TRIALS IN MILD-TO-MODERATE ALZHEIMER'S DISEASE

Anna Mammel[1], Lindsay Burns[2], Donald Biehl[1], Mary Encarnacion[3], Pankaj Kumar[3], Anna Cruz[3], Ryan Fortna[4], Ging-Yuek R Hsiung[5], James Kupiec[2], Ali Mousavi[3], Ian Mackenzie[6], Veronica Hirsch-Reinshagen[6], Hans Frykman[5,7]
[1]Neurocode USA Inc., Neurology, Bellingham, United States of America, [2]Cassava Science Inc., Neurology, Austin, United States of America, [3]BC Neuroimmunology lab, Bc Neuroimmunology Lab, vancouver, Canada, [4]Avero Diagnostics, Pathology, Bellingham, United States of America, [5]University of Bristish Columbia, Medicine, Vancouver, Canada, [6]University of British Columbia, Neuropathology, Vancouver, Canada, [7]BC Neuroimmunology lab, Bc Neuroimmunology, Vancouver, Canada

Aims: To evaluate the clinical performance of a plasma pTau181 assay as an entry criterion for two phase 3 clinical trials.
Methods: The University of British Columbia (UBC) biobank plasma samples from clinically diagnosed AD patients were used to establish clinical and analytical validity of the pTau181 plasma assay per CLSI guidelines. RETHINK-ALZ and REFOCUS-ALZ subject plasma samples, along with clinical diagnosis, MMSE and PET data were also used to evaluate performance of the pTau181 biomarker.
Results: The clinical decision point for this plasma pTau181 assay for clinical trial inclusion was set as ≥ 30 ng/L using the ROC curve (AUC - 0.92) and the Youden Index (34.3 ng/mL). The analytical performance of the assay meets method validation guidelines of ≤ 20% intra-laboratory variation, linearity to 300 ng/L, and sample stability up to three freeze-thaw cycles. Current data show 84.6% (n = 415) and 89.7% (n = 438) of subjects screened for RETHINK-ALZ and REFOCUS-ALZ, respectively, met the ≥ 30 ng/L pTau181 concentration cut-off. 84.6% of the sites participating in the REFOCUS-ALZ study and 79.7% of sites participating in the RETHINK-ALZ had at least 70% of screened subjects meet this criterion. We also compared plasma pTau181 concentrations in RETHINK-ALZ and REFOCUS-ALZ subjects with MMSE and PET findings. However, pTau181 concentrations were elevated (> 50 ng/L) in all subjects with prior Tau or amyloid-beta PET confirmation of pathology (8 of 8) enrolled in these studies, suggesting an excellent correlation of plasma pTau181 with AD neuropathology.
Conclusions: This pTau181 assay performs well as a screening method for inclusion of mild-to-moderate AD in Phase 3 clinical trials. This RUO assay has great potential as a diagnostic tool streamlining AD clinical trials.

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OD296 / #1761

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

NOVEL SIMOA ASSAY FORMATS CAPABLE OF MEASURING VAMP2 AND SNAP25 IN PLASMA AND CSF: ANALYTICAL VALIDATION ASPECTS

Eugeen Vanmechelen[1], Charlotte De Rocker[1], Shreyasee Das[1], Alberto Lleó[2], Olivia Belbin[3], Julie Goossens[1]
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Aims: New developments in ultra-sensitive measurements of brain-specific proteins are likely to change the Alzheimer diagnostic criteria, but analytical aspects of assay performance are often poorly reported. In this work we describe an approach to develop two promising CSF biomarkers, pre-synaptic VAMP2 and SNAP25, into an assay format capable to measure analytes in plasma and CSF.
Methods: Novel Simoa immunoassays were optimized for two matrices and quantified presynaptic VAMP2 and SNAP25 in a paired CSF-plasma clinical cohort in which CSF synaptic markers were available for half of the samples.
Results: For both synaptic markers, a change of detector antibody allows for an improved analytical sensitivity of at least 4-fold. Other optimizations of the two assays included buffer formulation, dilution factors and the use of peptide calibrators. For VAMP2, we were able to quantify VAMP2 levels in all samples with an optimal dilution factor of 16. Compared to a previously described clinical CSF study, the clinical performance of this new VAMP2 format was confirmed: Bland-Altman method comparison showed less than 10% deviation on the absolute VAMP2 concentrations between the two formats. With a dilution factor of three we were also able to quantify VAMP2 in all plasma (n>350) but one. Plasma precision profiles ranges from 0,1-16,7% with an median of 3,5%, while for CSF this was 4% (0,02-17,7%). SNAP25 data are being generated and will be reported side-by-side with VAMP2.
Conclusions: Using a rational approach, we have demonstrated analytically validated formats for two synaptic proteins in CSF and plasma. Further Clinical performance evaluation with respect to recent promising plasma biomarkers will determine potential added value for Alzheimer or dementia diagnosis of these synaptic markers in plasma.

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OD297 / #2287

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

CSF P-TAU181, P-TAU231, AND P-TAU217 MEASUREMENTS WITH SIMOA AND IP-MS SHOW SIMILAR PERFORMANCE IN IDENTIFYING AD BUT DISTINCT MAGNITUDE OF CHANGE IN RELATION TO CONTROLS

Arlec Cabrera[1], Firoza Lussier[1], Pamela Ferreira[1], Bruna Bellaver[1], João Pedro Ferrari-Souza[1], Guilherme Povala[1], Joseph Therriault[2], Stijn Servaes[3], Cécile Tissot[3], Andrea L. Benedet[4], Nicholas Ashton[5], Thomas Karikari[6], Mira Chamoun[2], Jenna Stevenson[3], Alyssa Stevenson[3], Nesrine Rahmouni[2], Eduardo Zimmer[7], Henrik Zetterberg[8], Kaj Blennow[5], Pedro Rosa-Neto[9], Tharick Pascoal[1]
[1]University of Pittsburgh, Department Of Psychiatry, Pittsburgh, United States of America, [2]McGill University, Neurology, Montreal, Canada, [3]McGill University Research Centre for Studies in Aging, Neurology, Montreal, Canada, [4]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [5]Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Department Of Psychiatry And Neurochemistry, Gothenburg, Sweden, [6]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Mölndaln, Sweden, [7]Universidade Federal do Rio Grande do Sul, Graduate Program In Biological Sciences: Biochemistry, Porto Alegre, Brazil, [8]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden, [9]Montreal Neurological Institute/McGill University, Neurology And Neurosurgery, Montreal, Canada

Aims: Single-molecule array (Simoa) and immunoprecipitation-mass spectrometry (IP-MS) methods have been used to quantify CSF p-tau epitopes in the context of AD. However, there is a lack of literature comparing their diagnostic performance across the cognitive decline and Aβ pathology spectrum. Our aim was to compare the performance of CSF p-tau epitopes measured with different analytical methods.
Methods: Utilizing the TRIAD (Translational Biomarkers in Aging and Dementia) cohort (n=144), stratified in cognitively unimpaired (CU) and cognitively impaired (CI) and Aβ PET-positive and negative, we compared Simoa and IP-MS CSF p-tau181, 231, and 217 measurements using ANOVA, Spearman correlation, and receiver operating characteristic curve (ROC) analyses.
Results: Strong correlations (ρ_{181}=0.69, ρ_{231}=0.88, ρ_{217}=0.86; p< 0.0001) were found between Simoa and IP-MS measures of CSF p-tau 181, 231, and 217 (Figure 1). IP-MS and Simoa discriminated CI Aβ+ from CU Aβ- and CI Aβ- individuals, as well as from young adults, with similar and high accuracy in all CSF p-tau epitopes. Simoa outperformed IP-MS when predicting CI Aβ+ from CU Aβ+ using p-tau 181 (IP-MS AUC_{181}=41.72%, Simoa AUC_{181}=72.80%; p=0.0083) (Table 2). However, the magnitude of fold change anchored in CU young individuals was higher for Simoa using p-tau181, for IP-MS using p-tau231, and similar between methods using p-tau217 (Table

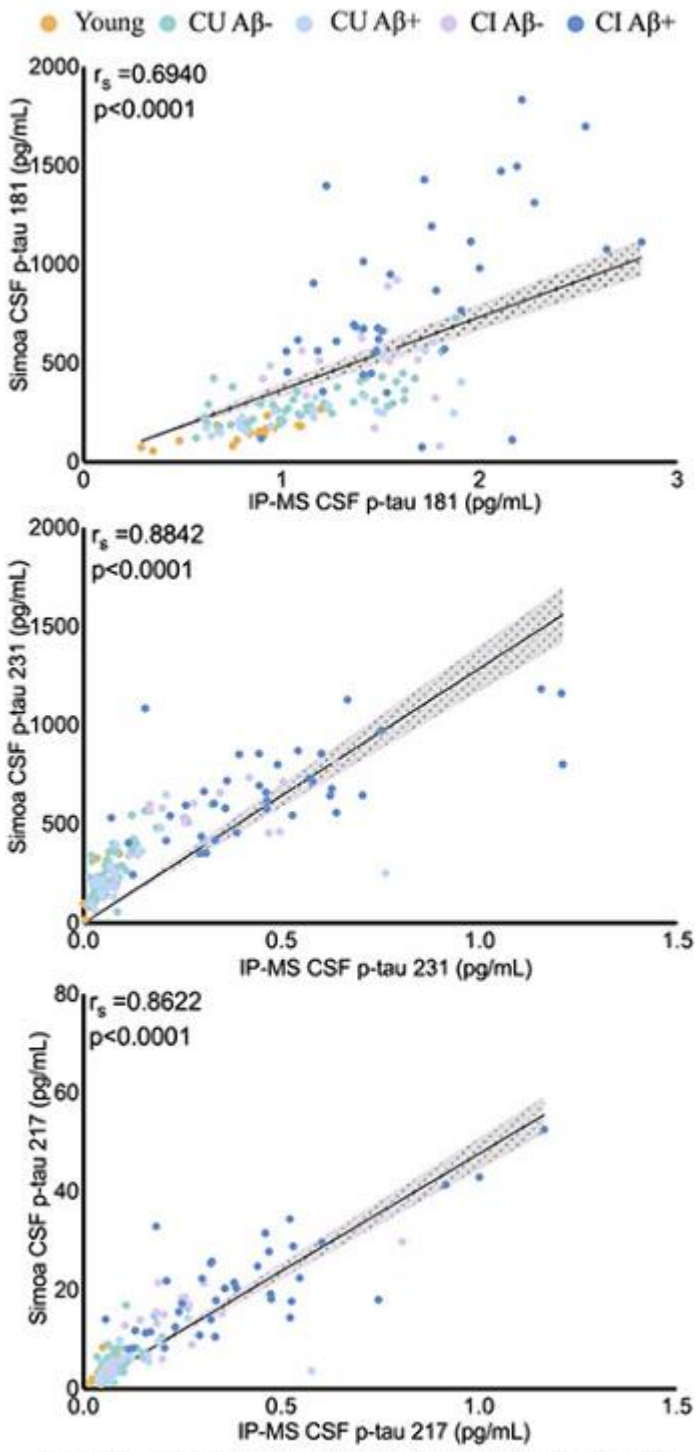

Figure 1. Spearman Correlation between IP-MS and Simoa methods in CSF p-tau 181, 231, and 217 concentrations

3).

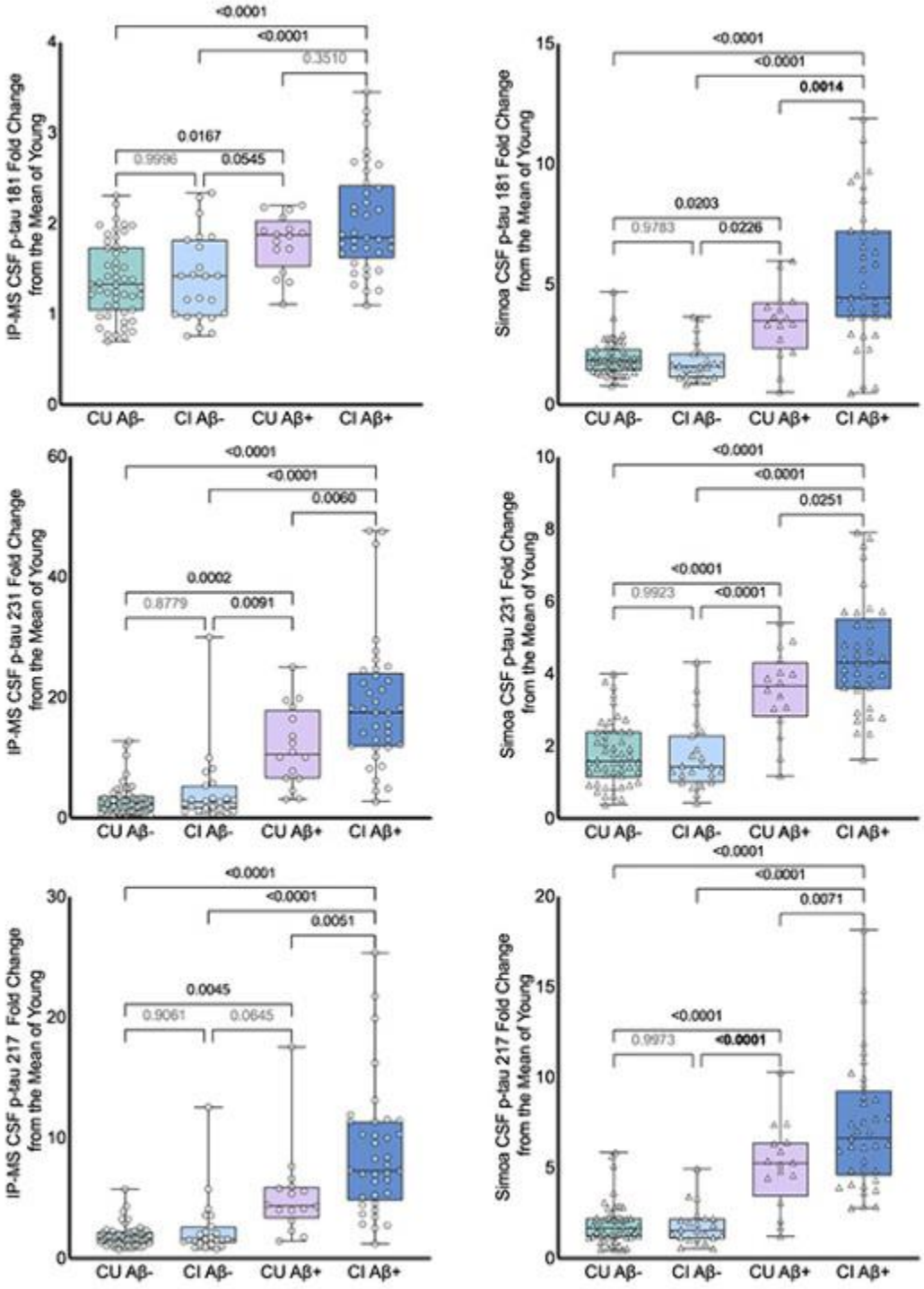

Figure 2. Fold Change differences between IP-MS and Simoa methods in CSF p-tau 181, p-tau 231, and p-tau 217 concentrations ○ IP-MS △ Simoa

	TRIAD cohort (n=144)				
	Young Adults (n=18)	CU Aβ- older adults (n=50)	CU Aβ+ older adults (n=16)	CI Aβ- older adults (n=23)	CI Aβ+ older adults (n=37)
Age, years					
mean	23	70	69	67	69
(SD)	1.0	7.5	11.5	10.4	7.1
Sex					
Female					
mean	11	28	10	14	19
(%)	(61%)	(56%)	(63%)	(61%)	(51%)
Male	7	22	6	9	18
mean					
(%)	(39%)	(44%)	(37%)	(39%)	(49%)
MMSE Score					
mean	30	29	29	27	26
(SD)	0.5	1.0	1.0	4.9	4.6
IP-MS CSF p-Tau 181 (pg/mL)					
mean	0.8	1.1	1.5	1.1	1.7
(SD)	(0.2)	(0.3)	(0.3)	(0.4)	(0.5)
IP-MS CSF p-Tau 231 (pg/mL)					
mean	0.03	0.08	0.3	0.1	0.5
(SD)	(0.0)	(0.1)	(0.2)	(0.2)	(0.3)
IP-MS CSF p-Tau 217 (pg/mL)					
mean	0.05	0.09	0.2	0.1	0.4
(SD)	(0.0)	(0.0)	(0.2)	(0.1)	(0.2)
IP-MS CSF p-Tau 181 (pg/mL)					
mean	154.3	299.3	523.9	272.5	824.6
(SD)	(54.1)	(108.1)	(225.0)	(123.3)	(440.1)
IP-MS CSF p-Tau 231 (pg/mL)					
mean	149.8	269.1	526.1	256.8	675.6
(SD)	(88.6)	(132.5)	(173.4)	(145.1)	(232.3)
IP-MS CSF p-Tau 217 (pg/mL)					
mean	2.9	5.4	14.8	5.1	21.3
(SD)	(1.9)	(3.5)	(6.8)	(3.0)	(10.3)

Abbreviations: *Aβ, amyloid-β; CI, Cognitively Impaired; CSF, cerebrospinal fluid; CU, Cognitively Unimpaired; IP-MS, Immunoprecipitation- Mass Spectrometry; MMSE, Mini-Mental State Examination; p-Tau, phosphorylated-Tau; Simoa, Single-Molecule Array; Translational Biomarkers in Aging and Dementia, TRIAD*

Table 1. Demographics

CI Aβ+ and Young	AUC	95% CI	p-value of AUC curves
IP-MS CSF p-Tau 181	0.9730	0.9309-0.997	0.3057
Simoa CSF p-Tau 181	0.9370	0.8603-1	
IP-MS CSF p-Tau 231	0.9985	0.991-1	0.7282
Simoa CSF p-Tau 231	0.9970	0.9865-1	
IP-MS CSF p-Tau 217	0.9940	0.9775-1	0.8721
Simoa CSF p-Tau 217	0.9955	0.982-1	

CI Aβ+ and CU Aβ+	AUC	95% CI	p-value of AUC curves
IP-MS CSF p-Tau 181	0.4172	0.2686-0.5642	0.0083
Simoa CSF p-Tau 181	0.7280	0.5844-0.8581	
IP-MS CSF p-Tau 231	0.7061	0.5591-0.848	0.6729
Simoa CSF p-Tau 231	0.6774	0.5219-0.8176	
IP-MS CSF p-Tau 217	0.7365	0.5861-0.8716	0.3633
Simoa CSF p-Tau 217	0.6807	0.5185-0.826	

CI Aβ+ and CU Aβ-	AUC	95% CI	p-value of AUC curves
IP-MS CSF p-Tau 181	0.8119	0.7092-0.8941	0.1566
Simoa CSF p-Tau 181	0.8946	0.794-0.9703	
IP-MS CSF p-Tau 231	0.9681	0.9314-0.993	0.3329
Simoa CSF p-Tau 231	0.9486	0.8989-0.9827	
IP-MS CSF p-Tau 217	0.9616	0.9097-0.9951	0.5966
Simoa CSF p-Tau 217	0.9735	0.94-0.9941	

CI Aβ+ and CI Aβ-	AUC	95% CI	p-value of AUC curves
IP-MS CSF p-Tau 181	0.7979	0.6686-0.9025	0.1617
Simoa CSF p-Tau 181	0.8954	0.7967-0.9753	
IP-MS CSF p-Tau 231	0.9307	0.839-0.9906	0.7355
Simoa CSF p-Tau 231	0.9459	0.8837-0.9906	
IP-MS CSF p-Tau 217	0.9119	0.8143-0.9847	0.1067
Simoa CSF p-Tau 217	0.9800	0.9424-1	

Table 2. Receiver Operating Curves predicting CI Aβ+ in CSF p-tau 181, 231, and 217 by IP-MS and Simoa

	IP-MS	Simoa
p-tau 181		
CU Aβ-	1.37934	1.94012
CU Aβ+	1.78903	3.39609
CI Aβ-	1.39197	1.76657
CI Aβ+	2.02424	5.34573
p-tau 231		
CU Aβ-	3.07701	1.79621
CU Aβ+	11.7618	3.51073
CI Aβ-	4.40237	1.71397
CI Aβ+	18.8057	4.50865
p-tau 217		
CU Aβ-	1.89733	1.87587
CU Aβ+	5.25385	5.11065
CI Aβ-	2.47763	1.76283
CI Aβ+	8.71229	7.35360

Table 3. Mean Fold Changes in CSF p-tau 181, 231, and 217 across clinical diagnosis groups

Conclusions: Our results indicate that CSF p-tau epitopes and analytical methods (Simoa and IP-MS) show similar performance for the diagnosis of AD at the population level. On the other hand, analytical methods showed differences in the magnitude of change in AD patients in relation to controls. Future studies should consider the magnitude of effect when comparing p-tau assay methods, which is crucial for the use of these markers at the individual level in clinical trials and practice.

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ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
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EVALUATION OF SECOND GENERATION AUTOMATED ELECSYS FOR FRESH CSF BIOMARKERS TO SUPPORT THE DIAGNOSIS OF ALZHEIMER'S DISEASE

Qiao-Xin Li[1], James Doecke[2], Shiji Varghese[1], Colin Masters[1], Steven Collins[1,3]
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Aims: Cerebrospinal fluid (CSF) biomarkers Aβ42, pTau181 and tTau are used to support a clinical diagnosis of AD and participant eligibility for enrolment into therapeutic trials. This study correlated biomarker levels obtained using the Roche automated Elecsys Generation I (GI) with the new Generation II (GII) platform. Additionally we examined the effect of pre-analytical conditions on these biomarkers measured through the GII assay.
Methods: CSF samples were collected from local hospitals/clinics into standard polypropylene tubes (PP) and/or low binding polypropylene tube (LBPP). Paired (i.e. same lumbar puncture) PP frozen (as per GI requirements) and fresh (4oC or room temperature; as per GII requirements) CSF samples were assayed for Aβ42 in parallel with both GI and GII. The effect of freeze-thawing on Aβ42 levels, as well as long term storage (one and two weeks at room temperature) on all three biomarker levels was also evaluated using the GII platform.
Results: The correlation between GI and GII for paired CSF (n=34) samples was 0.9495 for Aβ42, with the mean value obtained through the GI platform being 88.7% of the value of the GII. The effect of freeze-thawing (n=56) on Aβ42 was a 10% reduction on average after one freeze-thaw cycle. When CSF (n=11) was stored in the LBPP for up two weeks at room temperature, there were no significant differences between paired observations for all analytes or time points ($p>0.05$).
Conclusions: The GI and GII assays are highly correlated. The use of the GII platform for fresh CSF minimises pre-analytical handling of the sample and increases the reliability of results. Our study supports the use of the GII platform for CSF AD diagnostics in routine clinical practice.

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ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

ESTIMATED CAPACITY AND WAIT TIMES FOR IDENTIFYING ALZHEIMER'S DISEASE PATIENTS ELIGIBLE FOR FUTURE DISEASE-MODIFYING TREATMENTS IN SWEDEN

Anders Gustavsson[1,2], Soeren Mattke[3]
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Aims: A 2018 study analyzed the preparedness of Sweden's health care system to deliver a disease-modifying treatment for Alzheimer's disease (AD) and predicted substantial wait times. We have updated the prediction of wait times, focusing on the identification of AD patients, who would be eligible for future disease-modifying treatments, with an improved model and newer data over a 2023-2043 time horizon.
Methods: The model tracks patients from initial evaluation in primary care, formal diagnosis by an AD specialist, and confirmatory biomarker testing with PET scan or CSF testing. Capacity for specialist visits and PET scans is assumed to be constrained. Model parameters and assumptions about care-seeking behavior were derived from the published literature and expert input. We assume that 69% of geriatricians, 36% of neurologists and 29% of psychiatrists qualify as AD specialists, and that CSF testing would account for 90% of biomarker tests in Sweden.
Results: If patients were referred from primary care to an AD specialist based on a brief cognitive test, average wait times for specialist visits would reach around 60 months and remain similarly long over the model horizon, whereas wait times for biomarker testing would be two months or less, partly as people queue for specialist appointments.
Conclusions: Sweden could face substantial wait times for access to future disease-modifying treatments for AD because of a limited number of AD specialists per capita, which would lead to avoidable disease progression to a more severe disease stage, in which patients might no longer be eligible for treatment. Efforts are needed to train more physicians as AD specialists and to improve triage in primary care with tools like blood-based biomarker tests and digital cognitive assessments.

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OD300 / #2201

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

BLOOD NTA: A NOVEL BIOMARKER CAPABLE OF SPECIFICALLY TRACKING TAU DEPOSITION IN ALZHEIMER'S DISEASE PATIENTS.

Juan Lantero-Rodriguez[1], Gemma Salvadó[2], Laia Montoliu-Gaya[1], Wagner Brum[1,3], Shorena Janelidze[4], Nicholas Ashton[1,5,6,7], Henrik Zetterberg[1,8,9,10,11], Kaj Blennow[1], Oskar Hansson[2,12]
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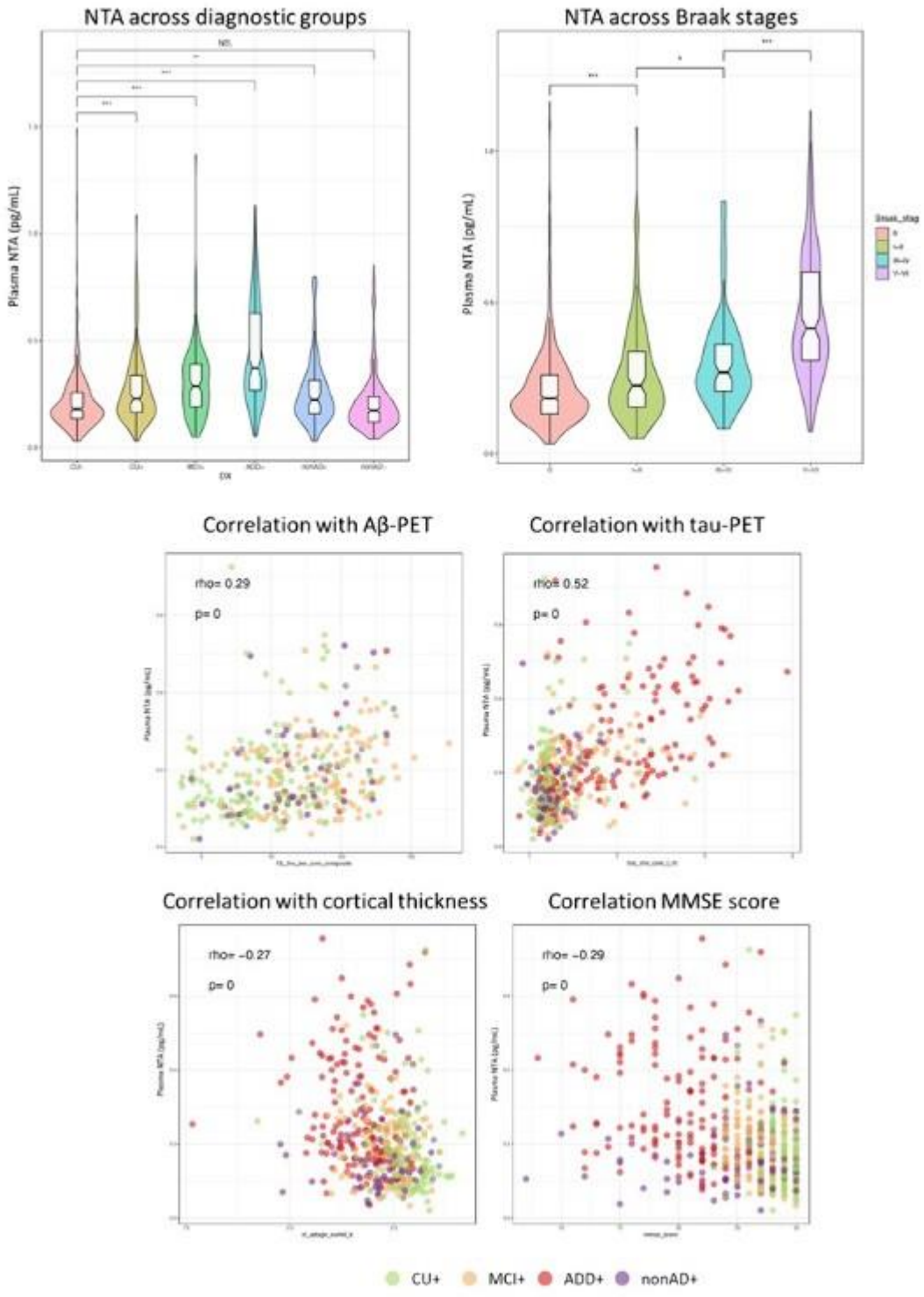
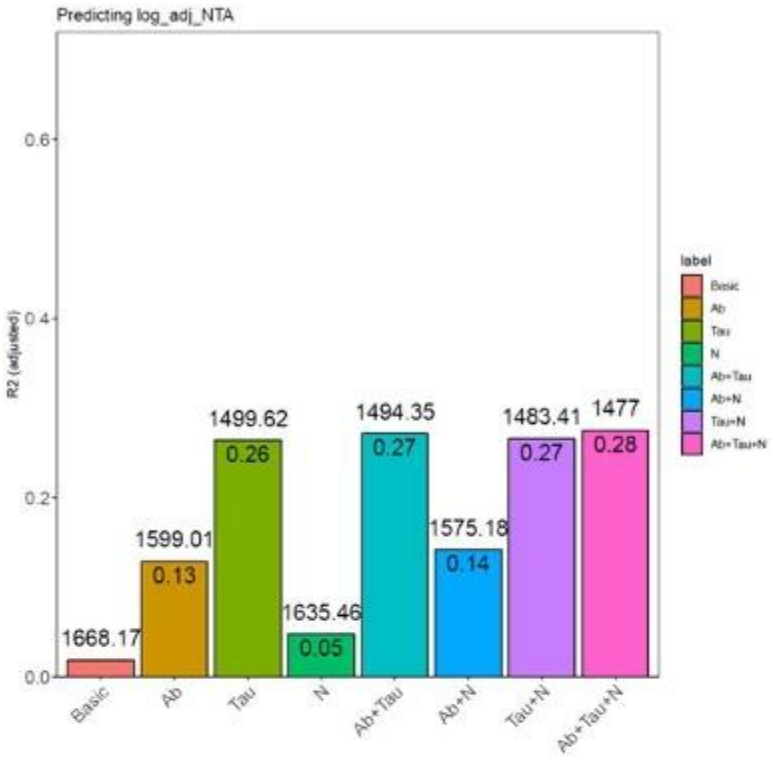
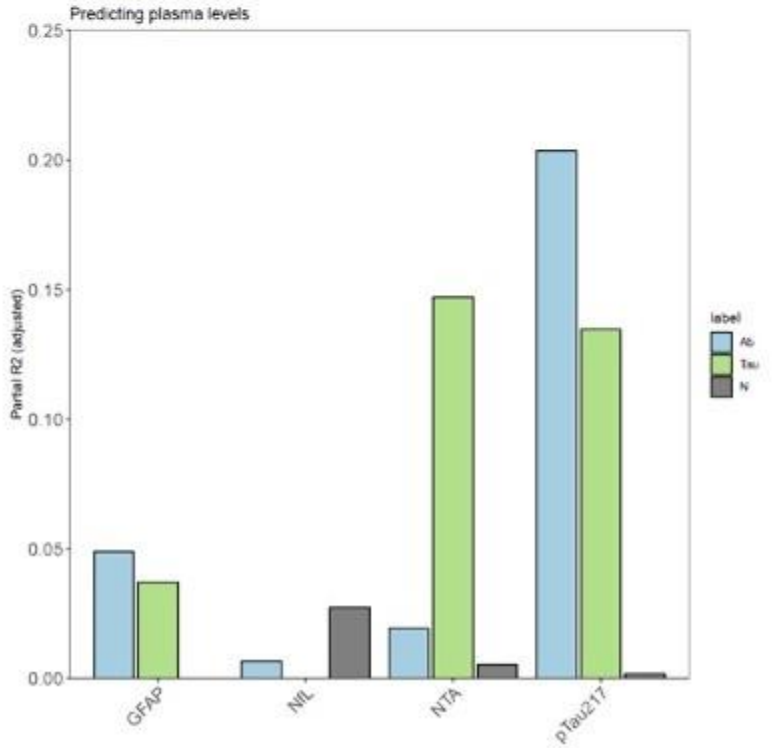
Aims: Novel blood biomarkers, e.g., p-tau181, p-tau217 or p-tau231, are highly specific for Alzheimer's disease (AD), and can track amyloid-β (Aβ) and tau pathology. However, because these biomarkers are strongly associated with the emergence of Aβ pathology, it is difficult to determine the contribution of tau deposition to the plasma p-tau signal in blood. Therefore, there remains a need for a biomarker capable of specifically tracking tau accumulation in brain.
Methods: We developed a Simoa method (NTA), capable of measuring non-phosphorylated tau fragments in blood. We examined NTA in the Swedish BioFINDER-2 study (n=1445), which includes cognitively unimpaired (CU), mild cognitive impairment (MCI), AD dementia (ADD), and non-AD individuals, well-characterized by clinically validated fluid and imaging biomarkers.
Results: Plasma NTA was increased across the AD *continuum* (CU+, MCI+, ADD+: $p<0.0001$ for all) and in Aβ+ non-AD ($p<0.001$). NTA showed subtle associations with Aβ-PET ($r=0.29$, $P=0.001$) and cortical thickness ($r=-0.27$, $P=0.001$), but strongly correlated with tau-PET ($r=0.52$, $P=0.001$). Interestingly, when evaluating the contribution of Aβ pathology, tau pathology and neurodegeneration to NTA levels, a tau pathology only model ($R^2=0.26$) was not substantially improved by including Aβ pathology ($R^2=0.26$), neurodegeneration ($R^2=0.27$) or both ($R^2=0.27$), suggesting NTA is mostly associated with tau pathology. Finally, when comparing the partial R^2 of a regression model including Aβ pathology, tau pathology and neurodegeneration, NTA was almost exclusively explained by tau pathology (unlike plasma GFAP, NfL and p-


NTA across diagnostic groups
Plasma NTA (pg/mL)
NTA across Braak stages
Plasma NTA (pg/mL)
Correlation with Aβ-PET
rho= 0.29
p= 0
Correlation with tau-PET
rho= 0.52
p= 0
Correlation with cortical thickness
rho= −0.27
p= 0
Correlation MMSE score
rho= −0.29
p= 0
CU+
MCI+
ADD+
nonAD+
Spearman's rho, only Ab+

tau217).





Conclusions: Our results indicate that NTA is a highly specific blood biomarker for AD, closely associated with *in vivo* tau deposition after the initial deposition of Aβ. This new biomarker has potential as an outcome measure in clinical trials which also need to assess downstream effects of successful Aβ removal.

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ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

IDENTIFICATION OF TMPRSS5 (SPINESIN) AS A CANDIDATE BIOMARKER IN CSF AND PLASMA FOR PARKINSON'S DISEASE DIAGNOSIS AND PROGRESSION

Julian Sefrin, Petra Jakob, Philipp Secker, Jennifer Mollon, Roland Heym, Stefan Barghorn
AbbVie Deutschland GmbH & Co. KG, Neuroscience Discovery, Ludwigshafen am Rhein, Germany

Aims: Using a multiplex immunoassay approach, we sought to identify novel fluid biomarkers differentially regulated in the CSF and plasma of Parkinson´s Disease (PD) patients.
Methods: Plasma and CSF of two independent PD cohorts were analyzed with the antibody-based Proximity Extension Assay (Olink™) technology. Subsequent analyses were performed using an in-house developed and validated TMPRSS5 immunoassay on the Ella platform. The following cohorts were analyzed: two commercially acquired cohorts (20 HC, 20 PD; 24 HC, 30 PD), one cohort from the University Clinic Tuebingen (25 HC, 25 PD, 25 MSA, 15 DLB) and the PPMI round robin SAA cohort (30 HC, 30 PD, 20 SWEDD).
Results: Olink analysis of a commercially acquired cohort and the Tuebingen cohort revealed that TMPRSS5 was significantly ($p<0.05$) increased in the CSF and plasma of PD patients versus healthy controls with a fold change of 1.3 to 1.5 in both cohorts and biofluids. These results were subsequently verified using the TMPRSS5 Ella assay (Olink vs. Ella Spearman correlation $r=0.95$ and 0.87). Importantly, there was significant correlation between TMPRSS5 in plasma and CSF in both cohorts (Spearman $r=0.48$ and 0.44, $p<0.01$). Similar increase in TMPRSS5 was observed in the CSF of PD patients in the second commercially acquired cohort ($FC=1.5$, $p<0.001$), while no group differences were detected in the PPMI cohort that comprises early PD patients. ROC curve analysis generated AUC values between 0.69 and 0.80 for the three cohorts with significantly altered TMPRSS5 levels.
Conclusions: Our results highlight TMPRSS5 as a promising biomarker in CSF and plasma for PD diagnosis and/or progression alone or in combination with other markers. Further analyses, especially of longitudinal samples, are required to decipher the potential as progression biomarker.

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OD303 / #2050

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

ASSIGNING AND MONITORING PERFORMANCE OF CUT POINTS FOR PLASMA P-TAU181 FOR USE IN PROSPECTIVE STUDIES

Jeffrey Dage[1,2,3,4], Kristen Russ[2,4], Ralitsa Kostadinova[4,5], Sujuan Gao[4,6], Steve Brown[4,6], Liana Apostolova[1,2,3,4,5], Shannon Risacher[3,4,5], Bernardino Ghetti[2,3,4,7], Kathy Newell[4,7], Andrew Saykin[3,4,5], Tatiana Foroud[2,3,4]
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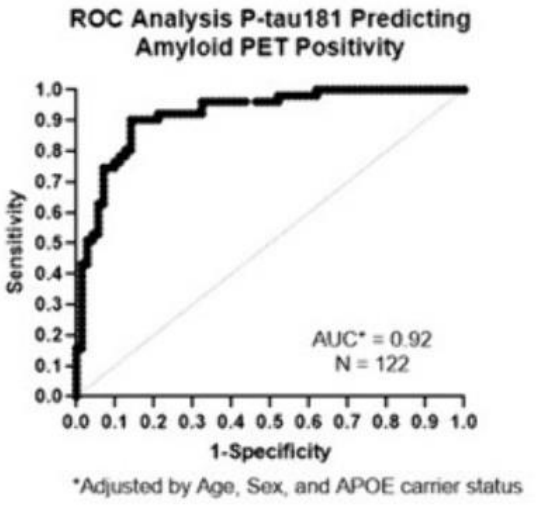
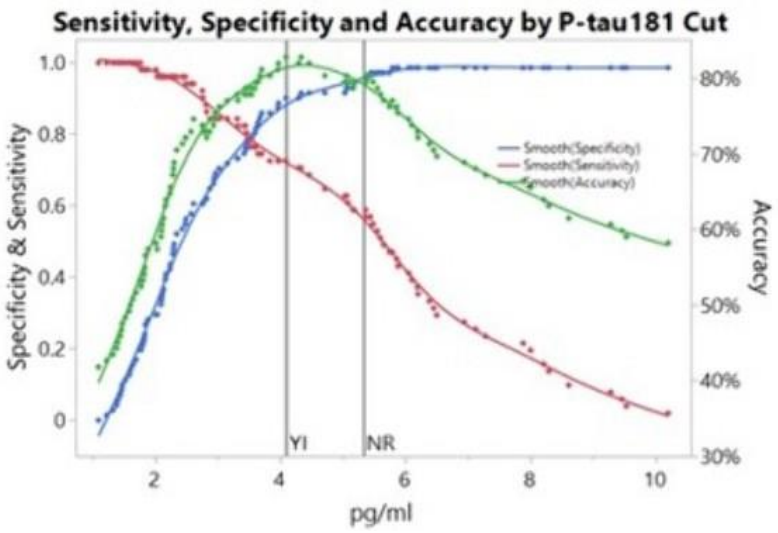
Aims: Plasma P-tau has demonstrated clinical utility for determination of the presence of Alzheimer's pathology across many studies and P-tau isoforms. However, few studies have attempted to assign cut points or normative ranges and prospectively apply them in future studies. Using samples from the Indiana Alzheimer's Disease Research Center (IADRC), our study assigns a cut points using Amyloid PET as a reference method, validates the cut points against neuropathology and Tau PET, and demonstrates the performance in the ongoing Alzheimer Disease Center Fluid biomarker (ADCFB) initiative.
Methods: Previously collected IADRC samples (N=275) were provided blinded for analysis, diluted on a Tecan Fluent, and assayed in duplicate (Simoa HD-X, Ptau181). Post-analysis, participant clinical diagnosis, demographics, neuroimaging, and neuropathological data were provided. Statistical analyses included receiver operating characteristics curve analysis (ROC). Cut points were assigned using the Youden's Index (YI) and a nonparametric method to assign normal range (NR).
Results: ROC analyses followed by assessment of the YI determined a cut point of 4.1 pg/mL using Amyloid PET as reference. The NR cut point was determined by evaluating the 97.5% quantile of the Amyloid negative normal group between ages of 55-81 (< 5.3 pg/mL). The YI cut point identified Intermediate or high Alzheimer's disease neuropathologic change (ADNC) with a higher overall accuracy (84%) compared with the normative range (76%). The performance of these cut points were evaluated in an ADCFB data snapshot and showed a positivity rate of 49% or an abnormal rate of 33%. Full data analysis will be presented.





Conclusions: Assignment of cut point values depend on the specific context of use. Prospective application of a cut point

require knowledge of cohort differences, control of preanalytical factors, and a stable implementation of the biomarker assay.

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ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
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BLOOD CELL-SPECIFIC EXTRACELLULAR VESICLES FOR BLOOD-BASED STRATIFICATION OF DEMENTIA PATHOLOGY

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[1]NeuroDex, R&d, Arlington, United States of America, [2]NeuroDex, Consultant, Arlington, United States of America

Aims: Dementia affects over 50 million people worldwide, and over 80% of cases are caused by mixed pathology. The definition of disease is shifting from the traditional symptom-based understanding to being more heavily based on biomarkers. At NeuroDex, we develop extracellular vesicles (EVs) based blood biomarkers to improve specificity and identify dementia pathologies, including Tau, amyloid, alpha-synuclein, and TDP43.
Methods: ExoSORT is an optimized immunoaffinity method for isolating cell-specific EVs from blood plasma samples. Lumin-EX is an optimized immunoassay for multiplex analysis of plasma EV surface proteins. These methods were tested on a cohort of 50 Alzheimer's Disease (AD) patients, 45 Lewy-Body Dementia (LBD) patients, 40 Parkinson's Disease (PD) patients, 30 Multiple System Atrophy (MSA) patients, 60 Amyotrophic Lateral Sclerosis (ALS) patients, and 50 healthy controls.
Results: ALS samples have significantly (1.8-fold, $P<0.001$, AUC=0.81) more neuron-derived EV (NDE) associated TDP43 than controls. PD and LBD samples have significantly (2.4-fold, $P<0.001$, AUC=0.86) more NDE associated alpha-synuclein than controls. AD and LBD have significantly (2.1-fold, $P<0.01$, AUC=0.78) more NDE-associated p181-Tau than controls. TDP43 and alpha-synuclein split the AD samples into two groups of high and low, suggesting subgrouping. Ongoing studies with 45 plasma samples from LBD and AD with postmortem pathological analysis will answer if the subgroups correlate with brain pathology. In addition, we measured EV-associated synaptic proteins and autophagy biomarkers, which generated significant changes across diseases and significant correlation ($R^2=0.41$, $P<0.002$) with cognitive tests.
Conclusions: NeuroDex's novel EVs-based biomarkers constitute a platform that enables measuring different dementia-related pathologies. NeuroDex seems to identify the expected changes between diseases, and future studies will determine if co-morbidities can also be detected. We predict that dementia stratification based on pathology will boost therapeutic development.

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OD305 / #1713

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

SEX-SPECIFIC CSF PROTEOMIC PROFILING OF SPORADIC ALZHEIMER'S DISEASE

Anh Do[1], Muhammad Ali[2], Jigyasha Timsina[3], Lihua Wang[2], Agustín Ruiz[4], Pau Pastor[5], Carlos Cruchaga[1], Yun Ju Sung[2]
[1]Washington University School of Medicine, Neurogenomics And Informatics Center, 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, Neurogenomics And Informatics Center, St. Louis, United States of America, [4]Ace Alzheimer Center Barcelona, Universitat Internacional De Catalunya, Barcelona, Spain, [5]University Hospital Mutua Terrassa, Neurology, Terrassa, Spain

Aims: To investigate the role of sex in the relationship between proteomic alterations and preclinical AD and to elucidate proteomic underpinning for AD heterogeneity and susceptibility between sex.
Methods: A total of 599 preclinical AD cases and 435 controls in the discovery cohort underwent lumbar puncture. Over 7,000 protein abundance levels were measured in cerebrospinal fluid (CSF) samples using SomaLogic assay. Preclinical AD cases and controls were classified using Aβ42 and pTau 181 levels from the same CSF samples. Proteins with sex-specific effects were identified through linear regression models focusing on the interaction term between AD status and sex. They were tested in the independent cohort (N=732) using identical approaches. The replicated proteins with sex-specific effects were annotated and further validated in different omics data.
Results: We identified 594 proteins with sex-specific effects in the discovery cohort ($P<0.05$ and permutation FDR <0.05). Among them, 36 were replicated in the replication cohort ($P<0.05$ and the same direction). These proteins were found to be involved in neurologic disorders and highly enriched in axon regeneration (fold enrichment=9.38 and FDR=2.8×10^{-4}). The 36 proteins strongly predict AD outcomes (AUC=0.93), which is significantly improved comparing to age, sex, and APOE combined. Protein-protein and protein-gene interaction networks highlighted hubs including CCN2, which suggests important roles of these proteins in AD. The follow-up of 36 proteins using brain transcriptomics and proteomics data confirmed sex-specific effects of CCN2, HMGN1, IL20RA, and CHAD on AD in brain tissue.
Conclusions: We identified and replicated 36 proteins associated with preclinical AD that have distinct effects in females compared to those in males. The biological pathways and interaction networks highlighted in the study provide better understanding of sex differences in developing AD and progression.

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OD306 / #1974

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

ANALYTICAL AND CLINICAL PERFORMANCE OF A NOVEL PLASMA P-TAU217 ASSAY COMPARED TO P-TAU181 FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE

Sherif Bayoumy[1], Inge Verberk[1], Ben Den Dulk[1], Marissa Zwan[2], Wiesje Van Der Flier[3], Jeroen Vanbrabant[4], Eugeen Vanmechelen[4], Erik Stoops[4], Andreas Jeromin[5], Charlotte E. Teunissen[1]
[1]Amsterdam Neuroscience, Vrije Universteit, Amsterdam, Amsterdam UMC, Neurochemistry Laboratory Department Of Clinical Chemistry, Amsterdam, Netherlands, [2]Alzheimer Center, Vrije Universiteit Amsterdam, Amsterdam UMC, Department Of Neurology, AMSTERDAM, Netherlands, [3]Alzheimer Center, Vrije Universiteit Amsterdam, Amsterdam UMC, Department Of Neurology, AMSTERDAM, Netherlands, [4]ADx NeuroSciences, Development, Gent, Belgium, [5]Alzpath, Research And Development, Carslbad, United States of America

Aims: Several high-performing phosphorylated tau (p-tau) single-molecule array (Simoa) assays show reliable diagnostic capacity for Alzheimer´s disease (AD). However, some assays are less optimal with healthy control samples. There is a need for p-tau assays with enhanced analytical sensitivity. We aimed to validate the analytical and clinical performance of a novel plasma p-tau217 against a commercial p-tau181 Simoa assay.
Methods: We compared the analytical (sensitivity, precision, parallelism) and clinical (40 AD-dementia patients, age 68 years, 70%F; 40 age-matched controls) performance of the novel p-tau217^{Alzpath} assay against the commercial p-tau181^{Quanterix} assay.
Results: The p-tau217^{Alzpath}assay showed an average inter-assay precision of 12%CV using three quality controls over three independent runs, compared to 19%CV for p-tau181^{Quanterix}. Intra-assay precision of the 80 clinical samples was 8%CV (p-tau217^{Alzpath}) and 6%CV (p-tau181^{Quanterix}), respectively. Both assays measured p-tau levels above their assay blanks in all clinical samples, including controls. For p-tau217^{Alzpath}, 5 of the 80 samples were measured with >20%CV between duplicate measurements compared to 4 of the 80 with p-tau181^{Quanterix}. The assays showed good parallelism (figure 1) with an average of 89% (p-tau217^{Alzpath}) and 95% (p-tau181^{Quanterix}). P-tau levels were higher in patients with AD-dementia compared to controls (p-tau217^{Alzpath}: 4.2 fold; p-tau181^{Quanterix}: 1.8 fold). The p-tau217^{Alzpath} assay showed higher diagnostic accuracy (AUC of 0.92, 95%CI:0.85-0.98) compared to p-tau181^{Quanterix} assay (AUC=0.83, 95% CI:0.74-0.92)(DeLong's *p*=0.004)(figure 2).
Conclusions: The assays showed good analytical performance. Our results suggest that compared to published reports on p-tau217 immunoassays, the p-tau217^{Alzpath} assay has enhanced sensitivity to quantify p-tau reliably also in control samples with low p-tau217 concentrations. In our proof-of-concept cohort, the diagnostic value of the p-tau217^{Alzpath} assay showed better discriminative capacity for AD diagnosis. This will be further validated in larger and heterogeneous clinical cohorts.

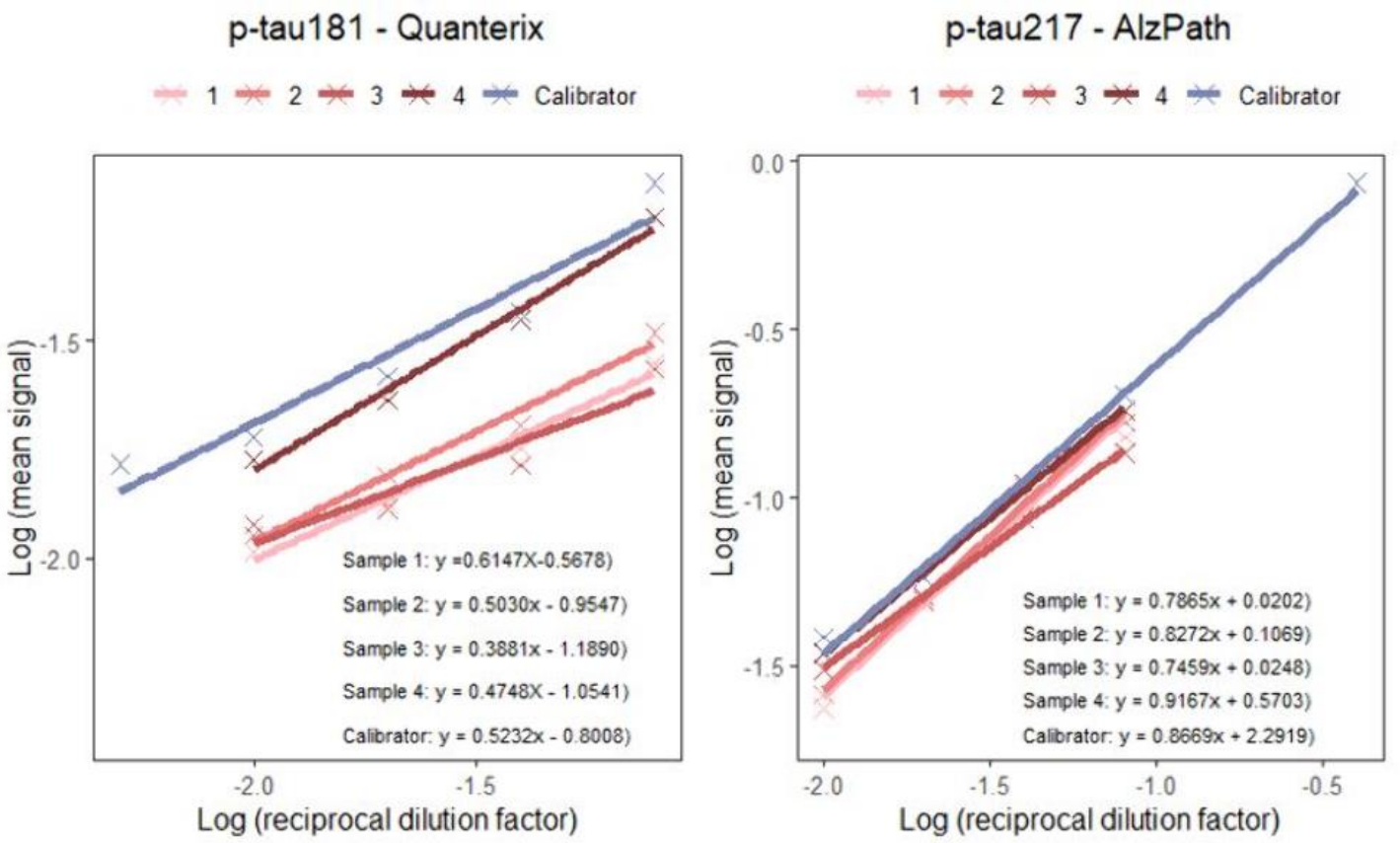

Figure 1. Parallelism of the p-tau assays. Serial dilution of four plasma samples (in red) and one calibrator (in purple) was performed for each of both p-tau assays. The selected samples had high endogenous p-tau concentrations. Crosses represent the individual measurements. A linear slope was fitted for each sample and for the calibrators. Equations of the slopes are presented in the figures. Parallelism results was acceptable when slopes were within the range of 80-120% comparability.

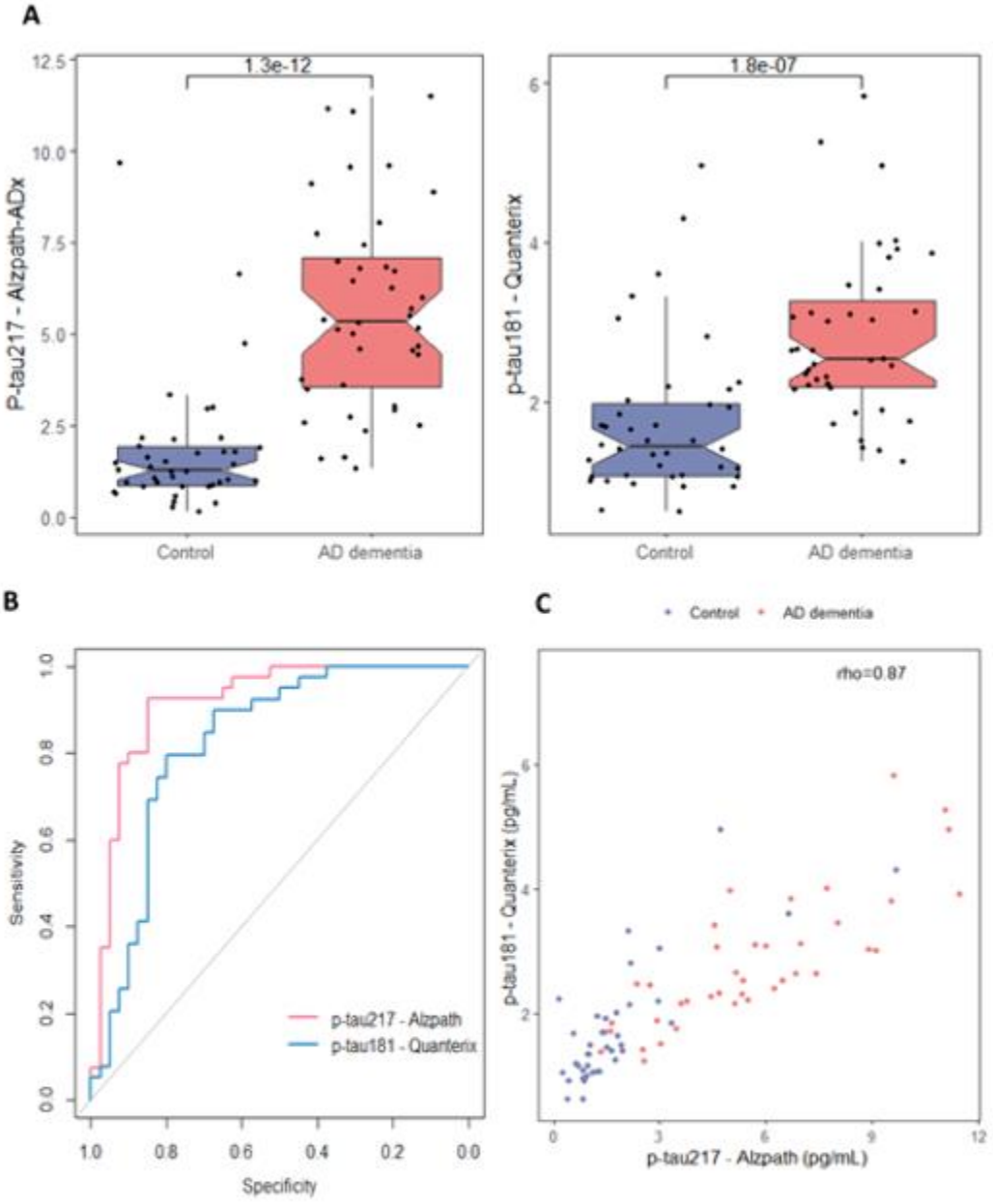

Figure 2. A) Boxplots to demonstrate p-tau levels measured in 40 AD dementia and 40 control samples. p-values for group differences were calculated using non-parametric Mann-Whitney U Test. **B)** ROC curves of the discrimination between controls and AD dementia for the p-tau assays. **C)** Scatterplots of the correlation between p-tau measurements, color-coded for diagnostic group. Correlation coefficient rho is calculated using Spearman's rank correlation. Controls are presented in purple and patients with AD dementia in red. p-tau: phosphorylated tau, AD: Alzheimer's Disease. Group comparisons using the p-tau assays were significant with p-values below 0.05.

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ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

BIOMARKER BASED CLUSTERING OF COGNITIVELY IMPAIRED ADULTS REVEALS DIFFERENT ALZHEIMER'S DISEASE CLINICAL SUBTYPES

Hussein Zalzale[1], Guilherme Povala[1], Carolina Soares[1], Cristiano Aguzzoli[1], Pamela Ferreira[1], Firoza Lussier[1], Bruna Bellaver[1], João Pedro Ferrari-Souza[1], Douglas Leffa[1], Sarah Abbas[1], Arlec Cabrera[1], Francieli Rohden[1], Peter Lemaire Iii[1], Joseph Therriault[2], Ghada Abdelhady[1], Cécile Tissot[2], Stijn Servaes[2], Mira Chamoun[2], Gleb Bezgin[2], Jenna Stevenson[2], Arthur Macedo[2], Alyssa Stevenson[2], Vanessa Pallen[2], Nicholas Ashton[3], Andrea L. Benedet[4], Kaj Blennow[3], Henrik Zetterberg[5], Thomas Karikari[1], Pedro Rosa-Neto[2], Tharick Pascoal[1]
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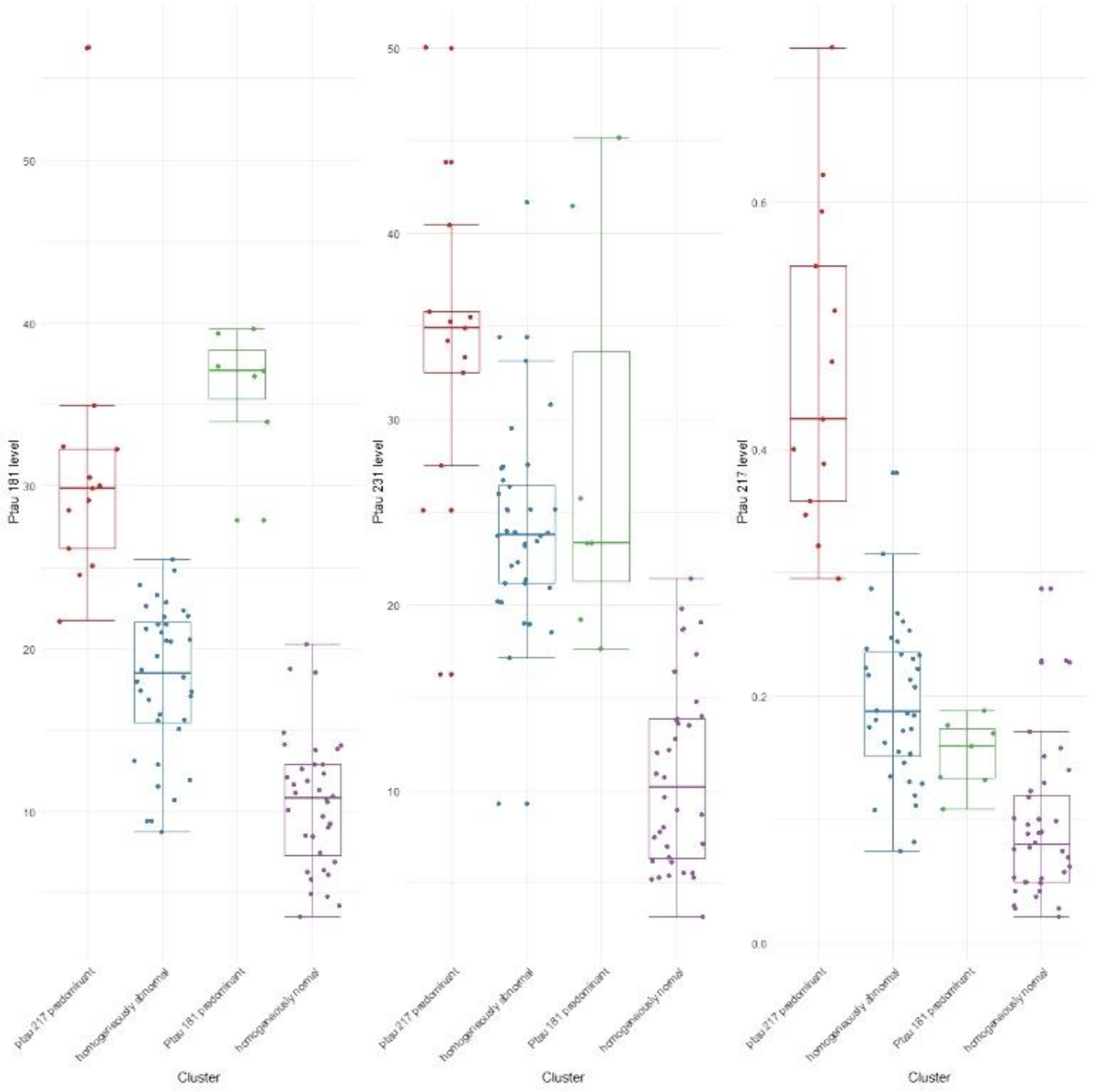
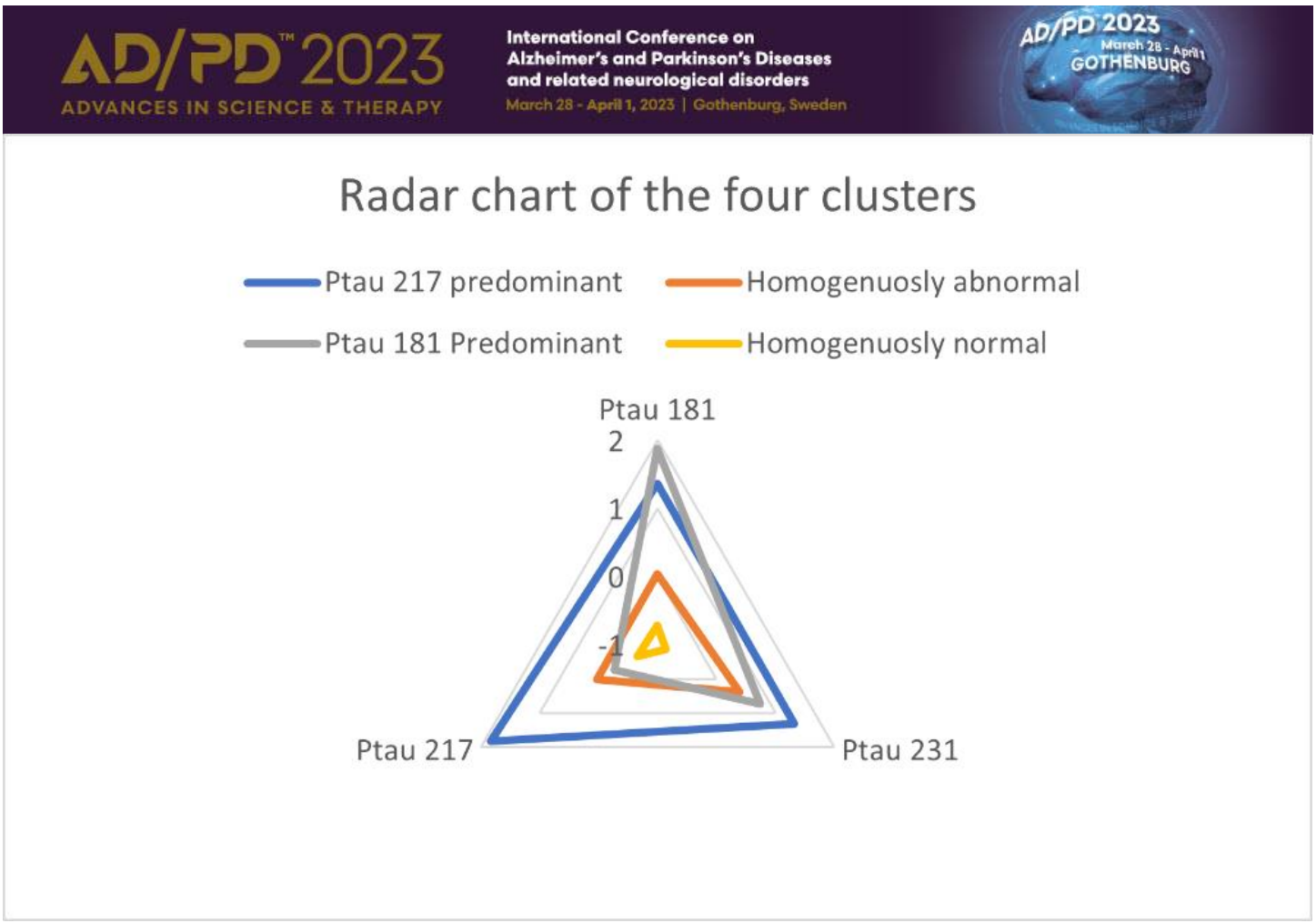
Aims: Recently, there has been a growing interest in the utility of plasma biomarkers, especially phosphorylated tau (ptau) isotopes in the diagnosis and monitoring of Alzheimer's disease (AD). Here, we aim to cluster patients with cognitive impairment based on their levels of plasma ptaus 181, 231, and 217, and explore the unique characteristics of the clusters present.
Methods: We employed a K-nearest means clustering algorithm to stratify patients with cognitive impairment (n = 92) from TRIAD cohort based on the levels of plasma ptau 181, 231, and 217. The optimal number of clusters was determined using the elbow method in addition to the Marriott and Ball indices. Clusters were then compared on various biomarker and neuropsychiatric measures using ANOVA with FDR multiple comparisons correction.
Results: Our analysis yielded four clusters (figures1-2, table 1). Two clusters displayed abnormalities in the 3 isoforms, one with predominance of ptau217 with and another of ptau181. The remaining two clusters presented homogenous levels across the p-tau isoforms, one having abnormal levels and the other normal levels. Individuals in the homogenously normal cluster displayed significantly better performance in memory cognitive tests compared to the other three clusters. The ptau217 predominant cluster displayed a significantly higher mean N-terminal A tau epitope and lower executive functioning scores when compared to the other three clusters
(matrix1).


Ptau 181 level
Ptau 231 level
Ptau 217 level
Cluster
ptau 217 predominant
homogeneously abnormal
Ptau 181 predominant
homogeneously normal


Radar chart of the four clusters
Ptau 217 predominant
Homogenuosly abnormal
Ptau 181 Predominant
Homogenuosly normal
Ptau 181
2
1
0
-1
Ptau 217
Ptau 231

Variable		217-predominant	Average	181-predominant
Plasma Biomarkers				
Ptau-217	Average	**<0.001**	-	-
	181-predominant	**<0.001**	0.17	-
	Lower level	**<0.001**	**<0.001**	0.07
Ptau-231	Average	**<0.001**	-	-
	181-predominant	**0.045**	0.15	-
	Lower level	**<0.001**	<0.001	<0.001
Ptau-181	Average	**<0.001**	-	-
	181-predominant	**0.039**	**<0.001**	-
	Lower level	**<0.001**	**<0.001**	**<0.001**
GFAP	Average	0.075	-	-
	181-predominant	0.075	0.54	-
	Lower level	**<0.001**	**<0.001**	0.075
NTA	Average	**<0.001**		
	181-predominant	**0.0016**	0.9042	
	Lower level	**<0.001**	**0.0053**	0.167
Nfl	Average	0.25	-	-
	181-predominant	0.57	0.83	-
	Lower level	**0.001**	**0.002**	0.08
Plasma Tau	Average	0.25	-	-
	181-predominant	0.71		-
	Lower level	**0.011**	**0.044**	**0.05**
CSF Biomarkers				
AB142	Average	0.59	-	-
	181-predominant	0.54	0.24	-
	Lower level	0.116	**<0.001**	0.62
AB42_40	Average	0.52	-	-
	181-predominant	0.89	0.71	-
	Lower level	0.32	**<0.001**	0.46
Ptau 181	Average	0.86		
	181-predominant	0.75	0.71	
	Lower level	0.37	**0.018**	0.71
Ptau 231 ELISA	Average	0.65	-	-

	181-predominant	0.7	0.54	-
	Lower level	0.54	**0.004**	0.68
Ptau 231 Simoa	Average	0.8	-	-
	181-predominant	0.8	0.93	-
	Lower level	0.09	**0.02**	0.25
Ptau 217 UGOT	Average	0.84	-	-
	181-predominant	0.84	0.86	-
	Lower level	0.24	**0.003**	0.25
Ptau 235	Average	0.86	-	-
	181-predominant	0.86	0.86	-
	Lower level	0.09	**0.003**	0.25
Total Tau	Average	0.77		
	181-predominant	0.77	0.71	
	Lower level	0.37	**0.018**	0.71
CSF Glucose	Average	0.91		
	181-predominant	0.78	0.78	
	Lower level	0.37	0.09	0.78
Neurocognitive domains				
Memory composite	Average	0.31	-	-
	181-predominant	0.52	0.84	-
	Lower level	**<0.001**	**<0.001**	**<0.001**
Executive function composite	Average	**0.018**	-	-
	181-predominant	**0.006**	0.19	-
	Lower level	**<0.001**	0.18	0.6217
PBR burden				
Caudate	Average	0.047	-	-
	181-predominant	0.44	0.48	-
	Lower level	**0.014**	0.35	0.35
Middle Temporal Cortex	Average	0.19	-	-
	181-predominant	0.19	0.48	-
	Lower level	0.19	0.35	0.35

Table 4 Matrix showing the differences between the four clusters on variables that were significantly different according to ANOVA.

Conclusions: Ptau levels may be better interpreted in relationship to each other rather than individually. Individuals with a predominant elevation of ptau217 may have more severe form of the disease, as opposed to those with predominant elevation of ptau181. Future research should examine if the observed clusters are also present in cognitively unimpaired older adults and examine their utility in clinical prediction of conversion to AD.

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OD308 / #2776

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

POSITIONING THE FINGER STUDY AS AN OPTIMAL PLATFORM FOR EVALUATION OF AD TREATMENT RESPONSE MARKERS: PROOF OF CONCEPT STUDY EVALUATING CORTISOL BIOAVAILABILITY

Chinedu Udeh-Momoh[1,2], Ruth Stephen[3], Tiia Ngandu[4], Miia Kivipelto[1], Alina Solomon[2,3]
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Aims: Therapeutic strategies modulating cortisol hyper-secretion, a putative risk factor for accelerated Alzheimer's disease (AD) progression may serve to impede disease risk. Leveraging data from the landmark multidomain lifestyle clinical trial – FINGER, that reported cognitive benefits post intervention, we investigated the impact of the FINGER intervention on change in cortisol bioavailability, including demographical, clinical and brain pathological determinants of the hypothesised treatment response.
Methods: The FINGER study included 1260 older Finnish individuals aged 60-77 years old, at increased risk for dementia. Morning plasma cortisol data were available for 646 participants (325 intervention, 321 control) at baseline and 619 participants (306 intervention, 313 control) at Year 2. Associations between study groups (intervention and control) and change in cortisol (modelled as mean difference of baseline and Year 2 cortisol levels) were explored, followed by effect modification analyses by age and sex. Associations of cortisol with baseline and longitudinal changes in brain AD pathological (beta-amyloid PiB-PET), MRI structural (regional brain volumes, cortical thickness, and white matter lesion (WML) volume) and metabolic (FDG-PET) markers were further evaluated in *a priori* confounder-adjusted multivariate regression models.
Results: Cortisol levels decreased over time across study groups. Increased cortisol levels were noted for women APOE-4 carriers while older age (>70 yo) predicted higher odds of reduced cortisol levels post lifestyle intervention. Differential associations were noted for brain biological measures, with amyloid pathology and brain vascular and metabolic markers showing strongest associations with plasma cortisol independent of group assignation.
Conclusions: Cortisol changes preceded pronounced increase in brain AD pathological measures, irrespective of lifestyle trial participation. Subsequent studies will explore the potential of cortisol bioavailability to predict AD progression, and as a treatment-response marker in individuals with distinct risk profiles including age and genetic risk.

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OD309 / #197

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

SALIVARY PROTEIN AGGREGATES AS A BIOMARKER FOR PARKINSON'S DISEASE

Martin Furlepa[1], Yu Zhang[2], Evgeniia Lobanova[2], Lakmini Kahanawita[1], Caroline Williams-Gray[1], David Klenerman[2]
[1]University of Cambridge, Department Of Clinical Neurosciences, Cambridge, United Kingdom, [2]University of Cambridge, Department Of Chemistry, Cambridge, United Kingdom

Aims: This study aimed to explore whether the number and shape of protein aggregates present in saliva, a readily accessible biofluid, could be used as a sensitive biomarker for the diagnosis of Parkinson's disease (PD).
Methods: We collected saliva samples using passive drool, enzyme inhibitors were then added before centrifugation and storage. We used a single-molecule pull down assay (SIMPull), utilising antibodies for capture and imaging, to quantify different species of protein aggregates present in collected saliva. Subsequently, using direct stochastic optical reconstruction microscopy (dSTORM) we super resolved the captured aggregates to 30nm resolution providing aggregate size and morphology information. These methods allowed us to compare the number and characteristics of alpha-synuclein (αS) and amyloid-beta (Aβ) containing aggregates present in the saliva of PD patients (n=10) and age-matched controls (n=10).
Results: We were able to image αS and Aβ containing aggregates in saliva with a high signal to noise ratio. The ratio of αS to Aβ containing aggregates (αS/Aβ) is higher in the saliva of patients with PD ($p=0.029$) and this ratio can distinguish between PD patients and controls (AUC = 0.79). Applying dSTORM revealed the aβ containing aggregates are larger and more fibrillary in saliva from PD patients compared to controls. Combining the αS/Aβ with size and circularity thresholding improves the ability the distinguish between the two groups (AUC = 0.90).
Conclusions: Protein aggregates present in PD patients saliva differ in number and morphology compared to controls. Our results suggest that changes in protein structure in PD are not limited to αS. Combining the relative number of aggregates present in saliva with their morphological features provides better discrimination between groups than either measure individually and shows promise as a potential biomarker for PD.

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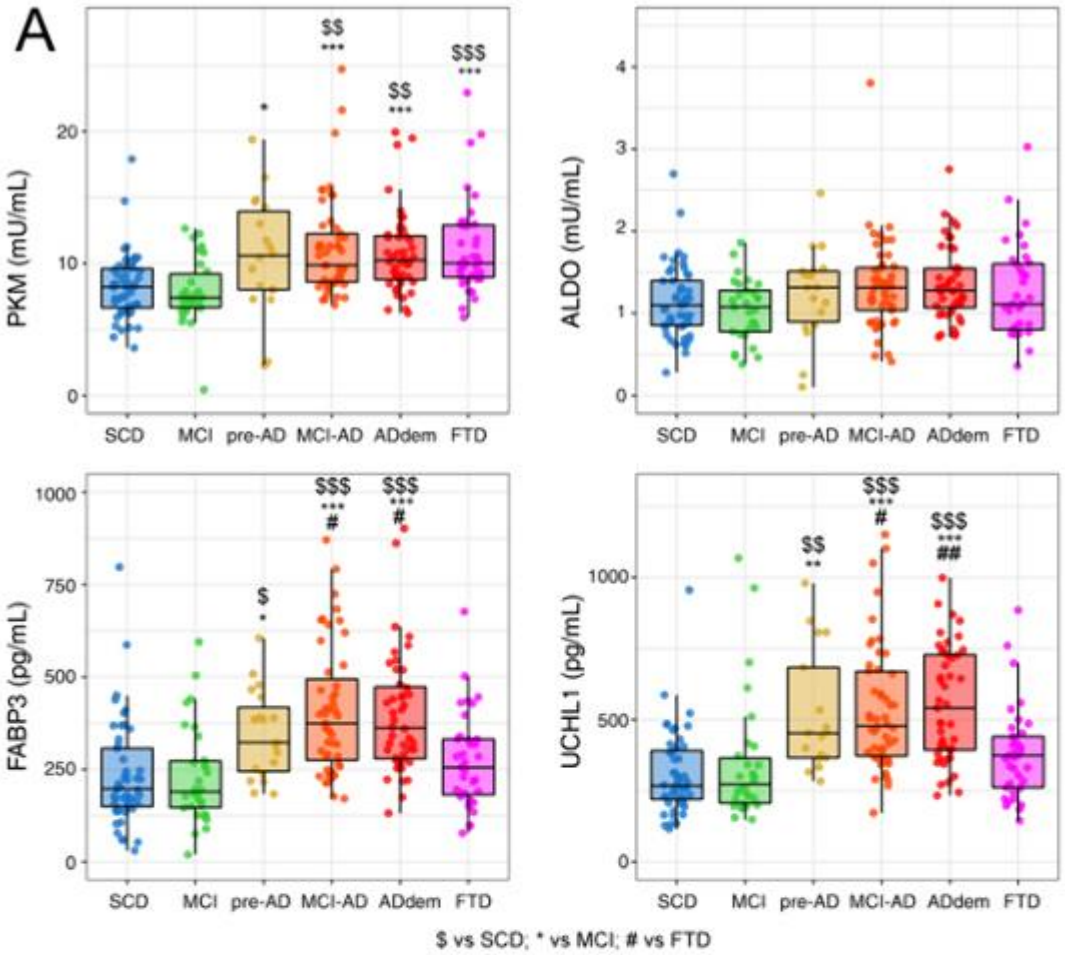
OD310 / #567

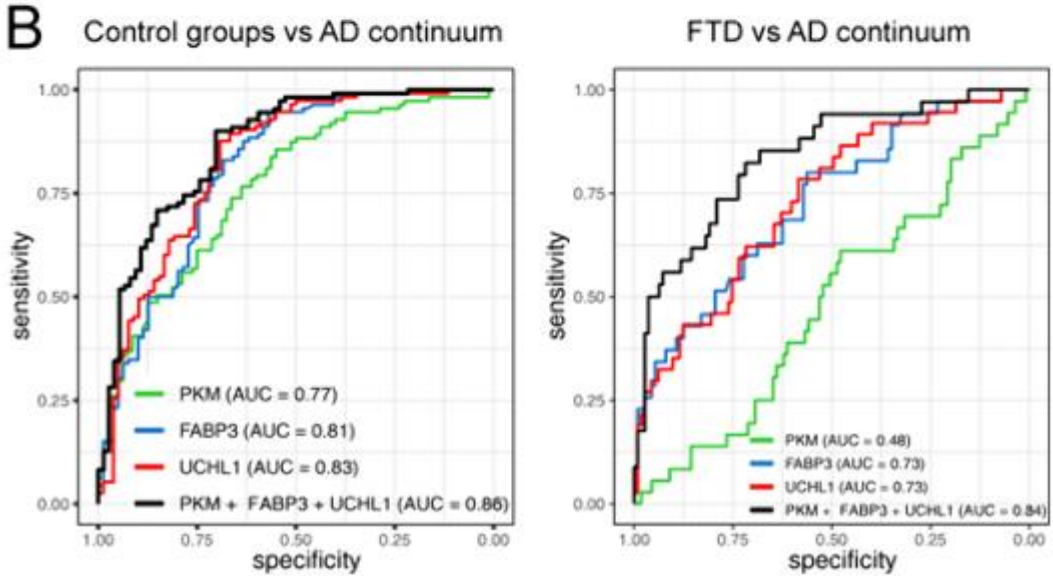
ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

DIAGNOSTIC PERFORMANCE OF METABOLISM-RELATED PROTEINS PKM, UCHL1 AND FABP3 IN CSF ACROSS THE AD CONTINUUM

Silvia Paciotti, Anna Wojdała, Giovanni Bellomo, Andrea Toja, Elena Chipi, Lorenzo Gaetani, Lucilla Parnetti, Davide Chiasserini
University of Perugia, Department Of Medicine And Surgery, Perugia, Italy

Aims: We evaluated the diagnostic performance of cerebrospinal fluid (CSF) metabolism-related proteins not directly linked to amyloid- and tau-pathways (i.e., pyruvate kinase, PKM; aldolase, ALDO; ubiquitin C-terminal hydrolase L1, UCHL1, and fatty acid-binding protein 3, FABP3) across the Alzheimer's disease (AD) continuum, including patients at very early stages.
Methods: PKM and ALDO activity and UCHL1 and FABP3 levels were measured in CSF. The cohort included patients with preclinical AD (pre-AD, n=19, without cognitive impairment), mild cognitive impairment due to AD (MCI-AD, n=50) and overt AD (ADdem, n=45), all with positive CSF AD-profile and patients with frontotemporal dementia (FTD, n=37). Individuals with MCI not due to AD (MCI, n=30) and subjective cognitive decline (SCD, n=52) with negative CSF AD-profile, were enrolled as control groups.
Results: UCHL1, FABP3 and PKM were significantly increased in AD patients, already at the pre-clinical stage. FTD patients showed similar PKM activity to AD patients and increased compared with control groups. No difference was found for ALDO among the groups (Figure 1A). UCHL1 showed good performance in discriminating early AD patients (pre-AD and MCI-AD) from MCI and SCD (AUC~0.83), as assessed by ROC analysis. Similar results were obtained for FABP3. Conversely, PKM provided the best performance when comparing FTD vs. MCI (AUC=0.80), for which UCHL1 and FABP3 showed lower diagnostic accuracy. Combination of PKM, FABP3 and UCHL1 improved the diagnostic accuracy for the detection of patients within the AD continuum when compared with single biomarkers (Figure





1B).

Conclusions: PKM activity might be useful as general neurodegeneration biomarker, being elevated in both AD and FTD, while UCHL1 and FABP3 are specifically increased across the AD continuum, also at the preclinical stage before cognitive impairment occurs.

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OD311 / #618

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

ASSOCIATIONS BETWEEN NEUROTICISM AND CSF BIOMARKERS OF ALZHEIMER'S DISEASE IN A COHORT OF SWEDISH SEPTUAGENARIANS.

Jonas Molinder[1], Therese Sterner[1], Silke Kern[2], Hanna Falk Erhag[1], Henrik Zetterberg[1,3], Kaj Blennow[1], Anna Zettergren[1], Ingmar Skoog[1], Robert Sigström[1]
[1]Sahlgrenska Academy of Gothenburg University, Neuroscience And Physiology, Section Of Psychiatry And Neurochemistry, Mölndal, Sweden, [2]Sahlgrenska Academy at the University of Gothenburg, Neuroscience And Physiology, Section Of Psychiatry And Neurochemistry, Mölndal, Sweden, [3]University of Gothenburg, Department Of Psychiatry And Neurochemistry, Mölndal, Sweden

Aims: It has previously been shown that personality traits, specifically high levels of Neuroticism (N) and low levels of Conscientiousness (C), are associated with an elevated risk of developing dementia. This study investigated the relationships between personality traits, and Cerebrospinal Fluid (CSF) biomarkers of Alzheimer's Disease (AD). Of specific interest was the association between traits N and C and AD-signature CSF biomarkers.
Methods: We used data from a sample of 311 (160 males and 151 females) 70-year-old individuals from the Gothenburg H70 birth cohort study. CSF was analyzed for amyloid beta (Aβ) 42/40 ratio, phosphorylated tau (ptau-181), total-tau (tau), and neurofilament light (NFL). The short version of the Five Factor Personality Inventory (FFI) was also administered.
Results: A linear regression analysis revealed a negative association between trait N and CSF Aβ42/Aβ40 ratio (B=-.004 S.E.=.002 p=.024). Specifically, the association indicated that the higher N-scores, the lower levels of Aβ42/Aβ40 were detected. No association was found between trait C and Aβ42/Aβ40 (B=.001 S.E.=.002 p=.585). No associations were found between any of the other big five personality traits and any other CSF biomarkers.
Conclusions: Our findings indicate that higher neuroticism associates with lower levels of CSF Aβ in a cohort of Swedish septuagenarians. Further, the lack of association between conscientiousness and AD-signature biomarkers could suggest that its negative association to dementia is primarily driven by other factors.

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OD312 / #746

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

EVALUATION OF PHOSPHO-TYROSINE 39 ALPHA-SYNUCLEIN AS BIOMARKER FOR PARKINSON'S DISEASE

David Holzinger[1], Ivonne Wollenberg[2], Anikó Kárpáti[2], Ravindran Kumaran[2], Simone Giaisi[1], Stefan Barghorn[1], Roland Heym[1]
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Aims: There is a high need for biomarkers to confirm and follow α-Synuclein pathology in Parkinson's disease (PD) patients. Both total and phospho-Serine 129 (pS129) α-Synuclein have limited utility as biomarkers for PD and data on additional phosphorylation sites of α-Synuclein in body fluids are scarce. Here, we developed immunoassays for investigation of α-Synuclein phosphorylated on Tyrosine 39 (pTyr39) in human brain and body fluids.
Methods: Using the Singulex platform, we tested 10 monoclonal rabbit antibodies directed against pTyr39 α-Synuclein in combination with N- and C-terminal anti-α-Synuclein antibodies and selected two assays based on signal/noise ratio. After validation, we applied these assays to brain, cerebrospinal fluid (CSF), and plasma from PD patients and age-matched healthy controls. Total α-Synuclein was measured using a commercially available MSD assay and pS129 α-Synuclein using an in-house Singulex assay.
Results: The rabbit monoclonal antibodies were highly specific for α-Synuclein phosphorylated by Tyrosine kinase, whereas unmodified α-Synuclein was not detected. In PD brain samples pTyr39 α-Synuclein was significantly elevated compared to age-matched healthy brains. While this modification was not detectable in human PD CSF pools, a signal was detected in human plasma. No statistically significant group difference was found in a plasma cohort of 25 healthy controls and 25 PD patients. Interestingly, there was no correlation between pTyr39 α-Synuclein and total or pS129 α-Synuclein, while total and pS129 α-Synuclein were highly correlated.
Conclusions: Our results show that pTyr39 α-Synuclein is elevated in PD brain. In contrast, no disease difference was observed in plasma and no signal was detected in CSF. Therefore, the developed immunoassays are valuable tools for investigation of pTyr39 α-Synuclein in PD brain, but increased assay sensitivity is required for studies in CSF.

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OD313 / #845

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

CSF TAU AND P-TAU BIOMARKERS IN THE 1946 BRITISH BIRTH COHORT: ASSOCIATIONS WITH DEMOGRAPHIC FACTORS, CONCORDANCE WITH CEREBRAL AMYLOID DEPOSITION

Ashvini Keshavan[1], Elena Camporesi[2], Will Coath[1], David Cash[1], Nick Fox[1], Eugeen Vanmechelen[3], Thomas Karikari[2], Nicholas Ashton[2], Kaj Blennow[2], Henrik Zetterberg[2,4], Jonathan Schott[1]
[1]UCL Queen Square Institute of Neurology, Dementia Research Centre, Department Of Neurodegenerative Disease, London, United Kingdom, [2]the Sahlgrenska Academy at the University of Gothenburg, Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, Mölndal, Sweden, [3]ADx NeuroSciences NV, Research And Development, Ghent, Belgium, [4]UCL, Uk Dementia Research Institute, London, United Kingdom

Aims: In the Insight 46 sub-study of the 1946 British birth cohort (at age 72 years) we investigated cerebrospinal fluid (CSF) biomarkers of amyloid, tau, neurodegeneration and glia for associations with demographic factors and concordance with cerebral amyloid deposition defined either by CSF or position emission tomography (PET).
Methods: Biomarkers were quantified using Simoa (Quanterix) commercial kit digital immunoassays (NFL, GFAP, Aβ42, Aβ40, p-tau181V2) and homebrew assays (NTp181, NTp217, NTp231, NTp235: University of Gothenburg); NT1 tau (Harvard University); Lumipulse (Fujirebio) automated immunoassays (Aβ42, Aβ40, p-tau181, tau); and ELISA (ADx) Midp231. Associations of log-transformed CSF biomarkers with age, sex and APOE ε4 carrier status were investigated by linear regression. ROC analysis was used to ascertain concordance of CSF biomarkers with cerebral amyloid positive status defined either as Lumipulse Aβ42/40 ratio<=0.0075 or as 18F-florbetapir SUVR>=0.605 normalized to eroded white matter without partial volume correction (22.6 centiloids).
Results: 134 participants donated CSF at mean age 72.9 (SD 0.6) years (63% male, 26% APOE ε4 positive). CDR 0/0.5/1 score distribution was 89.6%, 9.7%, 0.7%. For every additional year of age, participants had a 13% lower CSF NTp235. No biomarker showed significant sex differences. Significant fold increases in biomarker levels with APOE ε4 carrier status were seen for NTp217 (2.05), NTp231 (1.30) and Midp231 (1.32). These three biomarkers also had the highest areas under the curve for concordance with amyloid status defined by either CSF (NTp217 0.973, NTp231 0.946, Midp231 0.958) or PET (NTp217 0.934, NTp231 0.910, Midp231 0.928); all outperformed a base model incorporating age, sex and APOE ε4 (AUC CSF 0.691; PET 0.716).
Conclusions: CSF phosphorylated tau NTp217, NTp231 and Midp231 showed excellent concordance with cerebral amyloid status in a birth cohort of predominantly cognitively normal individuals.

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OD314 / #1023

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

IMPACT OF COMORBIDITIES ON THE DIAGNOSTIC PERFORMANCE OF PLASMA PHOSPHORYLATED TAU 181 IN THE BALTAZAR COHORT

Sylvain Lehmann[1], Schraen-Maschke Susanna[2], Jean-Sébastien Vidal[3], Constance Delaby[1], Frédéric Blanc[4], Claire Paquet[5], Bernadette Allinquant[6], Bombois Stéphanie[7], Audrey Gabelle[8], Olivier Hanon[3]
[1]CHU Montpellier, Lbpc-ppc, Montpellier, France, [2]CHU Lille, Umr-s-u1172, Lille, France, [3]Université Paris Cité, Hopital Broca, Paris, France, [4]Strasbourg University Hospital, Memory Center For Ressources And Research, Strasbourg, France, [5]Inserm, Umr 1144 Oten, Paris, France, [6]Univ Paris Cité, Umr-s 1266, Paris, France, [7]Assistance Publique-Hôpitaux de Paris (AP-HP), Gh Pitié-salpêtrière, Paris, France, [8]Université de Montpellier, Cmrr, Montpellier, France

Aims: Our objectives were to validate in a large cohort the value of plasma P-tau181 for the prediction of brain amyloid status and the conversion of mild cognitive impairment to Alzheimer's disease. And on the other hand, to study the confounding factors that could influence its blood concentration and thus its diagnostic performance.
Methods: This study is ancillary to the prospective multicenter BALTAZAR cohort that enrolled patients with mild cognitive impairment (MCI). Comorbidities were recorded in this population, and biological confounders (fasting glucose, cholesterol, prealbumin, albumin, creatinine) were measured in initial blood samples. An ultrasensitive SIMOA assay of phosphorylated forms at position 181 of the tau protein (ptau181) was performed on the initial plasma sample of MCI patients (N=476).
Results: Among MCI participants, 30% developed dementia over a three year period and 67% were Aβ+. Plasma P-tau181 was increased significantly in the Aβ+ population (3.9 [SD 1.4] vs. 2.6 [SD 1.4] pg/mL) and in MCI that converted to dementia (3.8 [SD 1.5] vs. 2.9 [SD 1.4] pg/mL, p<0.0001). These differences remain significant after adjustment with age, sex and APOEε4 status. Kaplan–Meier curve of conversion to dementia according to the tertiles of plasma P-tau181 revealed a significant overall difference (Log rank P<.0001) and an hazard ratio of 3.8 [95%CI=2.5-5.8]. Using a linear regression approach, chronic kidney disease (CKD), creatinine and glomerular filtration rate (eGFR) were independently associated with plasma P-tau181 concentrations. Concentrations of this analytes were significantly different in eGFR tertiles resulting in different optimal cutpoints.
Conclusions: Plasma P-tau181 effectively detects Aβ+ and conversion to dementia confirming the value of this blood biomarker in the management of AD. However, renal function significantly modifies its concentrations and may induce diagnostic errors if not taken into account.

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OD315 / #1067

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

PLASMA AMYLOID-BETA AND LONGITUDINAL COGNITIVE DECLINE AMONG CLINICALLY UNIMPAIRED LATE-MIDDLE AGED ADULTS

Karly Cody[1,2], Rachel Studer[2], Rebecca Langhough Koscik[1,2,3], Erin Jonaitis[1,2,3], Carey Gleason[1,2,4], Nia Norris[3], Thomas Loepfe[1,2,5], Cynthia Carlsson[1,2,3], Nathaniel Chin[1,2,3], Sanjay Asthana[1,2,4], Kristopher Kirmess[6], Matthew Meyer[6], Kevin Yarasheski[6], Tobey Betthauser[1,2], Sterling Johnson[1,2,3]
[1]University of Wisconsin - Madison, Department Of Medicine, Madison, United States of America, [2]University of Wisconsin - Madison, Wisconsin Alzheimer's Disease Research Center, Madison, United States of America, [3]University of Wisconsin – Madison, Wisconsin Alzheimer's Institute, Madison, United States of America, [4]Madison Veterans Administration, Geriatrics Research Education And Clinical Center, Madison, United States of America, [5]Mayo Clinical Health System, Geriatrics, La Crosse, United States of America, [6]C2N Diagnostics, C2n Diagnostics, St. Louis, United States of America

Aims: To investigate the clinical performance of plasma amyloid-beta (Aβ)for distinguishing brain amyloid and to examine the associations of plasma Aβ with longitudinal cognitive trajectories among late-middle-aged cognitively unimpaired individuals enriched for risk of Alzheimer's disease (AD).
Methods: Data from initially unimpaired individuals (N=291) with available plasma Aβ concentrations and serial (1 to 9) cognitive assessments were selected from the Wisconsin Registry for Alzheimer's Prevention (n=260) and Wisconsin AD Research Center (n=31) cohorts. Plasma Aβ42 and Aβ40 concentrations were quantified using a high-resolution mass spectrometry-based assay (C_2N Diagnostics). In the subset with amyloid PiB PET imaging (n=279), receiver operating characteristic curve (ROC) analyses were used to assess assay performance and accuracy for predicting PiB positivity (Global PiB DVR >1.19; Centiloid > 22). Associations of plasma Aβ42/40 and longitudinal retrospective decline on a Preclinical Alzheimer's Cognitive Composite were investigated using linear mixed effects (LME) models.
Results: Plasma Aβ42/40 concentration ratios were lower among PiB positive participants (p<.0001). The area under the ROC curve was 0.88 (95% CI = 0.84-0.92) with 83% agreement between plasma Aβ42/40 and PiB positivity at the optimal (Youden index) cutoff value of 0.093 (Figure 1). The LME indicated a significant interaction between plasma Aβ42/40 and time; participants with lower plasma Aβ ratio had faster cognitive decline over the retrospective period of observation when adjusting for relevant covariates (Figure 2).

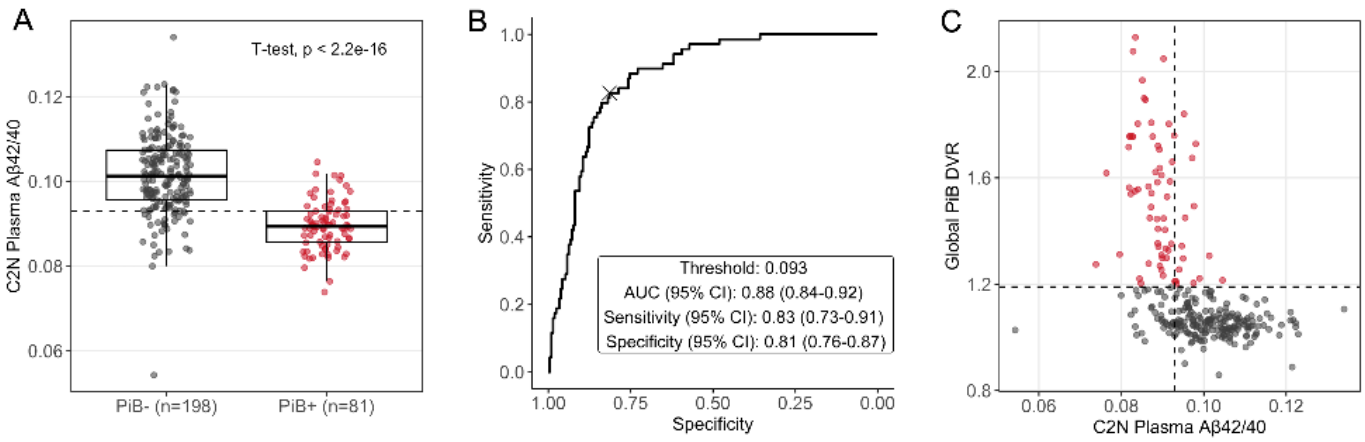

Figure 1. Performance of plasma amyloid-beta (Aβ) for distinguishing brain amyloid. A. Scatter-Box-Whisker plot of plasma Aβ42/40 for participants classified as PiB negative (gray) or positive (red) with plasma Aβ42/40 ratio threshold shown as the dashed horizontal line. B. Receiver Operating Characteristic (ROC) curve discriminating between PiB positive and negative individuals using participants' plasma Aβ42/40 ratio. C. Four-quadrant plot of the relationship between global PiB DVR values and plasma Aβ42/40 ratios and cutoff values (dashed vertical line: Plasma Aβ42/40=0.093; dashed horizontal line: Global PiB DVR = 1.19).

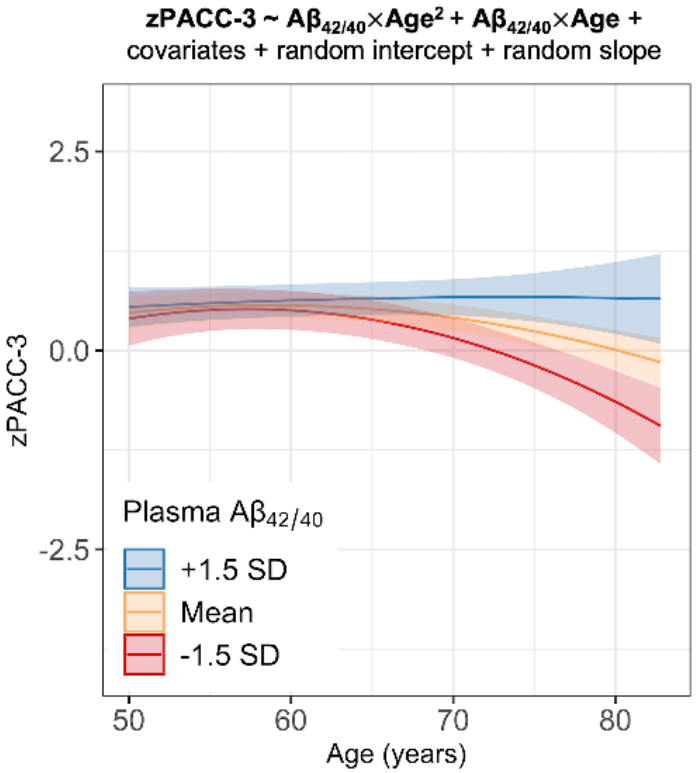

Figure 2. A linear mixed effects model (including subject-specific random intercepts and age-related slopes) adjusting for gender, education, cohort, *APOE*ε4 and the number of prior exposures to the cognitive battery was used to investigate the the association of plasma $A\beta_{42/40}$ with retrospective PACC-3 decline in late-middle-aged, initially unimpaired participants (n=291) with 8.9 (6.7 - 10.2) (Median(IQR)) years of cognitive follow-up. Time in the model was operationalized as age at visit. The plot shows the modeled age-related PACC-3 trajectories at the mean and the mean ± 1.5 SD of plasma $A\beta_{42/40}$ concentration ratio (plasma $A\beta_{42/40}$, mean(SD) =0.098 (0.015)). Results of the model indicated a significant quadratic age by plasma $A\beta_{42/40}$ interaction, suggesting that lower levels of plasma $A\beta_{42/40}$ were associated with faster retrospective PACC-3 decline. Analyses using C2N's amyloid probability score (APS) showed similar results.

Conclusions: These findings suggest that the mass-spectrometry-based Aβ42/40 concentration ratio has high concordance with amyloid PET status and is associated with cognitive decline in the preclinical timeframe.

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OD316 / #1168

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

CEREBROSPINAL FLUID PROTEOMICS FROM CAUCASIANS AND AFRICAN AMERICANS REVEALS SHARED AND DIVERGENT PATHOPHYSIOLOGY IN ALZHEIMER'S DISEASE

Nicholas Seyfried[1], Erica Modeste[1], Lingyan Ping[2], Duc Duong[1], Eric Dammer[1], James Lah[3], Allan Levey[3]
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Aims: Emerging evidence indicates that African Americans (AA) with AD have lower levels of cerebrospinal fluid (CSF) Tau compared to Caucasians (Cau). Other differences in AD CSF biomarkers between these populations have not been fully elucidated. Here, we performed unbiased quantitative proteomic analysis of CSF from both AA and Cau with AD to identify both shared and divergent pathophysiologies across race.
Methods: Tandem mass tag mass spectrometry (TMT-MS) from 105 controls and 99 AD CSF samples identified and quantified 1840 proteins. Of the 204 cases, 101 identified as Cau while 103 identified as AA. Differential expression was performed to prioritize changes in the AD CSF proteome within and across each racial group. Network analyses organized proteins in the CSF into modules enriched with specific brain cell type markers and biological functions. Proteins from these modules were further validated by targeted MS.
Results: The magnitude of Tau increase in AD by immunoassay was greater in Cau than in AA and significantly correlated to Tau proteomic measurements (cor=0.83, p=4.7e-47). Differential expression showed a bias towards downregulated proteins in AA with AD compared to Cau with AD. Network analysis resolved protein modules enriched with proteins associated pre-synaptic markers and glucose metabolism increased in AD, whereas modules enriched post-synaptic markers were decreased in AD. Modules associated with metabolism and 14-3-3 proteins were increased in both AA and Cau with AD. Notably, a module enriched with post-synaptic neuronal markers were significantly lower levels in African Americans with AD.
Conclusions: Unbiased proteomic analysis of the CSF identified shared and divergent cell-type biomarkers in AA and Cau with AD. Collectively, this highlights the utility of unbiased proteomics to identify CSF signatures that differ across race in AD.

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OD317 / #1330

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

THE ASSOCIATION BETWEEN ROUTINE BLOOD MARKERS AND SERUM NEUROFILAMENT LIGHT CHAIN IN A CONSECUTIVE COHORT OF MEMORY CLINIC PATIENTS

Anja Simonsen[1], Helena Sophia Gleerup[1], Christian Sandøe Musaeus[1], Finn Sellebjerg[2], Malene Hansen[2], Helle Søndergaard[2], Steen Gregers Hasselbalch[1]
[1]Rigshospitalet, Danish Dementia Research Centre, Copenhagen, Denmark, [2]Danish Multiple Sclerosis Centre, Rigshospitalet, Copenhagen, Denmark

Aims: Objectives: There is a need to explore the influence of biological factors on blood neurofilament light (NfL) levels to assess its clinical usefulness. The aim of this study was to investigate the influence of routine blood markers of organ health on serum NfL values in a mixed memory clinic cohort.
Methods: Methods: The cohort consisted of 1190 consecutive patients referred for diagnostic evaluation at the Memory Clinic, Danish Dementia Research Centre. Routine blood tests were performed as part of the diagnostic evaluation. Serum NfL was analyzed retrospectively using SIMOA.
Results: Results: As expected, NfL correlated highly with age and was inversely correlated with mini mental state examination (MMSE). Serum NfL was inversely correlated to estimated glomerular filtration rate (eGFR) and weakly with alanine transaminase (ALT), and low-density lipoprotein (LDL). Surprisingly, there was no correlation with hemoglobin A1c (HbA1c).
Conclusions: Conclusions: This large cohort highlights the importance of biological confounders in the interpretation of blood NfL levels for diagnostic purposes, especially in the elderly population with extensive comorbidities.

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OD318 / #1840

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

NEW SITE-SPECIFIC PHOSPHOR-TAU BIOMARKERS DISCOVERY FOR ALZHEIMER'S EARLY DIAGNOSIS AND TAUOPATHY DIFFERENTIATION

Bin Xu[1], Shih-Hsiu Wang[2], Ling Wu[1], Nailya Gilyazova[3], John Ervin[4]
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Aims: Alzheimer's disease (AD) and related tauopathies, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease, are characterized by hyperphosphorylated intracellular tau aggregates. Recently, CSF and blood-based biomarkers have been developed for premortem diagnosis of AD. However, there are no well-established biomarkers for early detection of AD in patients with mild cognitive impairment (MCI), a transitional stage between normal cognition and dementia. We sought to develop novel methods and biomarkers for early diagnosis of AD and tauopathy differentiation.
Methods: We identified high-molecular-weight (HMW) "smear-like" tau aggregates from brain extracts that are specific for AD subjects. Using tau antibody screening approach targeting HMW misfolded tau aggregates, we tested a comprehensive set of site-specific phosphor-tau (p-tau) antibodies targeting tau phosphorylation sites showing high frequencies in AD subjects. Selected candidates were further tested for their ability to differentiate subjects with AD vs. other tauopathies and MCI vs. cognitively normal subjects by ELISA assays. Ultrasensitive assays, such as home-brew SIMOA and novel amyloid precipitation capture molecule are being developed to detect these new misfolded tau biomarkers from patient blood and CSF.
Results: Multiple new p-tau sites have been identified and characterized. Our data showed p-tau198, p-tau396 and several others are novel promising AD biomarkers with sensitivity and specificity comparable to existing p-tau biomarkers, p-tau181, p-tau217, and p-tau231. Significantly, p-tau198, p-tau396, and additional biomarkers were able to discriminate MCI from cognitively normal controls with AUCs of 0.80-0.90, showing better diagnostic performance than those for the existing p-tau biomarkers.
Conclusions: Several promising novel p-tau biomarkers for AD early diagnosis and tauopathy differentiation were identified. Our work provides new avenues for developing new diagnostic technologies for AD and potentially broader neurodegenerative protein misfolding diseases.

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OD319 / #2145

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

PLASMA LEVELS OF AB42, AB40, T-TAU AND NFL AS BIOMARKERS OF COGNITIVE DECLINE IN PATIENTS WITH PARKINSON'S DISEASE

Maria Teresa Dell'Abate[1], Chiara Zecca[1], Daniele Urso[1,2], Marco Filardi[1,3], Davide Vilella[1], Giancarlo Logroscino[1,3]
[1]Center for Neurodegenerative Diseases and the Aging Brain University of Bari "Aldo Moro"/ AO Card. G. Panico Hospital, Center For Neurodegenerative Diseases And The Aging Brain, Tricase, Italy, [2]King's College London, Department Of Neurosciences, Institute Of Psychiatry, Psychology & Neuroscience, De Crespigny Park, London, United Kingdom, London, United Kingdom, [3]Department of Basic Medicine, Neuroscience and Sense Organs, University of Bari Aldo Moro, Bari, Italy, Department Of Basic Medicine, Neuroscience And Sense Organs, Bari, Italy

Aims: Objectives. Accessible blood-based biomarkers could provide additional information for Cognitive dysfunction in Parkinson's disease (PD). The aims of the study were to evaluate the plasma levels of Aβ42, Aβ40, t-Tau and NfL in PD-MCI patients and PD patients with normal cognition (PD-NC) and to correlate them with the functioning domains of neuropsychological test.
Methods: Methods. The study was conducted at the Center for Neurodegenerative Diseases University of Bari, "Pia Fondazione Card G. Panico" Hospital Tricase. 33 PD-NC (16 females and 17 males; age at diagnosis: 70.26 ± 6.57) and 34 PD-MCI (17 females and 17 males; age at diagnosis: 70.35 ± 7.39) were included. Each patient underwent neuropsychological assessment, and a venous blood sample. Biomarkers plasma levels were measured using ultrasensitive single molecule array (Simoa) technology.
Results: Results. Statistically significant differences were found in the plasma levels of Aβ42 ($p = 0.001$), Aβ40 ($p = 0.036$), t-Tau ($p = 0.038$) between PD-NC and PD-MCI, but no differences were found in NfL plasma levels ($p = 0.409$). The Aβ42 levels showed a correlation with the Aβ40 levels ($r = 0.873$; $p < 0.001$) and with t-Tau levels ($r = 0.350$; $p = 0.009$). The Aβ40 levels showed a correlation with the t-Tau levels ($r = 0.488$; $p < 0.001$). Statistically significant correlations were found between the Aβ42 levels and the neuropsychological domains: attention ($r = 0.519$; $p = 0.007$), executive ($r = 0.529$; $p = 0.005$) and language ($r = 0.502$; $p = 0.009$). Plasma levels of NfL correlate with the visuospatial domain ($r = -0.596$; $p = 0.001$).
Conclusions: Conclusions. Plasma Aβ42, Aβ40, t-Tau levels significantly differentiate PD-MCI from PD-NC patients and may serve as biomarkers of cognitive impairment in PD.

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OD320 / #2371

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

SPECIFIC ALTERATIONS IN PLASMA GLUTAMINE AND HYDROXYLATED SPHINGOMYELINS OCCUR IN DEMENTIA WITH LEWY BODIES AND CORRELATE WITH CARDIAC DENERVATION

Joseph Kane[1], Xiaobei Pan[2], Paul Donaghy[3], Gemma Roberts[3], John O'Brien[4], Alan Thomas[3], Brian Green[5]
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Aims: We aimed to: a) profile the plasma metabolome of dementia with Lewy bodies (DLB), using a targeted quantitative methodology; and, b) identify metabolomic biomarkers capable of differentiating DLB from Alzheimer's disease (AD), and from cognitively healthy controls (HCs).
Methods: Targeted metabolomic profiling was performed on plasma samples from patients with probable DLB (n=15; age 77.6±8.2 years) and probable AD (n=15; 76.1±6.4 years) using a Biocrates MxP Quant500 kit. Each had undergone cardiac MIBG with uptake quantified using the heart-to-mediastinum count ratio (HMR). Samples from age-matched HCs (n=15; 75.2±6.9 years) were also analysed. Amino acid and biogenic amine separation employed a reversed-phase UHPLC column and triple-quadrupole mass spectrometer in multiple reaction monitoring (MRM) mode. All other metabolites were quantified using flow injection analysis in MRM mode. Data underwent multivariate, univariate and receiving operator characteristic (ROC) analysis.
Results: Principal component analysis plot separated DLB, AD and HC groups (R2=0.518, Q2=0.348) with significant alterations in 17 of 530 detected metabolite parameters (FDR ≤ 0.05), which included neurotransmitters, amino acids and glycerophospholipids. Hydroxylated to non-hydroxylated sphingomyelins ratio (SM-OHs/SM-Non-OHs) was significantly reduced in DLB versus AD and HCs, and glutamine was significantly elevated in DLB versus AD. Both glutamine and SM-OHs/SM-Non-OHs significantly correlated with HMR (Figure 1). The ratio of glutamine to LysoPC a C(24:0) differentiated between AD and DLB groups with ROC of 0.92.
Conclusions: Two altered metabolites markers specific to DLB (elevated SM-Non-OHs and glutamine), have previously been reported in Parkinson's disease populations, and perhaps reflect axonal degeneration. However, our novel finding that these alterations correlate with HMR may suggest that these are linked to peripheral neurodegeneration. Analysis of larger DLB cohorts will allow further interrogation of this relationship.

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OD321 / #2403

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

PROGNOSTIC AND MONITORING CAPACITY OF SERUM GFAP AND NFL IN COGNITIVELY INTACT ELDERLY

Steffi De Meyer[1,2,3], Elena Raluca Blujdea[4], Jolien Schaeverbeke[1,3], Mariska Reinartz[1,3], Patrick Dupont[1,3], Charlotte E. Teunissen[5], Rik Vandenberghe[1,3,6], Koen Poesen[2,3,7]
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Aims: To evaluate the ability of serum glial fibrillary acidic protein (GFAP) and neurofilament light (NfL) to predict and monitor cognitive decline in asymptomatic elderly.
Methods: We included 186 asymptomatic elderly (mean age=69, 48% female), that underwent baseline amyloid-PET, 2-yearly extensive cognitive follow-up including assessment of global cognition as well as memory, language & executive function for up to 11 years (mean=5 years) and 1 (N=77), 2 (N=83) or 3 (N=27) serum samplings (mean time interval=6, range 3-10 years). GFAP and NfL were quantified using the Simoa N4PE kit (Quanterix). Raw values were used for linear models and continuous variables were converted to z-scores in mixed-effects models. All models were corrected for age, sex and education.
Results: At baseline**,** serum GFAP (β=0.11, *p*<0.0001), but not NfL, was associated with amyloid load, while neither biomarker was associated with cognitive function. However, both serum GFAP (β=-0.06, p=0.001) and NfL (β=-0.05, p=0.003) predicted a longitudinal decline in cognition (Figure 1A-E). In particular, the two serum biomarkers were predictive for a decline in memory (GFAP: β=-0.07, p=0.003; NfL: β=-0.10, p<0.001) as well as language performance (GFAP: β=-0.07, p<0.001; NfL: β=-0.05, p=0.01) and this to a comparable extent. No such predictive effect was observed for amyloid-PET and both serum biomarkers predicted decreasing memory and language function when correcting for cerebral amyloid load in addition to age, sex and education. Repeated serum sampling revealed that GFAP and NfL rise respectively 2.9 and 0.8 pg/mL each year (Figure 2A,B). These increases were associated with concomitant decreases in memory (GFAP: β=-0.07, *p*=0.01; NfL: β=-0.12, *p*<0.001) and language function (GFAP: β=-0.05, *p*=0.03; NfL: β=-0.06, *p*=0.008).

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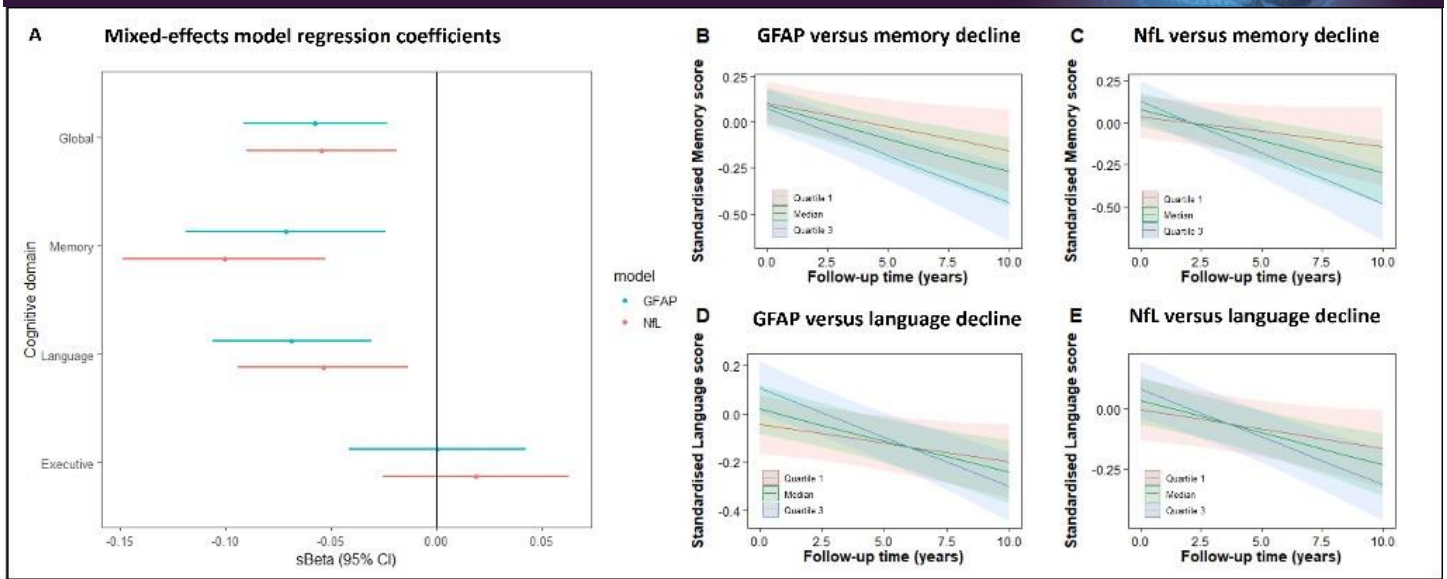

Figure 1. Predictive potential of serum biomarkers for cognitive decline in asymptomatic elderly. (A) Standardised (z-score) regression coefficients of the interaction term between baseline biomarker values and time to cognitive testing. (B-E) Interaction plots visualising the relationship between biomarker levels and cognitive decline

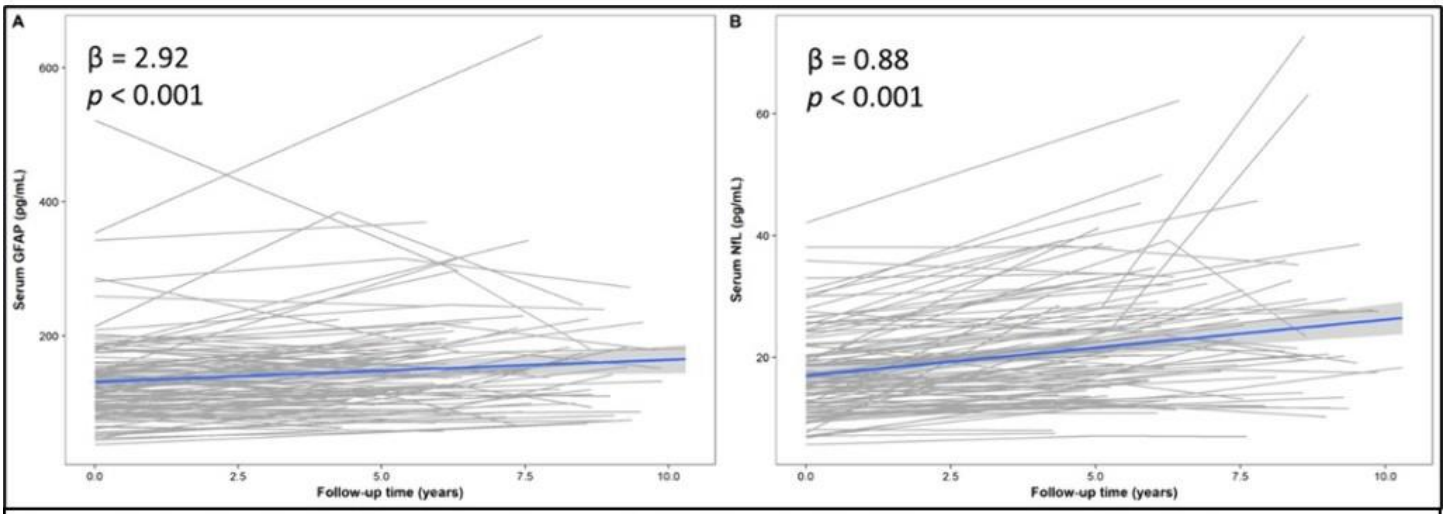

Figure 2. Longitudinal trajectories of serum GFAP (A) and NfL (B) in asymptomatic elderly

Conclusions: Serum GFAP and NfL levels have good prognostic and monitoring potential for cognitive decline in asymptomatic elderly.

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OD322 / #2524

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

DEVELOPMENT OF PLASMA P-TAU231 ASSAY ON A FULLY AUTOMATED IMMUNOASSAY SYSTEM

Kengo Ishiki[1], Teresa Lukaszewska[2], Shunsuke Watanabe[1], Kazuto Yamashita[1], Masahiro Miura[1], Shigeki Iwanaga[1], Eugeen Vanmechelen[3], Toshiyuki Sato[1]
[1]Sysmex Corporation, Central Research Laboratories, Kobe, Japan, [2]Sysmex R&D Center Americas, R&d, Mundelein, IL, United States of America, [3]ADx NeuroSciences NV, Research And Development, Ghent, Belgium

Aims: Biomarker profiling, such as ATN classification, is actively being studied to characterize the pathological processes in different stages of Alzheimer's disease (AD). Recently, many studies have focused on plasma phosphorylated tau (p-tau), which is known to have multiple molecular species with different phosphorylation sites. It has been pointed out that each of these species may exhibit concentration changes at different disease stages. Therefore, measuring simultaneously multiple p-tau species with other ATN biomarkers may allow more detailed biomarker profiling. High sensitive, simple and high performing methods in plasma will accelerate such studies and improve clinical trial set-up. Previously, we have developed the fully automated assays for measuring plasma Aβ40, Aβ42, tau, neurofilament light chain, and p-tau181. In this study, as a candidate of multi p-tau spieces, a newly developed p-tau231 assay was analytically and clinically explored on our immunoassay platform (HISCL™ series).
Methods: We developed the plasma p-tau231 assay using HISCL series, which can achieve highly precise, sensitive, and rapid measurements. Analytical characteristics, such as dilutional linearity and repeatability were evaluated. We measured plasma p-tau231 in commercially available plasma samples from cognitive normal (CN) and from patients with clinically diagnosed AD.
Results: Developed assay had the required performance characteristics to measure p-tau231 levels in CN plasma. The dilution linearity and repeatability met established criteria. There was a significant difference in the concentration of plasma p-tau231 between the AD and CN groups.
Conclusions: A novel plasma p-tau231 assay has sufficient performance to measure p-tau231 levels in plasma. Disease-dependent concentration changes in plasma samples were also observed, suggesting that p-tau231 may have potential values in more precise staging in AD pathology to be coupled with other ATN biomarkers and other p-tau species.

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OD323 / #2536

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

COLORIMETRIC AND SURFACE-ENHANCED RAMAN SCATTERING DUAL-MODE MAGNETIC IMMUNOSENSOR FOR ULTRASENSITIVE DETECTION OF BLOOD PHOSPHORYLATED TAU IN ALZHEIMER'S DISEASE

Haiming Luo
Huazhong University of Science and Technology, Wuhan National Laboratory For Optoelectronics, Wuhan, China

Aims: Phosphorylation of tau at Ser 396, 404 (p-tau^{396,404}) is the earliest phosphorylation event and a promising biomarker for the early diagnosis of Alzheimer's disease (AD). However, detection of blood p-tau is challenging because of its low abundance, easy degradation, and form complexes with various blood proteins or cells, which often lead to the underestimation of p-tau levels when based on plasma detection. How to detect blood p-tau^{396,404} accurately and sensitively?
Methods: we developed a colorimetric and surface-enhanced Raman scattering (SERS) dual-mode magnetic immunosensor for the highly sensitive, specific, and robust detection of p-tau^{396,404} in the whole blood samples. The detection assay is based on the immunoreaction between the p-tau^{396,404} protein, of which antibody modified superparamagnetic iron oxide nanoparticles as a recognition element to capture blood p-tau^{396,404}, and then horseradish peroxidase and Raman reporter dual-labeled corresponding paired antibody as a reporter to provide a high signal-to-noise ratio for the immunosensor.
Results: This dual-mode immunosensor achieved a low limit of detection down to 1.5 pg/mL in SERS mode, and 24 pg/mL in the colorimetric mode by naked eyes. More importantly, this immunosensor can rapidly and accurately differentiate between AD patients and healthy individuals based on blood p-tau^{396,404} level, and also has the potential to distinguish patients with different severities of AD.
Conclusions: this immunosensor can rapidly and accurately differentiate between AD patients and healthy individuals based on blood p-tau^{396,404} level, indicating that it is promising for clinical point-of-care diagnosis of AD, especially in large-scale AD screening.

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OD324 / #2566

ON-DEMAND SYMPOSIUM: FLUID BIOMARKERS 03
01-04-2023 07:00 - 08:30

PLASMA GFAP IS ELEVATED IN ADAD FROM THE ASYMPTOMATIC STAGE AND IS ASSOCIATED WITH DISEASE RELATED PATHOLOGY AND COGNITIVE IMPAIRMENT

Pratishtha Chatterjee[1], Lisa Vermunt[2], Brian Gordon[3], Steve Pedrini[4], Lynn Boonkamp[5], Nicola Armstrong[6], Chengjie Xiong[3], Abhay Singh[7], Yan Li[3], Hamid Sohrabi[8], Kevin Taddei[4], Mark Molloy[9], Tammie Benzinger[10], John Morris[11], Celeste Karch[12], Sarah Berman[13], Jasmeer Chhatwal[14], Carlos Cruchaga[15], Neill Graff-Radford[16], Gregory Day[16], Martin Farlow[17], Nick Fox[18], Alison Goate[19], Jason Hassenstab[20], Jae-Hong Lee[21], Johannes Levin[22], Eric Mcdade[11], Hiroshi Mori[23], Richard Perrin[24], Raquel Sanchez-Valle[25], Peter Schofield[26], Allan Levey[27], Mathias Jucker[28], Colin Masters[29], Anne Fagan[20], Randall Bateman[3], Ralph Martins[30], Charlotte E. Teunissen[31]
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Aims: Recent studies show that glial fibrillary acidic protein (GFAP), a marker of astrocyte reactivity, has potential in serving as a blood-based biomarker for Alzheimer's disease (AD) diagnosis and prognosis across the AD continuum [1-3]. We therefore evaluated plasma GFAP in families with autosomal dominant AD (ADAD), leveraging the predictable age at symptom onset, to determine the timing of disease associated GFAP changes and the clinical correlates of GFAP that will influence its clinical utility.
Methods: Plasma GFAP in families with ADAD from the Dominantly Inherited Alzheimer Network was measured using the Single Molecule Array platform.
Results: Plasma GFAP elevations appeared a decade before expected symptom onset, after beta-amyloid accumulation and prior to neurodegeneration and cognitive decline. Plasma GFAP distinguished beta-amyloid-positive from beta-amyloid-negative ADAD mutation carriers and showed a stronger relationship with beta-amyloid load in asymptomatic ADAD than symptomatic ADAD. Higher plasma GFAP was associated with the degree and rate of neurodegeneration and cognitive impairment. Longitudinal analyses for rates of change of plasma GFAP in ADAD with respect to disease stage, pathology and cognition are ongoing.
Conclusions: The current cross-sectional findings support the role of plasma GFAP as a clinical biomarker of Aβ related astrocyte reactivity that is associated with cognitive decline and neurodegeneration. **References** 1. Benedet, A.L., *et al.* Differences Between Plasma and CSF GFAP Levels Across the AD Continuum. *JAMA Neurol* **78** (2021). 2. Chatterjee,

P.*, et al.* Diagnostic and prognostic plasma biomarkers for preclinical AD. *Alzheimers Dement* **18** (2022). 3. Chatterjee, P.*, et al.* Plasma Aβ42/40 ratio, p-tau181, GFAP, and NfL across the AD continuum: A cross-sectional and longitudinal study in the AIBL cohort. *Alzheimers Dement* (2022).

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OD325 / #837

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

IMMUNOSUPPRESSIVE PROPERTIES OF EMBRYONIC STEM CELL-DERIVED DOPAMINERGIC PROGENITOR CELLS FOR USE IN PARKINSON'S DISEASE CELL REPLACEMENT STEM-PD TRIAL

Annabel Curle, Shaline Fazal, Sarah Howlett, Sophie Skidmore, Shamma Qarin, Roger Barker, Joanne Jones
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Aims: Cell replacement therapy provides a growing hope for the treatment of Parkinson's Disease (PD). Embryonic stem cell (ES)-derived dopaminergic neuron progenitor cells (NPCs) have been shown to generate mature dopaminergic neurons (DAn) when grafted into rodent models - providing targeted, physiological dopamine replacement and improving motor function. This work has now matured into early clinical trials; however, it remains unclear whether grafts of this type will trigger a host immune response leading to rejection.
Methods: We have utilised *in vitro* (PBMC/T cell mixed lymphocyte reactions and moDC co-culture assays) and *in vivo* (humanised mouse) models.
Results: We have observed no significant immune response to RC17-ES derived NPCs *in vitro*, despite their low expression of MHC-class I (up-regulated in response to IFNγ). *In vivo*, only a scanty T-cell infiltrate was seen in the brain at months 1 and 3, following NPC and sham injection. Instead, NPCs appear immunosuppressive; reducing T-cell proliferation and CD25 expression *in vitro.* The mechanism(s) underlying this are under exploration. To date we have found it to be largely contact-dependent and not due to IDO/tryptophan metabolism or the production of immunoregulatory adenosine as is the case with other PSC-derived products. Transcriptomic analysis of NPCs through their differentiation from ESC to mature DAn, previously implanted foetal ventral midbrain (FVM) and other cell therapy products (+/- inflammatory stimuli), has revealed similarities and differences in the expression of immunoregulatory and immunogenic molecules across cell type, differentiation stage and baseline/inflammatory conditions. We are now exploring the roles of some of these immunoregulatory molecules on T-cell suppression.
Conclusions: RC17 ES-NPCs do not appear immunogenic, but immunosuppressive, *in vitro*, suggesting a low risk of transplant rejection in upcoming clinical trials, though further *in vivo* work is still required.

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OD326 / #1902

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

DEFINING MOLECULAR PATHWAYS THAT RESTRICT IN VIVO SURVIVAL OF HPSC-DERIVED MIDBRAIN DOPAMINE NEURONS

So Yeon Koo[1], Tae Wan Kim[2], Lorenz Studer[2], Doron Betel[3]
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Aims: Poor *in vivo* survival remains an unresolved issue of mDA neuron and other neuronal grafting paradigms. While hPSC-based strategies can compensate for poor survival by producing larger numbers of cells, there are concerns that batch to batch differences in cell survival (e.g. 5% vs 20%) could lead to dramatic difference in cell dosing. Furthermore, the initial cell death of most of the grafted cells may contribute to the chronic inflammatory response around the graft core. Therefore, after more than 4 decades of neural grafting, it is important to finally define, in an unbiased manner, the mechanisms involved in restricting graft survival.
Methods: We have employed *in vivo* CRISPR/Cas9 library pool screen, sc-mRNA sequencing, histology to unbiasedly interrogate intrinsic regulators restricting the survival of hPSC-derived post-mitotic dopaminergic neurons upon transplantation.
Results: Barcode sequencing identified a key role for the hit pathway in restricting postmitotic dopamine neuron survival following transplantation. We further mapped the kinetics of the hit pathway induction upon grafting and examined the subsequent recruitment of host neuroimmune cells to the dying neurons. Transcriptomic analysis of grafted dying neurons reveals an upregulation of several pathways that are upstream of the hit-dependent dopamine neuron death. To further exploit those insights towards translational use, we identified a set of two cell surface markers to reliably match post-mitotic dopamine neurons. To this end, we propose a clinically applicable therapeutic strategy to evade the induction of the hit-dependent post-mitotic dopamine neuron death by blocking an upstream trigger using FDA approved monoclonal antibodies.
Conclusions: Our work offers a better understanding of the mechanisms that drive postmitotic dopamine neuron death upon transplantation and establishes a clinically relevant strategy for future implementation in cell therapy approaches for PD.

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OD327 / #2413

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

A-BETA PEPTIDE AFFECTS THE MECHANICAL PROPERTIES OF HUMAN BRAIN NEURAL PROGENITOR CELLS

Miglena Angelova[1], Sophie Asnacios[1], Galya Staneva[2], Felix Vannier[3], Gabriel Thon[4], Nicolas Puff[1], Florent Carn[4], Benoit Sorre[5], Atef Asnacios[4]
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Aims: The brains of adult humans contain small populations of cells that are capable of dividing and differentiating into neurons and glial cells. Abnormalities in the proliferation, differentiation and/or survival of NPC may play a role in the memory impairment that occurs in neurodegenerative disorders such as Alzheimer's disease (AD). Nowadays NPC and neuron differentiation are well known to be affected by A-beta (Tincer, YaleJBiolMed, 2016). This work aims **quantifying** the global cell mechanical visco-elastic rigidity as well as the local molecular membrane order of **living** human brain neural progenitor cells (h-brainNPC) differentiated from human embryonic pluripotent stem cells (h-ESC) derived from blastocysts, and, the effects of A-beta oligomers on these properties in relation with the Alzheimer's disease.
Methods: -h-brainNPC were generated using 4-day protocol adapted form Gouti, PLoS Biol 2014 and Maury Nature Biotech,2015. -Measurements of visco-elastic mechanical properties of h-brainNPC using microplates-based rheometer able to measure the static (elastic) modulus as well as dynamical storage and loss moduli (Bufi, Methods Cell Biol 2015). -Quantitative imaging of membrane lipid order and dipole potential of h-brainNPCs based on the ratiometric imaging using the generalized polarization (GP) parameter of polarity-sensitive membrane dyes (Owen, Nat Protoc 2011).
Results: Our results indicate **a rigidification effect of A-beta on the mechanical properties of h-brainNPC**, correlating well with the **increase of cell membrane molecular order and dipolar potential changes**. The latter are known to be coupled with protein structures and physiology.
Conclusions: Possible pathways which may explain the observed global rigidification are: (i) lipid membrane rigidification related to the A-beta oligomers interaction with the cell membrane; (ii) increased osmotic pressure, as A-beta oligomers may form ion channels and thereby induce Ca^{2+} influx; (iii) actin polymerization due to enhanced Ca^{2+}.

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OD328 / #836

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

ANCESTRY-SPECIFIC STUDIES ON ALZHEIMER'S DISEASE USING IPSC-DERIVED MICROGLIA.

Sofia Moura[1], Aura Ramirez[1], Jihanne Shepperd[1], Maria Muniz[1], Shaina Simon[1], Wanying Xu[2], Patrice Whitehead[1], Larry Adams[1], Takiyah Starks[3], Pedro Mena[1], Maryenela Illanes-Manrique[4], Sergio Tejada[1], Goldie Byrd[3], Mario Cornejo-Olivas[4], Briseida Feliciano-Astacio[5], Liyong Wang[1], Fulai Jin[2], Anthony Griswold[1], Juan Young[1], Margaret Pericak-Vance[1], Jeffery Vance[1], Derek Dykxhoorn[1]
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Aims: Most Genome Wide Association studies (GWAS) in AD have been focused on Non-Hispanic Whites (NHW) individuals. However, more recent studies have begun to study admixed populations (e.g., African Americans and Hispanics). We have shown genomic architecture varies amongst different ancestries leading to differing genetic susceptibility in AD. Thus, we assessed whether iPSC-derived central nervous system (CNS) cell types recapitulate the regulatory architectures observed in the brain and serve as model systems to study the functional mechanisms associated with AD-GWAS loci in these admixed populations. Specifically, we characterized the regulatory maps in iPSC-derived microglia from individuals with high global African (AF), Amerindian (AI), or NHW ancestries.
Methods: iPSCs lines were derived from AD patients and controls with >90% genomic content from different ancestries – NHW, AF, and AI. iPSC lines were validated for pluripotency and chromosomal stability and were differentiated into microglia, termed iPSC-derived microglia (iMGLs). iMGLs were validated via immunocytochemistry (ICC) and qRT-PCR for the expression of cell type-specific markers. To study the regulatory architecture and the associated impact on gene expression, we performed ATAC-seq, Hi-C, and RNA-seq.
Results: We optimized the differentiation of iMGLs and validated it using ICC and qRT-PCR for lineage-specific markers. We analyzed and compared the regulatory maps of AF, AI, and NHW ancestries in both cases and controls by aligning chromatin accessibility data (ATAC-seq) with the promoter-enhancer interactions (Hi-C) and investigated the downstream effects the regulatory architecture might have on transcription (RNA-seq) specific for each ancestral background.
Conclusions: We report novel data on chromatin accessibility, promoter-enhancer interactions, and transcriptome in iMGLs with AF and AI ancestries. Since microglia is a key player in AD pathology, our data provide novel insights into ancestry-specific genetic risk factors in AD pathophysiology.

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OD329 / #1723

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

IPSC-DERIVED MONONUCLEAR PHAGOCYTES HAVE REGENERATIVE EFFECTS ON COGNITION AND NEURAL HEALTH IN MOUSE MODELS OF AGING AND ALZHEIMER'S DISEASE

V. Alexandra Moser, Shaughn Bell, Rachel Lipman, Luz Dimas-Harms, Clive Svendsen
Cedars Sinai Medical Center, Board Of Governors Regenerative Medicine Institute, Los Angeles, United States of America

Aims: Several studies have demonstrated that treatment with young blood or plasma has restorative effects on cognition and neural health in mouse models of aging and Alzheimer's disease (AD), and our lab has previously shown that bone marrow transplants from young to aged mice have similar benefits. These approaches have profound practical disadvantages, as they may result in graft vs. host disease, immune system rejection, or the transfer of communicable diseases from donor to recipient. Thus, the aim of the current work is to identify the cell type responsible for the beneficial effects of young blood and bone marrow, and to develop a cell-based therapy using human induced pluripotent stem cells (iPSC).
Methods: We generated iPSC-derived mononuclear phagocytes (iMPs) and administered them to aging, genetically immunocompromised NOD-scid-gamma (NSG) mice, as well as to the 5xFAD mouse model of AD.
Results: Treatment with iMPs significantly improved performance in tasks relying on spatial working memory and on hippocampus-dependent short-term memory in both aging and AD mice. Moreover, a number of neural health markers were improved by iMPs, including hippocampal expression of the synaptic transporter VGLUT1. iMPs also modulated neuroinflammation, as both astrocyte and microglia numbers were increased, while microglial branching was decreased, in aging and AD mice; changes that were reversed by iMP treatment. Single nucleus RNA sequencing of hippocampus and proteomic analysis of plasma revealed several genes and proteins that were significantly altered by iMP treatment, pointing to potential pathways that may be underlying the regenerative effects of iMPs.
Conclusions: These findings demonstrate the potential of using an autologous iPSC-based product as a new therapeutic strategy for aging and AD-associated declines in cognition and neural health.

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OD330 / #1238

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

L1 MOBILE DNA: DRIVER OR PASSENGER IN PARKINSON'S DISEASE PATHOGENESIS?

Gabriela Bodea, Eugenia Ferreiro, Juan Botto, Geoffrey Faulkner
The University of Queensland (UQ), Queensland Brain Institute, Brisbane, Australia

Aims: Long-Interspersed Element-1 (LINE-1 or L1) is a mobile genetic element that comprises over 17% of human DNA. To mobilize, L1 can copy itself from one genomic location into another via an RNA intermediate. L1 insertions can act on gene expression in various ways, such as providing a source of regulatory sequences. Neuronal genomes are a "hot spot" for L1 mobilization, and aberrant L1 activation has been reported in several neurological diseases, including Parkinson's disease (PD). L1 contribution to PD and L1 expression in dopaminergic (DA) neurons, which selectively degenerate in PD, are very poorly understood. Here, we aim to dissect the mechanisms of L1 involvement in PD pathophysiology by 1) assessing L1 expression in dopaminergic neuron subpopulations under normal and stress-induced conditions and 2) modulating L1 expression in a PD context.
Methods: To address these aims we are employing cutting-edge RNA *in situ* hybridization and long-read Oxford Nanopore RNA sequencing in PD animal models, as well as assays using human-induced pluripotent stem cells (iPSC)-derived neurons to modulate L1 via dCas9/CRISPR.
Results: We found that L1 mRNA is differentially expressed in different DA neuron subsets, with the highest expression level in substantia nigra (SN) neurons. In mice unilaterally injected with 6-hydroxydopamine (6-OHDA), L1 mRNA expression is further exacerbated in the ventral tier of the SN population on the neurotoxin-injected hemisphere. This area has been shown to correspond to the most vulnerable DA neuron population in PD.
Conclusions: L1 expression is highly specific to SN neurons and exacerbated upon toxic stress. Currently, we are modulating L1 activity by using dCas9/CRISPR to investigate whether L1 is a driver of neurodegeneration, relevant in PD pathogenesis.

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OD331 / #798

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

TO IMPROVE COGNITIVE FUNCTION IN ALZHEIMER'S DISEASE, BOTH ABNORMAL PROTEIN REMOVAL AND NEURONAL REPAIR, WHICH MESENCHYMAL STEM CELLS HAVE, WOULD BE NECESSARY.

Kazuo Shigematsu[1], Naoyuki Komori[2], Mitsuko Ideno[3], Hisakazu Yamagishi[4]
[1]Minami Kyoto Hospital, National Hospital Organization, Neurology, Joyo, Japan, [2]Nagitsuji Hospital, Ceo, Kyoto, Japan, [3]Takara Bio Inc, Gene And Cell Processing Center, Kusatsu, Japan, [4]Kyoto Prefectural University of Medicine, Surgery, Kyoto, Japan

Aims: Mesenchymal stem cell administration may improve cognitive function. In Alzheimer's disease, β-amyloid has been hypothesized to deposit in the brain and damage nerve cells, resulting in cognitive dysfunction. The administration of antibodies against β-amyloid to eliminate β-amyloid deposition in the brain has been successful, but unfortunately, the corresponding improvement in cognitive function does not appear to be sufficient. We hypothesized that removal of β-amyloid alone would not be sufficient for the damaged neurons to recover, since β-amyloid-induced neuronal damage is expected to be decades lasting.
Methods: Mesenchymal stem cells (MSCs), especially adipose tissue-derived stem cells (ADSCs), are rich in several growth factors. Cognitive improvement after administration of ADSCs was examined by cognitive assessment tests, neurological examinations, and caregiver evaluation. We investigated the presence of neprilysin activity, a β-amyloid-degrading enzyme, in the administered ADSCs. Brain β-amyloid was assessed by imaging studies as well as biomarkers combined with metabolites in blood.
Results: Neprilysin activity was confirmed in all ADSCs administered. Imaging showed a decrease of about 30%, and blood biomarkers indicated a decrease in brain β-amyloid in all cases examined. The improvement in cognitive function was more pronounced than the change, suggesting that, in addition to β-amyloid removal, the neurorestorative, anti-inflammatory, and blood flow improving effects of ADSCs may be responsible for the effect. The possibility of phosphorylated tau removal in addition to β-amyloid was also investigated.
Conclusions: We propose a two-sided treatment for Alzheimer's disease; more specifically, the removal of the causative agents, abnormal proteins, and the repair and regeneration of nerve cells damaged by the abnormal proteins. Intravenous administration of ADSCs has both of these effects and would be a less invasive, safe, and feasible treatment for Alzheimer's disease.

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OD332 / #1090

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

DIFFERENTIAL ROLES FOR GSK3 AND ERK KINASES IN MUTANT HTT-MEDIATED DYSFUNCTION IN HD PATIENT-DERIVED NEURONS.

Shermali Gunawardena, Thomas Krzystek, Rasika Rathnayeke, Jia Zeng, Michael Yu
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Aims: Huntington's disease (HD) is a devastating neurodegenerative disorder that manifests from an N-terminal polyQ-expansion (>35) in the Huntingtin (*HTT*) gene leading to axonal degeneration and significant neuronal loss. Despite evidence for a scaffolding role for HTT in membrane-related processes such as endocytosis, vesicle transport, and vesicle fusion, it remains unclear how mutant HTT alters membrane associations.
Methods: By combining high-throughput proteomics in normal and HD patient iPSC-derived neurons with *Drosophila* genetics and pharmacological inhibition, we found intriguing changes to the kinome of pathogenic HTT-containing membranes in HD neurons.
Results: More specifically we found that GSK3 and ERK kinases have opposing effects on mutant HTT-mediated phenotypes. Inhibition of GSK3 decreased mutant HTT-mediated axonal transport defects, synaptic dysfunction and neuronal cell death while inhibition of ERK enhanced these defects. Intriguingly while GSK3 can phosphorylate HTT with mutant HTT enhancing GSK3β-mediated HTT phosphorylation, both GSK3 and ERK are predicted to phosphorylate HTT at the same Ser2657 site. Further, ERK-mediated effects on axonal transport are likely specific to HTT while GSK3 can also influence the function of molecular motors.
Conclusions: Together, this work identifies a novel mechanism in which GSK3 and ERK phosphorylation events play differential roles in mutant HTT-mediated neuronal dysfunction in HD.

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OD333 / #481

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

ASTROCYTIC UPTAKE OF NEURONAL CORPSES PROMOTES SPREADING OF TAU PATHOLOGY IN A HUMAN IPSC-BASED MODEL OF ALZHEIMER'S DISEASE

Tobias Mothes[1], Benjamin Portal[2], Evangelos Konstantinidis[1], Linn Streubel-Gallasch[1], Martin Ingelsson[1], Jinar Rostami[1], Maria Lindskog[2], Anna Erlandsson[1]
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Aims: Astrocytic inclusions of tau are frequently found in the Alzheimer disease brain. However, the mechanism behind the appearance of these tau deposits and their relevance for disease progression remain unknown. We have previously shown that astrocytes effectively engulf both aggregated proteins and dead cells. Here, we aimed to investigate astrocytes' ability to promote cell-to-cell spreading of toxic tau aggregates following ingestion of dead neurons.
Methods: To induce robust tau pathology, human iPSC-derived neurons were exposed to synthetic tau aggregates. Following UV exposure, the apoptotic neurons were co-cultured with human iPSC-derived astrocytes to allow phagocytosis. The now corpse-containing astrocytes were then moved to healthy neurons. In additional experiments, astrocytes were instead exposed to tau aggregates directly. Cell-to-cell spreading of tau pathology was analyzed using a FRET-based tau seeding assay, immunocytochemistry, live cell imaging and western blot analysis. How phagocytic astrocytes influence the synaptic function was studied with electrophysiology.
Results: Our western blot and immunocytochemistry data indicate that tau oligomers are more toxic than fibrils, but that tau fibrils possess greater seeding capacity. For that reason, we decided to use fibrils to induce tau pathology in neurons. Indeed, the astrocytes ingested and accumulated whole dead cells, as well as neuronal debris. Moreover, astrocytes exposed to sonicated tau fibrils were shown to pack and process the ingested tau, but not fully degrade it. Instead, astrocytes extensively transferred tau inclusions to nearby cells in a co-culture set-up and induced distinct tau pathology in healthy neurons-
Conclusions: Taken together, our data suggests that astrocytes, because of their ineffective degradation of ingested neuronal corpses and tau aggregates, serve as an intermediator promoting cell-to-cell spreading of pathological tau.

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OD333a / #1367

ON-DEMAND SYMPOSIUM: IPSC, STEM CELLS, CELL REPLACEMENT THERAPY
01-04-2023 07:00 - 08:30

MESENCHYMAL STEM CELL-DERIVED EXTRACELLULAR VESICLES AS PROPOSED THERAPY IN A RAT MODEL OF CEREBRAL SMALL VESSEL DISEASE

Reut Guy, Daniel Offen
Tel Aviv University, Human Molecular Genetics And Biochemistry, Petha Tikva, Israel

Aims: Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) have been employed in the last decade as therapeutic agents in various diseases, including central nervous system (CNS) disorders. We currently aimed to use MSC-EVs as potential treatment for cerebral small vessel disease (CSVD), a complex disorder with a variety of manifestations.
Methods: MSC-EVs were intranasally administrated to salt-sensitive hypertension prone SBH/y rats that were DOCA-salt loaded (SBH/y-DS), which we have previously shown is a model of CSVD.
Results: MSC-EVs accumulated within brain lesion sites of SBH/y-DS. An in vitro model of an inflammatory environment in the brain demonstrated anti-inflammatory properties of MSC-EVs. Following in vivo MSC-EV treatment, gene set enrichment analysis (GSEA) of SBH/y-DS cortices revealed downregulation of immune system response-related gene sets. In addition, MSC-EVs downregulated gene sets related to apoptosis, wound healing and coagulation, and upregulated gene sets associated with synaptic signaling and cognition. While no specific gene was markedly altered upon treatment, the synergistic effect of all gene alternations was sufficient to increase animal survival and improve the neurological state of affected SBH/y-DS rats.
Conclusions: Our data suggest MSC-EVs act as microenvironment modulators, through various molecular pathways. We conclude that MSC-EVs may serve as beneficial therapeutic measure for multifactorial disorders, such as CSVD.

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OD334 / #2446

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

PARTIAL VOLUME CORRECTION TECHNIQUES FOR LONGITUDINAL TAU-PET QUANTIFICATION. A COMPARISON STUDY

Alejandro Costoya-Sánchez[1], Alexis Moscoso[2], Pablo Aguiar[1], Jesús Silva-Rodríguez[3]
[1]University of Santiago de Compostela, Cimus, Santiago de Compostela, Spain, [2]University of Gothenburg, Wallenberg Centre For Molecular And Translational Medicine, Gothenburg, Sweden, [3]Institute of Biomedicine of Seville, Movement Disorders Unit, Seville, Spain

Aims: The selection of an appropriate Partial Volume Correction (PVC) is crucial for evaluating the accumulation rates of tau using ^{18}F-Flortaucipir (^{18}F-FTP). PVC can reduce the impact of off-target binding, but it is also well-known to increase noise and variability. While these effects may be averaged on cross-sectional studies, they might be of paramount importance when evaluating within-subject longitudinal tau-PET signals. The aim of this study is to investigate the robustness of different PVCs for their application on longitudinal ^{18}F-FTP studies.
Methods: 344 subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Harvard Aging Brain Study (HABS) with serial 18F-FTP PET and T1 images available were included in the study. ^{18}F-FTP PET images were corrected by applying a traditional deconvolution PVC (Grey matter only), the reblurred Van-Cittert (RVC) analytical PVC (grey + white matter), and 2 voxel-based PVCs, the region-based voxel-wise correction (RBV) and the iterative Yang (iY). Longitudinal rates of change for the regional standard uptake value ratios (SUVR) of different Braak Areas were computed for the images corrected for the different PVCs.
Results: Both RBV and iY corrections showed consistent elevated rates of change across all Braak Areas (z-score variations ≈ 0.4 z-score points/year). The iY was slightly superior to the RBV in statistical power, (i.e., when comparing rates between amyloid-positive and negative subjects). In contrast, the results of the deconvolutional PVC and the RVC where comparable to not applying any PVC method.
Conclusions: Our findings suggest that longitudinal FTP studies might benefit from the use of voxel-based PVC techniques. These methods have been shown to maximize the rates of change of FTP SUVR signal. We attribute these improvements to the inclusion of more sophisticated patient-derived atlases in these PVCs.

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OD335 / #2359

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

VALIDATION OF [18F]FLORBETABEN PET QUANTITATION BASED ON THE ANALYSIS OF 15 SOFTWARE PIPELINES

Aleksandar Jovalekic[1], Nuria Roe-Vellve[1], Norman Koglin[1], Mariana Lagos Quintana[1], Aaron Nelson[2], Markus Diemling[3], Johan Lilja[3], Juan Pablo Gomez Gonzalez[4], Vincent Dore[5], Pierrick Bourgeat[5], Alex Whittington[6], Roger Gunn[6], Andrew Stephens[1], Santiago Bullich[1]
[1]Life Molecular Imaging, Clinical R&d, Berlin, Germany, [2]MIM Software, R&d, Cleveland, United States of America, [3]Hermes Medical Solutions, R&d, Stockholm, Sweden, [4]QuBiotech, R&d, A Coruna, Spain, [5]CSIRO, R&d, Brisbane, Australia, [6]Invicro, R&d, London, United Kingdom

Aims: Amyloid positron emission tomography (PET) with [18F]florbetaben is an established tool for detecting Aβ deposition in the brain *in vivo* based on visual assessment of PET scans. Quantitative measures are, however, commonly used in the research context and allow continuous measurement of amyloid burden. The aim of this study was to demonstrate the robustness and added value of florbetaben PET quantification, focusing on Centiloid-based analysis.
Methods: This is a retrospective analysis of florbetaben PET images, consisting of 589 subjects. Florbetaben PET scans were quantified with 15 analytical pipelines using nine software packages (MIMneuro, Hermes BRASS, Neurocloud, Neurology Toolkit, statistical parametric mapping (SPM8), PMOD Neuro, CapAIBL, non-negative matrix factorization (NMF), Amyloid^{IQ}) that used several metrics to estimate Aβ load (SUVR, Centiloid, amyloid load and amyloid index). Six analytical pipelines reported Centiloid (MIMneuro, standard Centiloid pipeline, Neurology Toolkit, SPM8 (PET-only), CapAIBL, NMF). All results were quality controlled.
Results: The mean sensitivity, specificity and accuracy was 96.1±1.6%, 96.9±1.0% and 96.4±1.1%, respectively, for all quantitative methods tested and 96.1±1.6%, 97.4±1.2% and 96.7±1.2% for Centiloid-based approaches. The mean percentage of agreement between binary quantitative assessment across all 15 pipelines and visual majority assessment was 92.4±1.5% and 93.2±0.4% for the Centiloid-based sub-analysis.
Conclusions: Software quantification methods, such as Centiloid analysis, can complement visual assessment of florbetaben PET images. Based on this study, quantification of [18F]florbetaben PET as an adjunct to visual assessment was recently approved by the European Medicines Agency (EMA) in the EU for Neuraceq®.

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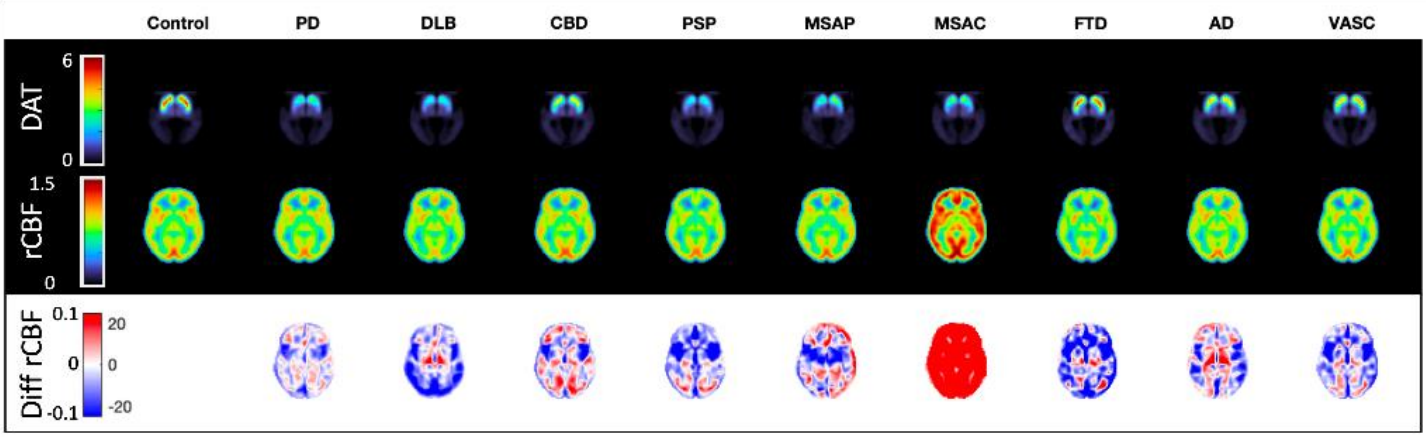
OD336 / #743

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

DIFFERENTIAL DIAGNOSIS OF PARKINSONISM USING PE2I-PET AND MACHINE LEARNING

Mark Lubberink[1], My Jonasson[1], Charles Widström[2], Elin Lindström[1], Lieuwe Appel[1], Joel Kullberg[3], Jens Sörensen[1], Dag Nyholm[4], Torsten Danfors[1]
[1]Uppsala University, Surgical Sciences / Nuclear Medicine & Pet, Uppsala, Sweden, [2]Uppsala University Hospital, Department Of Medical Physics, Uppsala, Sweden, [3]Uppsala University, Surgical Sciences/ Radiology, Uppsala, Sweden, [4]Uppsala University, Neurology, Uppsala, Sweden

Aims: We have developed methodology for differential diagnosis of parkinsonism using ^{11}C-PE2I-PET giving images of relative cerebral blood flow (rCBF) and dopamine transporter (DAT) availability based on a single 40-min scan. Image analysis is done using an automated pipeline which includes comparison to a normal database. The aim of this work was to develop and evaluate supervised machine learning (ML) to the support differential diagnosis with ^{11}C-PE2I.
Methods: Between 2015 and 2021, approximately 1100 patients referred for PET-based differential diagnosis of parkinsonism underwent ^{11}C-PE2I-PET/CT scans. DAT and rCBF images were read by an experienced nuclear medicine physician providing a diagnosis based on images and referral information. Images of patients with unambiguous diagnosis were used to compute disease-specific DAT and rCBF patterns. The contribution of each pattern to individual patients' images was estimated using regression and regression parameters were used to train a classification tree algorithm. Data was split evenly for ML training and testing.
Results: Approximately 60% of evaluable patients received an unambiguous diagnosis, of whom 34% normal scan, 31% PD, 16% DLB, 5% PSP, 4% CBD, 4% vascular parkinsonism, 2% MSA-P, 2% Alzheimer's and 1% MSA-C or frontotemporal dementia. ML-based classification accuracy varied from 96% for PD vs normal to 76% when including PD, DLB, and PSP subjects. Accuracy was always higher when including both DAT and rCBF images than for either image separately. For the other diseases, too few scans were available for ML training.



Disease-specific DAT and rCBF images, as well as difference rCBF images compared to controls.

Conclusions: ML-based differential diagnosis of parkinsonism with ^{11}C-PE2I-PET shows promising results considering the inherent inaccuracy of the ground truth diagnosis. More data is needed to train ML for the rarer diagnoses.

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OD337 / #1262

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

CONCORDANCE OF SINGLE-SUBJECT QUALITATIVE AND QUANTITATIVE EVALUATION OF [18F]MK-6240 TAU PET SCANS

Gloria Chiang[1], Yi Li[2], Xiuyuan Wang[2], Emily Tanzi[1], Silky Pahlajani[1], Tracy Butler[3], Lidia Glodzik[3], Ray Razlighi[3], Mony De Leon[3]
[1]Weill Cornell Medicine, Department Of Radiology, NY, United States of America, [2]Weill Cornell Medicine, Department Of Radiology, New York, United States of America, [3]Brain Health Imaging Institute, Radiology, New York, United States of America

Aims: [18F]MK-6240 is a second-generation tau PET tracer that detects neurofibrillary tangles in-vivo. However, early tau deposition in Braak I-II regions remains difficult to quantify given "spill-in" artifacts from adjacent bone and meningeal off-target binding. We assessed the reliability of qualitative, visual ratings of [18F]MK-6240 PET, their concordance with quantitative standardized uptake value ratio (SUVR) measurements, and whether discordance was related to bone and meningeal artifacts.
Methods: Fifty-eight subjects who underwent [18F]MK-6240 PET scans were included (mean age 69 +/-7.3 years, 60% female, 36% amyloid PET positive, 34% APOE4 carriers, 19% APOE2 carriers). SUVR images were created using the cerebellar cortex as the reference region, fused to structural MRI, then viewed with a 0-3 SUVR color scale. Images were read by two raters with >10 years of expertise in brain PET imaging. Regional SUVR in the entorhinal cortex (ERC) and parahippocampal gyrus (PHG), as well as in the frontal, parietal, temporal, and occipital lobes, was obtained using Freesurfer segmentation. Bone and meningeal signal were considered significant if SUVR>2.
Results: Qualitative reads were 97% concordant (Rater1: 17/58 positive, Rater2: 19/58 positive). Using an SUVR cutoff of 1.35 (Leuzy 2021), the qualitative reads were 86% (50/58) concordant with quantitative assessment. Seven discordant reads involved the ERC/PHG regions, and one involved the occipital lobe. Significant bone and meningeal signal was seen in 37 (64%) and 12 (21%) of subjects, respectively. APOE4 carriers had lower likelihood of having significant occipital (OR=0.22, p=0.048) or skull base bone signal (OR=0.21, p=0.04).
Conclusions: Qualitative assessment of [18F]MK-6240 PET by experienced readers is highly reliable and concordant with quantitative measures. Discordant reads commonly involve early Braak regions, likely related to bone and meningeal signal.

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OD338 / #262

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

89ZR-IMMUNO-PET FOR EVALUATION OF BISPECIFIC ANTI-ALPHA-SYNUCLEIN MONOCLONAL ANTIBODIES

Thomas Wuensche[1], Pedro Pereira[1], Albert Windhorst[1,2], Allan Jensen[3], Pekka Kallunki[3], Benny Bang-Andersen[3], Wissam Beaino[1,2], Guus A.M.S. Dongen[1,2], Danielle Vugts[1,2]
[1]Amsterdam UMC, Radiology And Nuclear Medicine, Amsterdam, Netherlands, [2]Amsterdam Neuroscience, Brain Imaging, Amsterdam, Netherlands, [3]Lundbeck A/S, Chemical Biology & Molecular Imaging Research, København, Denmark

Aims: The possible non-invasive detection of alpha-synuclein with immuno-PET could provide a powerful tool for early diagnosis and monitoring of disease progression of alpha-synucleinopathies and might reveal opportunities for therapeutic interventions. Thus, the combination of monoclonal antibodies' high affinity and specificity with the non-invasive imaging technique of ^{89}Zr-immuno-PET was investigated.
Methods: Anti-alpha-synuclein monoclonal antibody GM285 was engineered with one or two 8D3 moieties targeting the transferrin receptor (GM285-scFab8D3 and GM285-$(scFv8D3)_2$), enabling enhanced uptake across the BBB. Antibodies were conjugated with DFO*-NCS and subsequently radiolabeled with ^{89}Zr. The radioconjugates were evaluated *in vivo* and *ex vivo* in an alpha-synuclein deposition model by intracranial injection of unsonicated protofibrils (10 µg/2 µL) into the left striatum of C57Bl6 mice (n=5/group). Saline was injected into the right striatum as a control.
Results: Day 7 p.i. *ex vivo* autoradiography and immunofluorescence showed target engagement of both radioconjugates with the alpha-synuclein fibril deposition in the striatum. Quantification of the *ex vivo* autoradiography displayed a higher protofibril uptake for [^{89}Zr]Zr-GM285-scFab8D3. PET imaging day 7 p.i. showed uptake at the alpha-synuclein deposits in some mice. However, deposition visualization was hampered for most animals, possibly due to a combination of partial volume effects and sensitivity issues related to the limited size of the deposit target.
Conclusions: Successful target engagement by two ^{89}Zr-labeled anti-alpha-synuclein bivalent brain shuttles was shown in a murine alpha-synuclein deposition model. PET imaging showed variable results, in some cases, enabling *in vivo* detection of the protofibril depositions. Future investigations will focus on animal models with more extensive alpha-synuclein pathology.

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OD339 / #634

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

ASSOCIATION OF IN VIVO RETENTION OF [18F]FLORTAUCIPIR PET WITH THE DENSITY OF TAU NEUROPATHOLOGY IN CORRESPONDING BRAIN REGIONS

Daria Pawlik[1,2], Kevin Oliveira Hauer[1,3], Olof Strandberg[1], Antoine Leuzy[1], Cécilia Tremblay[4], Geidy Serrano[4], Michael Pontecorvo[5], Thomas Beach[4], Ruben Smith[1,2], Oskar Hansson[1,3]
[1]Lund University, Department Of Clinical Sciences, Clinical Memory Research Unit, Malmö, Sweden, [2]Skåne University Hospital, Lund, Department Of Neurology, Lund, Sweden, [3]Skånes Skåne University Hospital, Memory Clinic, Malmö, Sweden, [4]Banner Sun Health Research Institute, Civin Laboratory For Neuropathology, Sun City, United States of America, [5]Eli Lilly and Company, Neuroscience, Indianapolis, United States of America

Aims: To study the correlation of in vivo [^{18}F]flortaucipir PET uptake with *post mortem* tau pathology in corresponding brain regions.
Methods: 67 terminally ill participants older than 50 years with a projected life expectancy of less than six months were included. All the participants were examined with [^{18}F]flortaucipir PET within nine months prior to death and samples were obtained from 24 different brain regions at autopsy. Brain sections were stained using AT8 to detect tau pathology. The resulting 1608 neuropathology slides were scanned at 80x resolution using an automated Hamamatsu digital scanner and three 5x images of each of the different regions of interest (ROIs) were captured to assess the mean density of tau pathology. This approach allows us to estimate the tau load in a quantitative way compared to visual reads used in previous studies. Corresponding PET ROIs in the 67 PET scans were manually adjusted to correspond to sites of neuropathology sampling. Correlations between [^{18}F]flortaucipir standardized uptake value ratios (SUVR) and AT8 immunohistochemistry will be assessed across all sampled ROIs. In a subset of individuals (n=23) TDP-43 pathology was quantified in the temporal lobes.
Results: Data is being processed and we hypothesize that *in vivo* [^{18}F]flortaucipir SUVR and tau pathology density will be positively correlated. We will also investigate the relation between TDP-43 pathology and off-target binding.
Conclusions: Whether [^{18}F]flortaucipir PET reflects the amount of tau pathology in the brain needs to be confirmed, for future use of the radiotracer to track disease progression and treatment effects.

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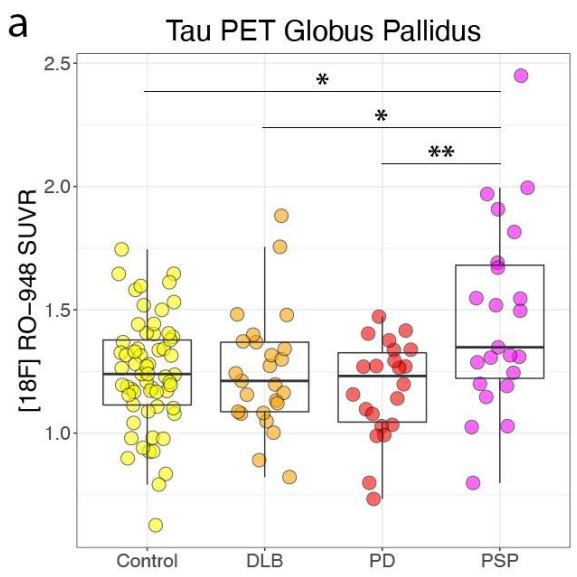
OD340 / #1002

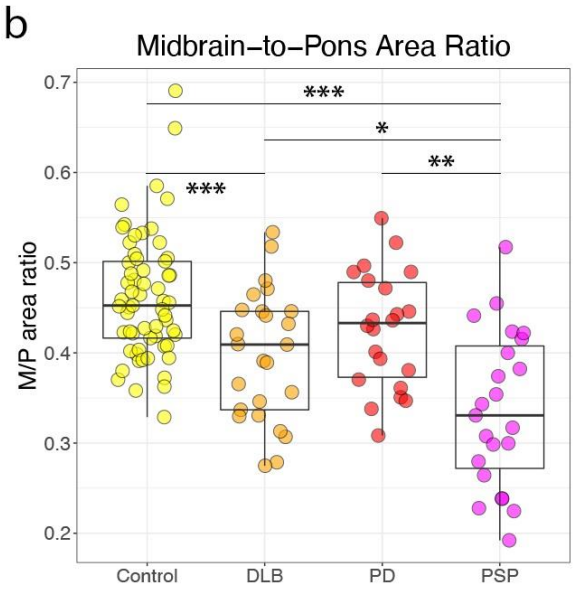
ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

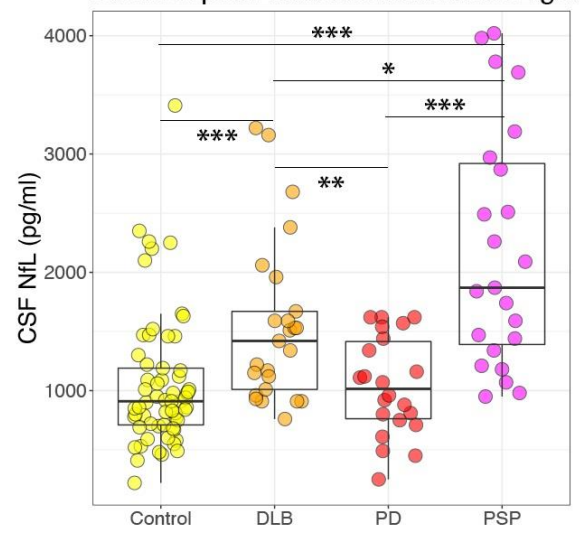
PERFORMANCE OF [18F]RO948 TAU PET, MRI AND CSF NEUROFILAMENT LIGHT IN THE DIFFERENTIAL DIAGNOSIS OF PROGRESSIVE SUPRANUCLEAR PALSY

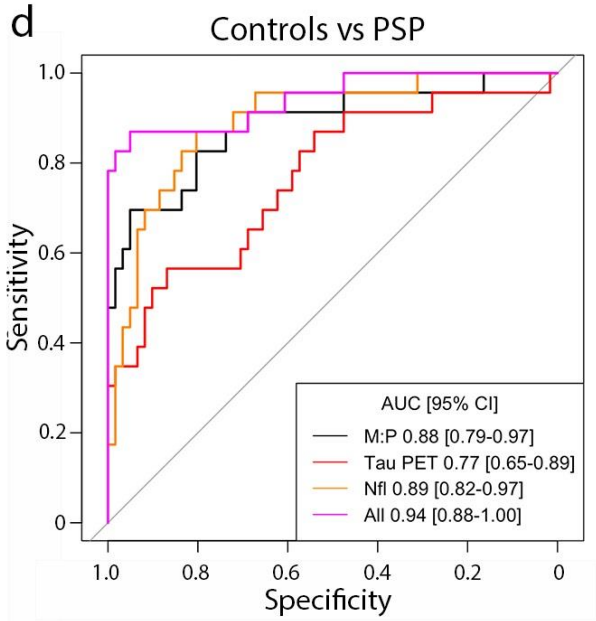
Kevin Oliveira Hauer[1,2], Daria Pawlik[1,3], Antoine Leuzy[1], Shorena Janelidze[1], Sara Hall[1,2], Oskar Hansson[1,2], Ruben Smith[1,3]
[1]Lund University, Department Of Clinical Sciences, Clinical Memory Research Unit, Malmö, Sweden, [2]Skånes Skåne University Hospital, Memory Clinic, Malmö, Sweden, [3]Skåne University Hospital, Lund, Department Of Neurology, Lund, Sweden

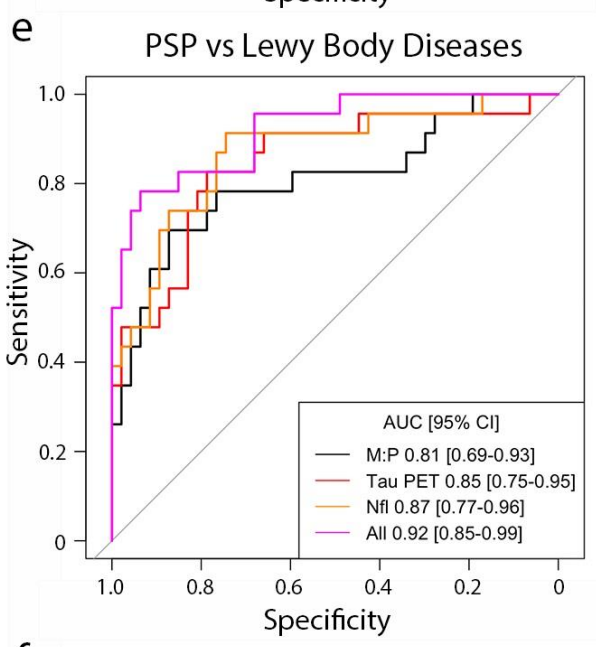
Aims: Differentiating progressive supranuclear palsy (PSP) from other neurodegenerative disorders is often challenging in clinical practice. This study aims to determine the capacity of magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) neurofilament light (NfL), and [^{18}F]RO948 positron emission tomography (PET), to separate PSP patients from healthy controls and from patients with Lewy body disease (LBD).
Methods: Patients with PSP (n=24), PD (n=22), DLB (n=25) and healthy controls (n=61) were selected from the BioFINDER-2 study. [^{18}F]RO948 standardized uptake value ratios (SUVR), MRI midbrain/pons ratio, and NfL levels were compared individually and in combination between the diagnostic groups.
Results: [^{18}F]RO948 PET SUVR in the globus pallidus, NfL and midbrain/pons area ratios were all able to separate PSP patients from controls and LBD patients ([^{18}F]RO948 [mean±SD]: controls 1.24±0.22; PSP 1.46±0.4; PD 1.2±0.2; DLB 1.25±0.24, $p<0.05$; NfL pg/mL [mean±SD]: controls 1055±569; PSP 2166±999; PD 1055±438; DLB 1548±687, $p<0.001$; and midbrain/pons ratio [mean±SD]: controls 0.46±0.07; PSP 0.34±0.09; PD 0.42±0.06; DLB 0.40±0.07, $p<0.01$; Figure 1 a-c). Receiver operating characteristic (ROC) analyses showed that combining the three biomarkers generated the highest area under the ROC values for distinguishing PSP from controls (0.94 [0.88-1.00]; Figure 1d) and LBD (0.92 [0.85-0.98]; Figure

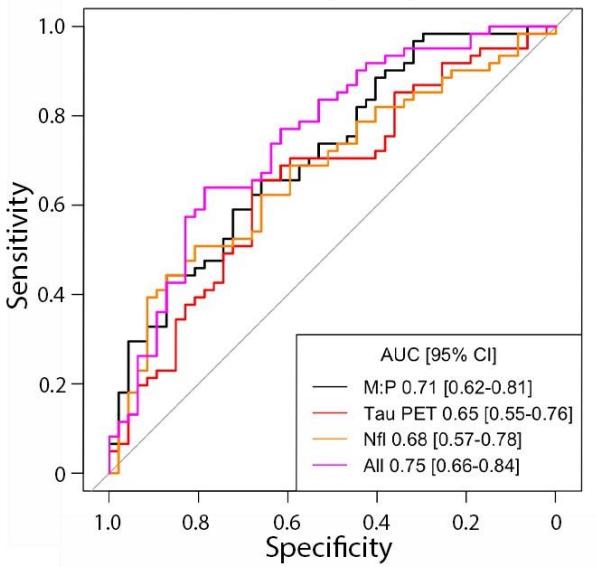

a
Tau PET Globus Pallidus
[18F] RO−948 SUVR
2.5
2.0
1.5
1.0
*
*
**
Control
DLB
PD
PSP


b
Midbrain−to−Pons Area Ratio
M/P area ratio
0.7
0.6
0.5
0.4
0.3
0.2
***
*
**
***
Control
DLB
PD
PSP


c
Cerebrospinal fluid Neurofilament Light
CSF NfL (pg/ml)
4000
3000
2000
1000
***
*
***
***
**
Control
DLB
PD
PSP


d
Controls vs PSP
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0
AUC [95% CI]
M:P 0.88 [0.79-0.97]
Tau PET 0.77 [0.65-0.89]
Nfl 0.89 [0.82-0.97]
All 0.94 [0.88-1.00]


e
PSP vs Lewy Body Diseases
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0
AUC [95% CI]
M:P 0.81 [0.69-0.93]
Tau PET 0.85 [0.75-0.95]
Nfl 0.87 [0.77-0.96]
All 0.92 [0.85-0.99]


f
Controls vs Lewy Body Diseases
Sensitivity
Specificity
1.0
0.8
0.6
0.4
0.2
0
AUC [95% CI]
M:P 0.71 [0.62-0.81]
Tau PET 0.65 [0.55-0.76]
Nfl 0.68 [0.57-0.78]
All 0.75 [0.66-0.84]

Conclusions: All biomarkers were able to individually separate PSP from controls and LBD patients at a group level. The optimal model for separating PSP from controls included NfL and midbrain/pons ratio and all three biomarkers for separating PSP from LBD.

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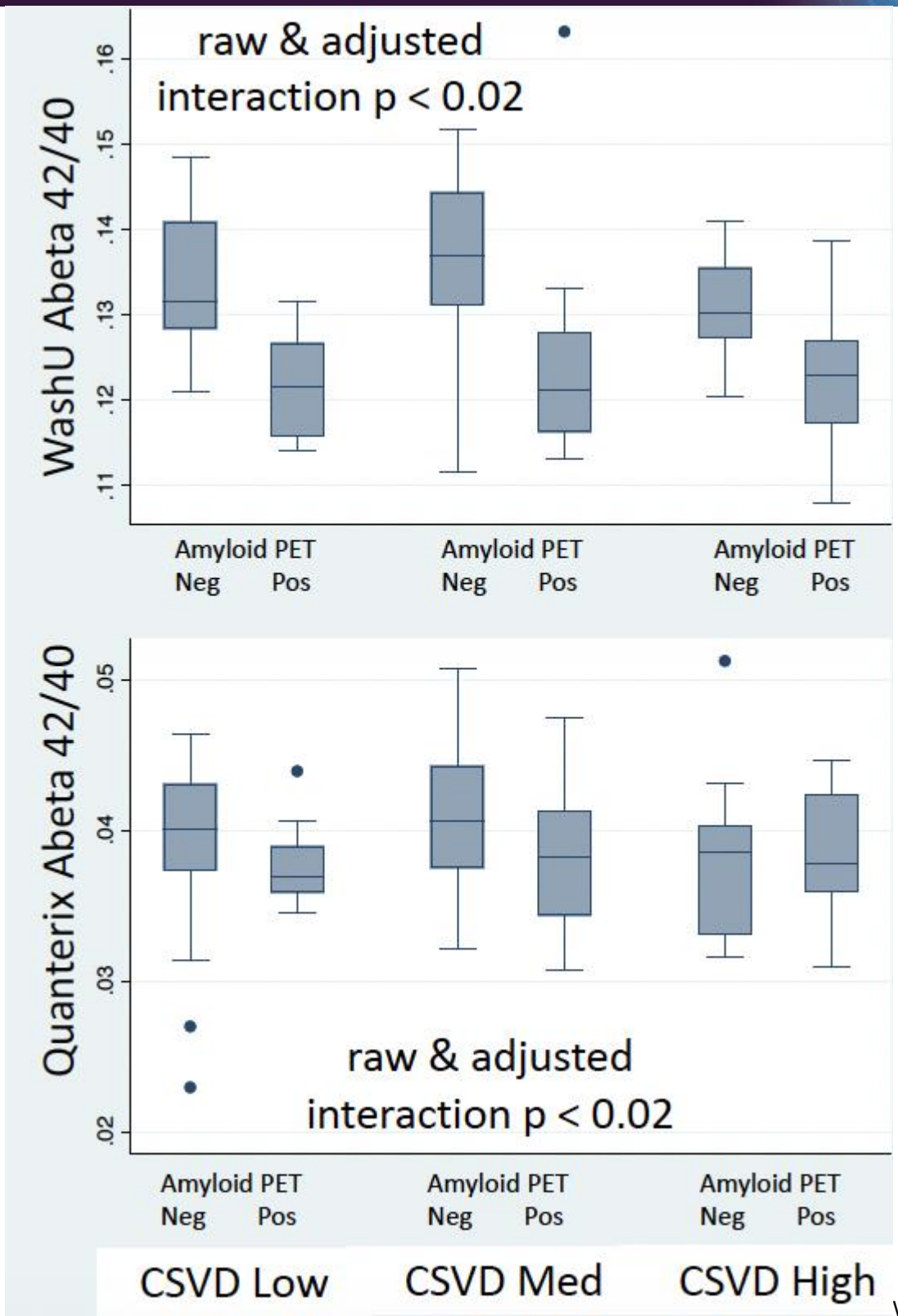
OD341 / #1795

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

BURDEN OF CEREBRAL SMALL VESSEL DISEASE MODIFIES RELATIONSHIP BETWEEN PLASMA ABETA 42/40 AND AMYLOID PET

Orit Lesman-Segev[1], Renaud La-Joie[2], Kristine Yaffe[3], Michael Weiner[4], Lisa Silbert[5], Leslie Shaw[6], Raquel Gardner[1]
[1]Sheba Medical Center, Joseph Sagol Neuroscience Center, Ramat Gan, Israel, [2]Univeristy of California San Francisco, Memory And Aging Center, San Francisco, United States of America, [3]UCSF, Psychiatry, San Francisco, United States of America, [4]University of California San Francisco (UCSF), Medicine, Radiology, Psychiatry, And Neurology, San Francisco, United States of America, [5]Oregon Health Sciences University, Neurology, Portland, United States of America, [6]University of Pennsylvania, Pathology, Philadelphia, United States of America



Aims: We aimed to determine if burden of cerebral small vessel disease (CSVD) modifies the relationship of plasma amyloid-beta (Abeta) 42/40 ratio and amyloid PET.

Methods: We studied N=94 participants from the Alzheimer's Disease Neuroimaging Initiative with Abeta-42/40 biomarker levels using Quanterix SIMOA (Quanterix) and Washington University Mass Spectroscopy (WashU), brain MRI, and amyloid PET data. We stratified by CSVD defined as total white matter T2 hyperintensity volume divided into tertile.

Amyloid positivity was defined as standardized uptake value ratio ≥ 1.11 for florbetapir PET scans. We used box plots to visualize plasma Abeta-42/40 level stratified by Amyloid PET positivity and CSVD tertile. Using logistic regression models, we tested for an interaction between CSVD and plasma Abeta-42/40 ratio on amyloid PET positivity in models adjusted for age, education, sex, race, ethnicity, Clinical Dementia Rating (CDR), and presence of ≥1 apolipoprotein E4 allele.

Results: The cohort had an average age of 77 years, was 62% female, 96% white, and 50% cognitively normal (32% mild cognitive impairment; 18% mild dementia). The **Figure** revealed that the Quanterix assay demonstrated near total overlap between amyloid PET positive vs. negative groups at the highest tertile of CSVD due to depressed Abeta42/40 in amyloid PET negatives. The WashU assay demonstrated slightly reduced discrimination between Amyloid PET positive vs. negative groups with increasing CSVD burden. We identified significant interactions between CSVD and plasma Abeta-42/40 ratio on amyloid PET positivity for both assays (adjusted models $p<0.02$).

Conclusions: These findings suggest that CSVD may result in false positives. Further research in larger more diverse cohorts with a high burden of CSVD is warranted to inform appropriate use of these blood assays and avoid false positives in this population.

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OD342 / #563

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

NOVEL SOFTWARE FOR AUTOMATED ANALYSIS OF 11C-PE2I POSITRON EMISSION TOMOGRAPHY IN PARKINSONISM PATIENTS

My Jonasson[1], Charles Widström[2], Elin Lindström[1], Paul De Roos[3], Martin Ingelsson[4,5,6], Lieuwe Appel[1], Jarmo Hietala[7], Jussi Hirvonen[8], Dag Nyholm[3], Torsten Danfors[1], Mark Lubberink[1]
[1]Uppsala University, Surgical Sciences / Nuclear Medicine & Pet, Uppsala, Sweden, [2]Uppsala University Hospital, Department Of Medical Physics, Uppsala, Sweden, [3]Uppsala University, Medical Sciences, Neurology, Uppsala, Sweden, [4]Uppsala University, Department Of Public Health / Geriatrics, Uppsala, Sweden, [5]University Health Network, Krembil Brain Institute, Toronto, Canada, [6]University of Toronto, Department Of Medicine And Tanz Centre For Research In Neurodegenerative Diseases, Toronto, Canada, [7]University of Turku, Department Of Psychiatry, Turku, Finland, [8]University of Turku, Radiology, Turku, Finland

Aims: [11]C-PE2I is a PET ligand with high affinity and selectivity for the dopamine transporter (DAT). Using tracer kinetic analysis of dynamic [11]C-PE2I PET-scans, both DAT availability and relative cerebral blood flow (rCBF) can be measured at the voxel level. An automated software was developed for data analysis and comparison to a normal database. The purpose of the software is to aid in differential diagnosis of parkinsonism, based on information regarding both DAT availability and rCBF, using a single PET-scan approach. The aim of this work is to describe the workflow and validate the software.
Methods: Dynamic PET images are motion corrected and PET volumes are transformed to MNI-space, normalized to a volume of interest (VOI) template which is transformed back to patient space. Images showing DAT availability and rCBF are generated. Average regional voxel values are extracted and compared to a normal database to calculate z-scores. In addition, surface projection maps of rCBF z-scores are computed. Twenty subjects (10 controls and 10 Parkinson patients) were analysed with the automated software and compared to a step-by-step research data analysis pipeline with VOI definition based on each subjects individual MRI. In addition, five test-retest [11]C-PE2I PET scans were analysed by the software to assess variability and reliability.
Results: Quantitative results from the automated software agreed well to the step-by-step method, with high correlations both for striatal DAT and rCBF ($r>0.90$) and cortical rCBF ($r=0.88$). Test-retest variability (3-7%) and reliability (ICC=0.66-0.89) in striatal and cortical VOIs agreed to what has previously been reported for [11]C-PE2I.
Conclusions: The single scan approach, together with the software, has been successfully introduced as a clinical routine investigation at Uppsala University Hospital, Sweden, with more than 1000 patients investigated so far.

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OD343 / #1029

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

DEEP-LEARNING ANALYSIS IN TAU PET FOR ALZHEIMER'S CONTINUUM

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Aims: We aim to develop a deep learning approach to detect the voxels in tau PET scans showing the relevant tau deposition across AD stages. We then compared the performance of this approach to distinguish different stages compared to the conventional ROI approach.
Methods: [18F]flortaucipir positron emission tomography (PET) scans were obtained from the Alzheimer's Disease Neuroimaging Initiative.
All subjects were classified into 4 groups based on the Abeta status on AV45 PET: 123 subjects that were cognitively normal and Abeta-negative in addition to 60 cognitive normal, 47 MCI, and 29 AD patients who are all Abeta-positive. We utilized the transfer learning approach with a base model Xceptioin to perform binary classifications across all combinations of the 4 groups.
Results: Our results showed that, first, the proposed deep learning method outperformed the conventional ROI-based analyses (the Braak-staging scheme) based on the 5-fold cross-validation analysis across the AD continuum (Table 1).

AU-ROC results across all binary classifications

	Braak12	Braak34	Braak56	DL model
CN- vs AD+	0.85	0.89	0.81	0.97
CN- vs MCI+	0.69	0.74	0.70	0.93
CN- vs CN+	0.63	0.64	0.62	0.68
CN+ vs AD+	0.73	0.82	0.73	0.88
CN+ vs MCI+	0.60	0.65	0.62	0.80
MCI+ vs AD+	0.62	0.70	0.64	0.78

Furthermore, mapping the occlusion sensitivity maps of the models onto the tau PET images enables us to present deep-learning-identified brain regions that significantly contribute to the classification tasks (Figure
1).

Conclusions: The proposed deep learning architecture was able to distinguish different AD stages to a greater extent than the conventional ROI approaches.

Our findings demonstrated that combining a deep learning framework can identify the key brain regions of tau deposition across different AD stages, extending the current understanding of AD pathological changes.

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OD344 / #2173

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

COMPARISON OF TAU ACCUMULATION IN FOUR DIFFERENT SUBTYPES OF ALZHEIMER DISEASE.

Takahito Yoshizaki[1,2], Shinobu Minatani[2], Hiroto Namba[2], Akitoshi Takeda[2], Yoshiaki Itoh[2]
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Aims: Now we know Alzheimer disease (AD) is a disease related with amyloid β (Aβ) which followed by tau aggregation, and we have confirmed the Aβ and tau deposition by positron emission tomography (PET) in AD brain. However, we know less about the categorization of AD through PET data including cerebral atrophy evaluated by MRI scans. Here we used a novel PET ligand for tau to estimate differential distribution of tau in subtypes of AD.
Methods: Patients with posterior cortical atrophy (PCA) (n=3), frontal variant of AD (FAD) (n=1), logopenic variant primary progressive aphasia (LPPA) (n=2) and typical AD (TAD) (n=6) as well as healthy controls (HC) (n=12) were studied. Aβ and tau accumulation was evaluated with [11C]PiB and [11C]PBB3, respectively.
Results: Aβ accumulation was confirmed in all PCA, LPPA and TAD cases. Tau accumulation was dominantly high in the occipital lobes in PCA, strikingly high in the frontal lobes in FAD and moderately high in the angular gyrus of the dominant hemisphere in LPPA. Tau accumulation in TAD cases was significantly higher than age-dependent tau accumulation in HC in these subtype-specific regions as well as AD signature regions. Glucose utilization was reversely correlated with PBB3 accumulation in the subtype-specific regions.
Conclusions: Tau accumulations in four subtypes of AD appeared differently, related with the higher cortical dysfunction and less glucose consumption. Tau pathology could be closely associated with unique clinical features.

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OD345 / #832

ON-DEMAND SYMPOSIUM: PET 03
01-04-2023 07:00 - 08:30

CHOROID PLEXUS ENLARGEMENT IS ASSOCIATED WITH LOWER CSF CLEARANCE FROM THE LATERAL VENTRICLES OF THE BRAIN, AS MEASURED BY 18F-MK-6240 PET

Liangdong Zhou, Tracy Butler, Gloria Chiang, Xiuyuan Wang, Emily Tanzi, Mony De Leon, Yi Li
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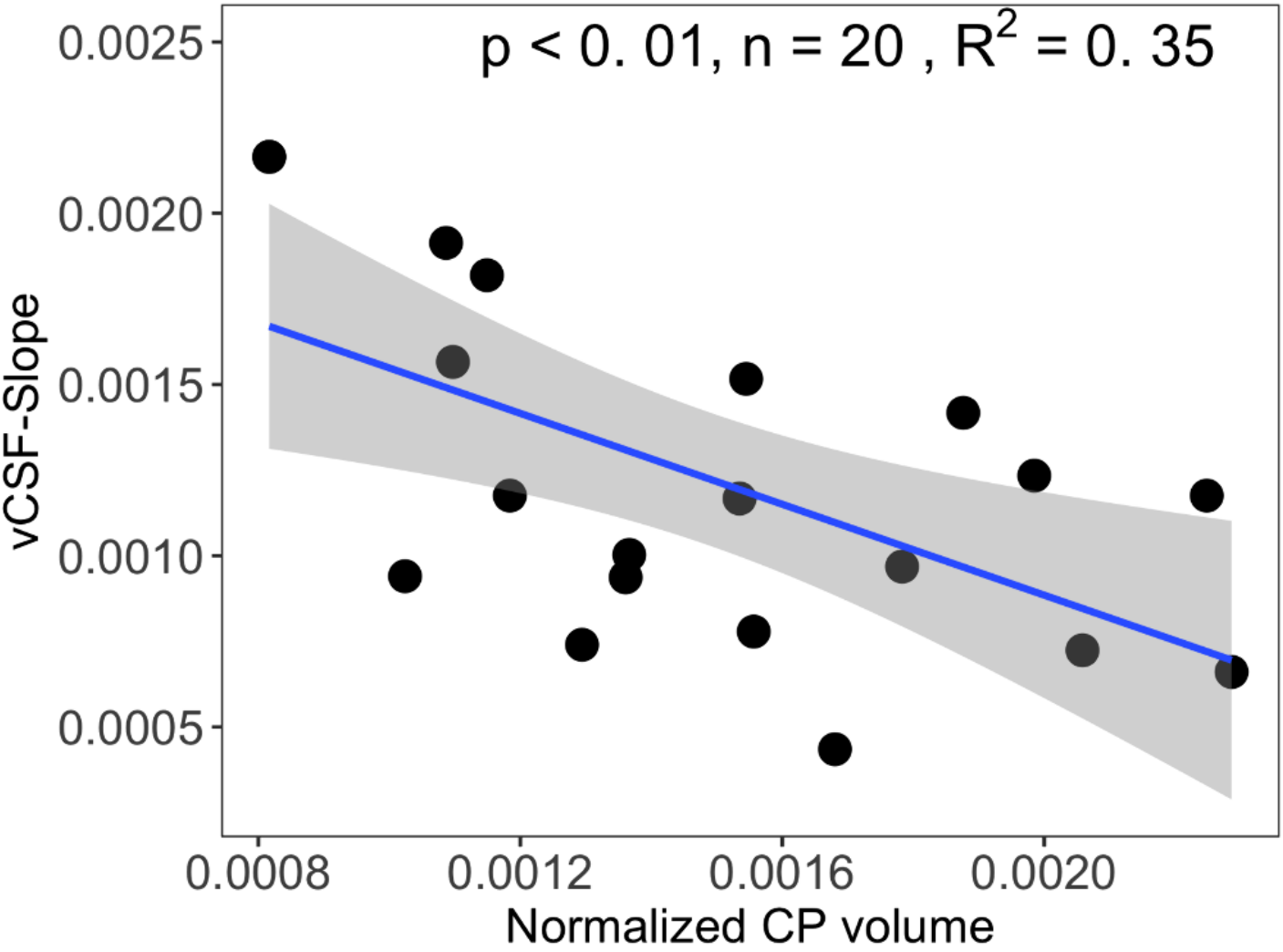
Aims: The glymphatic system is considered a key contributor to the pathophysiology of neurodegenerative diseases, including Alzheimer's disease (AD). The CSF, which is mostly produced by the choroid plexus (CP), is the fluid that carries metabolic waste for glymphatic clearance. Since the production of CSF could be related to the effectiveness of clearance, CP enlargement could potentially reflect morphological changes in its epithelial cells, calcification, and functional impairment. This study evaluates the relationship between CP volume and glymphatic clearance measured by dynamic PET.
Methods: We conducted both MRI and 18F-MK-6240 PET scans on 20 amyloid-positive subjects (Age: mean=68.4, std=6.8, M=7). T1W was acquired for ROI parcellation using FreeSurfer and for intracranial volume (ICV) using SPM12. T2-FLAIR was acquired for CP segmentation using a Gaussian mixture model. CP volume was normalized by ICV for analysis. Dynamic PET with 18F-MK-6240 tracer was used to compute ventricular CSF turnover rate, vCSF-Slope (Y. Li, 2021). The linear association between vCSF and CP volume was evaluated, adjusted for age and gender.
Results: Figure-1 shows that the enlargement of CP is associated with a lower CSF clearance rate ($r=-0.57$, $p<0.01$, $R^2=0.35$), where r is from the partial correlation test by controlling for gender and age.



Conclusions: Our preliminary results show that the CP enlargement might be indicative of CP dysfunction in producing CSF, thereby further impairing the circulation of CSF in the glymphatic clearance system.

OD346 / #72

ON-DEMAND SYMPOSIUM: A-BETA & TAU TARGETING THERAPIES IN AD AND DISEASE-MODIFYING THERAPIES
01-04-2023 07:00 - 08:30

NEW AND EMERGING TREATMENTS FOR ALZHEIMER'S DISEASE

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OD349 / #1688

ON-DEMAND SYMPOSIUM: A-BETA & TAU TARGETING THERAPIES IN AD AND DISEASE-MODIFYING THERAPIES
01-04-2023 07:00 - 08:30

A NOVEL ANTI-AMYLOID BETA (ABETA) VACCINE, A POTENT IMMUNOTHERAPY FOR THE PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE IN DOWN SYNDROME

Emma Fiorini, Rakel Carpintero, Rime Madani, Marcela Rincon, Pilar Lopez-Deber, Maxime Ayer, Inmaculada Rentero, Stefanie Siegert, Chiara Babolin, Eva Gollwitzer, Sophie Bravo-Veyrat, Catherine Morici, Marie-Gabrielle Beuzelin, Anthony Gesbert, Sébastien Rivot, Nathalie Chuard, Valerie Eligert, Saskia Delpretti, Piergiorgio Donati, Johannes Streffer, Andrea Pfeifer, Marie Kosco-Vilbois, Marija Vukicevic
AC Immune, Sa, Lausanne, Switzerland

Aims: Optimized ACI-24, an Abeta-targeting vaccine that safely drives immunity to pathological oligomers and pyroglutamate Abeta, is being developed for people with Down syndrome (DS). Due to the triplication of chromosome 21, containing the Abeta gene, there is a need to develop a treatment to avoid or clear plaques leading to AD in this vulnerable population.
Methods: The safety and efficacy of ACI-24, containing the B-cell peptide, Abeta1-15, were established in a mouse model of DS, Ts65Dn. In order to optimize vaccine immunogenicity, non-Abeta helper T-cell peptides were designed. In silico methodology was used to evaluate short sequences from different pathogens and the peptides combined to achieve the highest potential to recruit T-cell help without any Abeta-specific T-cell activation. Various candidates were formulated into the vaccine, administered to mice and non-human primates (NHPs) and anti-Abeta antibody levels in plasma/serum evaluated.
Results: In Ts65Dn mice, ACI-24 containing Abeta1-15 and no T-cell stimulating epitopes, induced anti-Abeta titers which correlated with reduction of Abeta and atrophy and an improvement in memory function. As Abeta1-15 only-containing vaccine was safe in humans, non-Abeta T-cell helper peptides were added to ACI-24 to enhance, boost and maintain antibodies. Different non-Abeta peptides were formulated in ACI-24 vaccine and evaluated in mice and NHPs, inducing different levels of improvements. Exploration of the quantities of B- and T-cell epitopes were optimized to achieve maximum titers.
Conclusions: An optimized formulation of the safe ACI-24 vaccine has been generated that enhances the production of antibodies to the pathological species of Abeta. Clinical trials with the optimized ACI-24 will commence envisioning annual/biannual vaccination of people with DS, following the initial priming period.

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OD350 / #201

ON-DEMAND SYMPOSIUM: A-BETA & TAU TARGETING THERAPIES IN AD AND DISEASE-MODIFYING THERAPIES
01-04-2023 07:00 - 08:30

SELECTION AND CHARACTERIZATION OF TAU TARGETING D-PEPTIDES AS A POTENTIAL THERAPEUTIC APPROACH FOR ALZHEIMER'S DISEASE

Susanne Aileen Funke[1], Isabelle Aillaud[1], Marwa Malhis[1], Senthilvelrajan Kaniyappan[2,3], Ram Chandupatla[4], Lisa Ramirez[5], Sewar Alkhashrom[6], Jutta Eichler[6], Anselm Horn[7,8], Markus Zweckstetter[5,9], Eckhard Mandelkow[3,4,10], Heinrich Sticht[7]
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Aims: In AD, Tau pathology strongly correlates with clinical symptoms, cognitive dysfunction and neuronal death. We have selected novel D-amino acid peptides as Tau aggregation inhibitors, composed of 12 amino acids. As demonstrated previously, D-amino acid peptides are protease stable and less immunogenic than L-amino acid peptides.
Methods: Two hexapeptide motifs within Tau, designated PHF6* (^{275}VQIINK^{280}) and PHF6 (^{306}VQIVYK^{311}), are known to be important for Tau aggregation because of their high propensity for beta structure. Using different phage display selection procedures against full-length Tau, PHF6* or PHF6, respectively, we selected novel Tau binding D-peptides binding to different parts of Tau. The ability of the D-peptides' for Tau binding and inhibition of Tau fibrillization were characterized using Enzyme Linked Immunosorbent Assays (ELISA), Thioflavin assays, dynamic light scattering (DLS), pelleting assays and *in silico* modeling. Using cell culture experiments, the cellular uptake and localization of the novel D-amino acid peptides were investigated as well as cell toxicity and the abilities to reduce Tau toxicity.
Results: D-peptides selected for binding to motifs PHF6* or PHF6 inhibited Tau fibrillization to a similar extent. Some of them induced the formation of aberrant high molecular weight Tau aggregates that lack proper Thioflavin-positive β-sheet conformation. Cell culture experiments demonstrated that the D-peptides were taken up by N2a cells efficiently and prevented cytotoxicity of Tau.
Conclusions: Based on our results, it appears that our D-peptides could emerge as a promising therapy for early intervention of AD, presumably by inhibiting toxic Tau oligomer formation and promoting off-pathway non-fibrillar assembly of Tau. D-peptides targeting either PHF6* or PHF6 have similar abilities to inhibit the fibrilization of Tau *in vitro*. **References:** Aillaud et al. (2022). Alzheimers Res Ther;14:15 Malhis et al. (2021). ChemBioChem 22:3049-3059

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OD351 / #417

ON-DEMAND SYMPOSIUM: A-BETA & TAU TARGETING THERAPIES IN AD AND DISEASE-MODIFYING THERAPIES
01-04-2023 07:00 - 08:30

META-ANALYSIS OF HIGH-CLEARANCE ANTI-AMYLOID IMMUNOTHERAPIES TRIALS IN EARLY ALZHEIMER'S DISEASE: A SIGNIFICANT CLINICAL EFFECT BUT A HIGH RISK/BENEFIT RATIO

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Aims: Three over four phase II or III clinical trials using high-dose anti-amyloid immunotherapies (AAI) in early Alzheimer's disease (AD) were recently positive on clinical outcomes: aducanumab, donanemab, and lecanemab. These drugs share a new characteristic: the high clearance of amyloid load. In the meantime, the Food and Drug Administration's conditional approval of aducanumab has led to unprecedented scientific controversies.
Methods: We meta-analyzed the data from the highest dose groups versus placebo after 18 months of the aducanumab, lecanemab, and donanemab phase II or III trials. We analyzed the CDR-SB, ADASCog, and MMSE results, and the occurrence of any Amyloid-Related Imaging Abnormalities (ARIA), of ARIA-edema (ARIA-E), of ARIA-hemorrhage (ARIA-H), and of symptomatic and serious ARIA.
Results: High-clearance AAI significantly slowed down cognitive decline after 18 months as measured with CDR-SB (weighted mean=-0.24 points; p=0.04), ADAS-Cog (weighted mean=-1.25 points; p=0.0003), but not with MMSE (weighted mean=+0.31 points; p=0.23) when compared to placebo. In parallel, the drugs significantly increased the occurrence of any ARIA (risk ratio=3.68; p<0.0001), of ARIA-E (risk ratio[RR]=13.39; p<0.0001), of ARIA-H (RR=2.78; p=0.0002), and of symptomatic and serious ARIA (7/1321=0.53% in the high dose groups versus 0/1446 in the placebo groups; RR=6.44; p=0.04).
Conclusions: When pooled together, the data from high-clearance AAI trials confirm a significant clinical effect after 18 months that remains below the established minimal clinically relevant values. Safety remains an issue with 0.5% of symptomatic and serious ARIA despite thorough in-trial monitoring and management. The risk/benefit ratio of this class of drugs in early AD is questionable after 18 months. Identifying better responders, longer follow-ups, and the perspective of combination therapies may help improve their clinical relevance.

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OD353 / #2561

ON-DEMAND SYMPOSIUM: A-BETA & TAU TARGETING THERAPIES IN AD AND DISEASE-MODIFYING THERAPIES
01-04-2023 07:00 - 08:30

TRAILBLAZER-ALZ 6: INVESTIGATING THE EFFECT OF DIFFERENT DONANEMAB DOSING REGIMENS ON ARIA-E IN ADULTS WITH EARLY SYMPTOMATIC ALZHEIMER'S DISEASE

Emel Serap Monkul Nery[1], Hong Wang[1], Dunlei Cheng[2], Diana Otero Svaldi[3], Emily Collins[1], Dulanji Kuruppu[4], Dawn Brooks[5], John Sims[1]
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Aims: Donanemab (LY3002813) is an immunoglobulin G1 antibody developed to remove existing amyloid plaques through microglial-mediated clearance. Amyloid-related imaging abnormalities (ARIA) have been observed with beta-amyloid plaque-targeted therapies, including donanemab. This study will investigate potential risk mitigation of ARIA through different donanemab dosing regimens, novel MRI sequences, and blood-based biomarkers.
Methods: This is a multicenter, randomized, double-blind, phase 3b study in participants with early symptomatic AD. Study duration will be approximately 91 weeks including screening, double-blind treatment period, and follow-up. Eligible participants are 60–85 years old, have gradual and progressive change in memory function reported by the participant or informant for ≥6 months from consent, Mini Mental State Examination score 20–28 (inclusive) at Visit 1, and amyloid positron emission tomography scan result consistent with presence of amyloid pathology. A total of 800 participants will be randomized 1:1:1:1 to one of four donanemab treatment arms. The standard donanemab dosing regimen is 700mg intravenously Q4W for 3 doses and then 1400mg intravenously Q4W. The goal is to investigate at least 3 dose regimens in addition to the standard. Novel exploratory MRI sequences including functional MRI, susceptibility weighted imaging, 3D fluid-attenuated inversion recovery imaging, diffusion tensor imaging, and 3D T2 weighted MRI will be incorporated. We will compare ARIA-E rate by Week 24 between each alternative dosing regimen and standard dosing regimen through Bayesian logistic regression models. The trial has >80% power to demonstrate that at least one alternative regimen will reduce ARIA-E rate by ≥20% with high probability, compared to standard regimen at 24 weeks.
Results: Trial design will be presented.
Conclusions: ARIA is a class effect of amyloid-targeting therapies. This study aims to explore new methods to reduce this risk.