SINGAPORE 2015 ESMO ASIA

PROFERRED PAPER SESSION

SARCOMA

Abstracts no. 3580, 3590, 3600

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SINGAPORE 2015 ESMO ASIA

Abstract 3580

Chemo-responsiveness predictive biomarker discovery for osteosarcoma using microRNA-microarray

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miRNAs

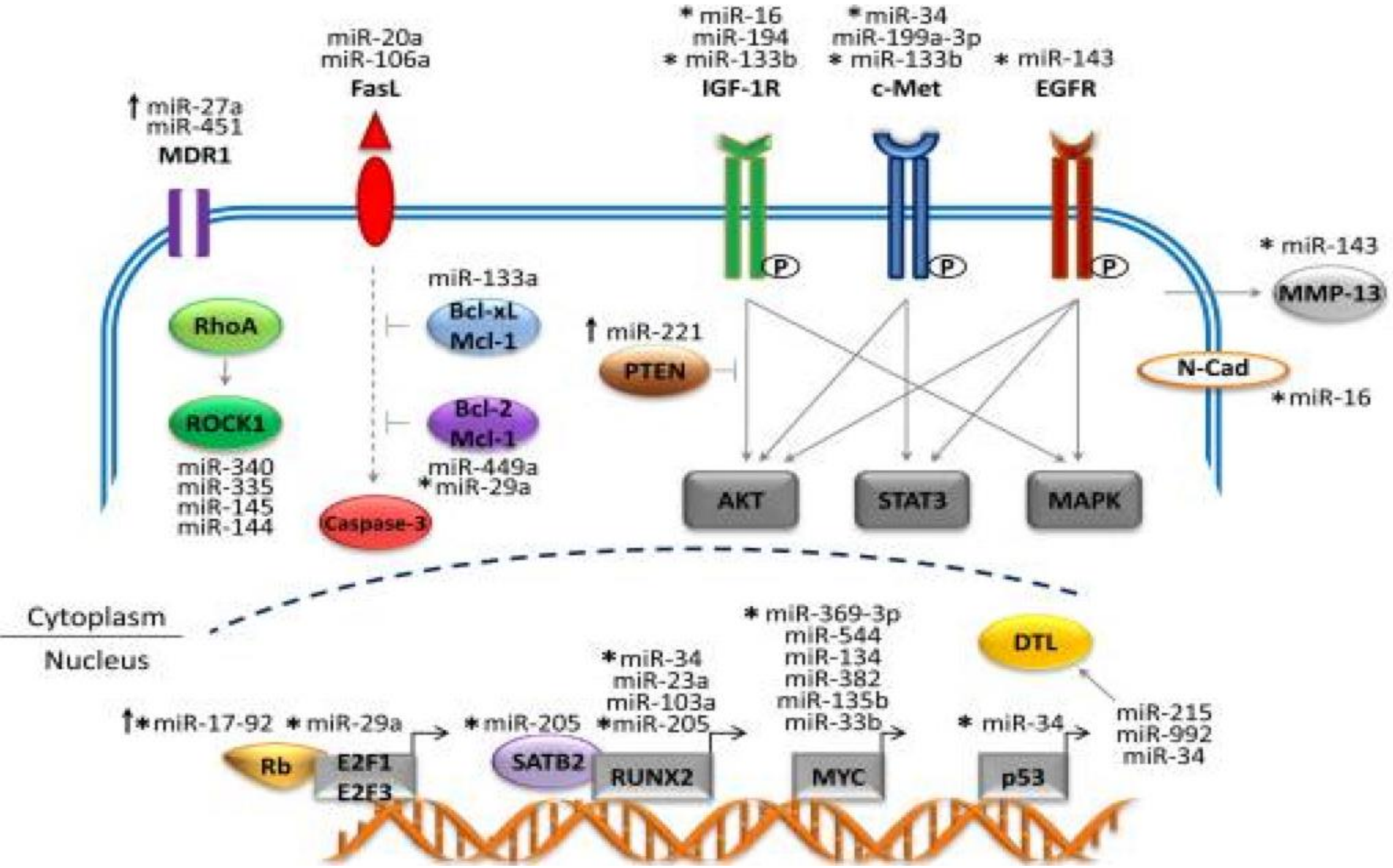
- MicroRNAs (miRNAs) are single-stranded noncoding RNAs involved in various biological processes through post-transcriptional modifications

- There are known to be at least 4000 miRNAs in human genome

- Regulate approx 50% of human genes. Each miRNA likely controls hundreds of gene transcripts

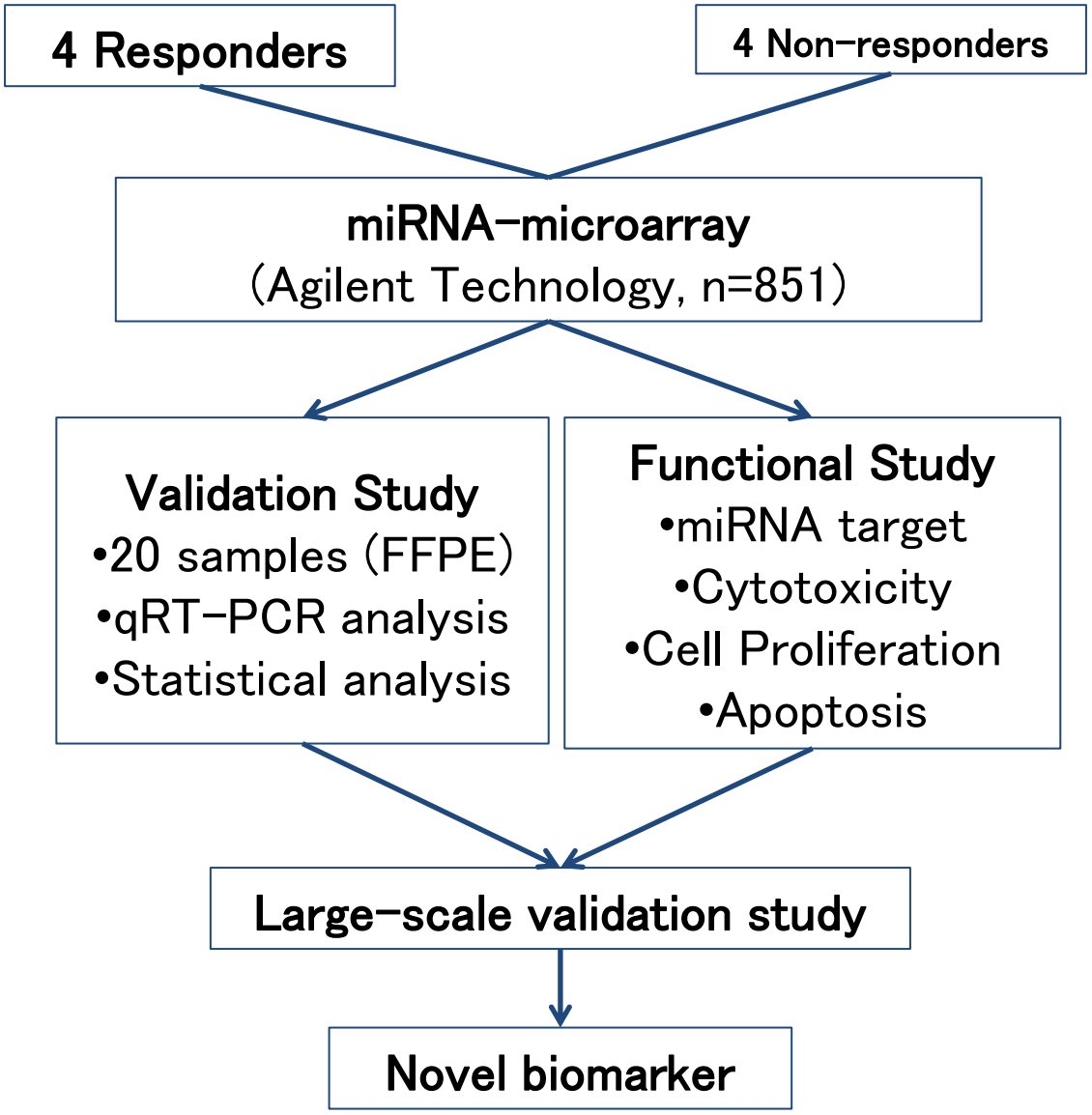
- Can have an oncogenic (overexpressed) or tumour suppressive role (underexpressed), hence their interest as a biomarker

miRNAs in Osteosarcoma



VB Sampson et al. Frontiers in Pediatrics. 2015

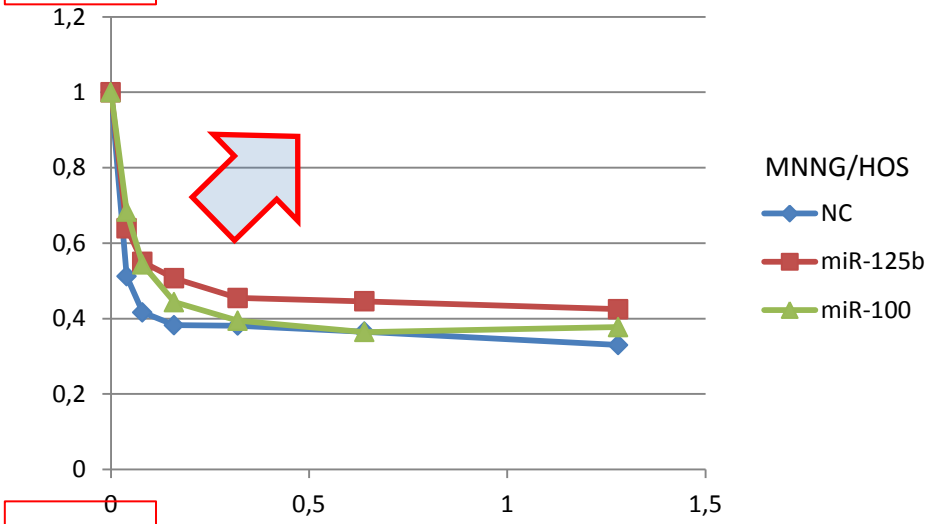
Work flow



- Identify potential miRNAs bases on chemo response
- Validation
- Functional Study
- Large scale validation

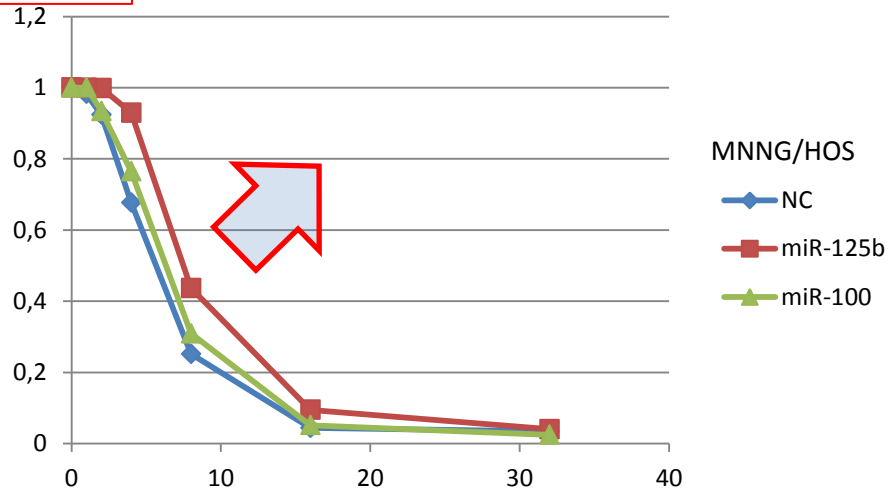
Functional study
Cytotoxicity

MTX

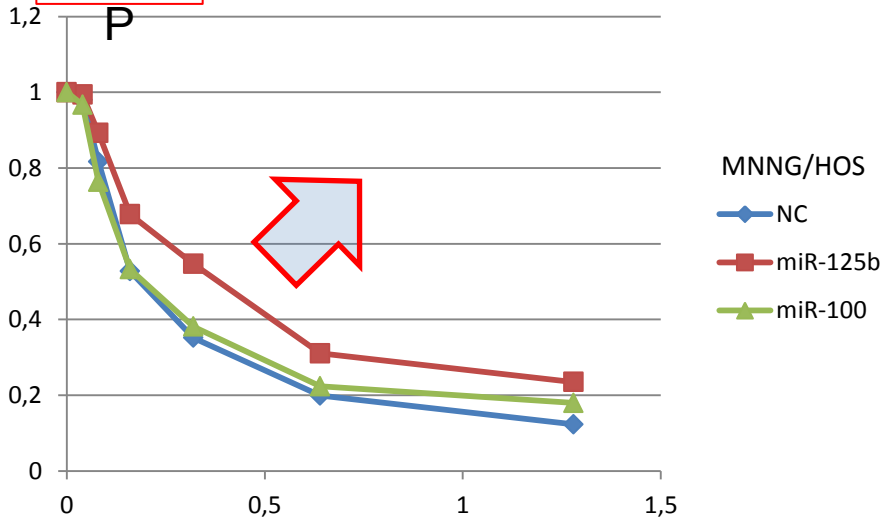


- Osteosarcoma cell line (MNNG/HOS, 143B, and MG63)
- The IC_{50} values were inspected before and after transfection of miR-125b and miR-100.
- Over expression of miRNAs resulted increasing drug resistance for MTX/DOX/CDDP.

DOX



CDDP



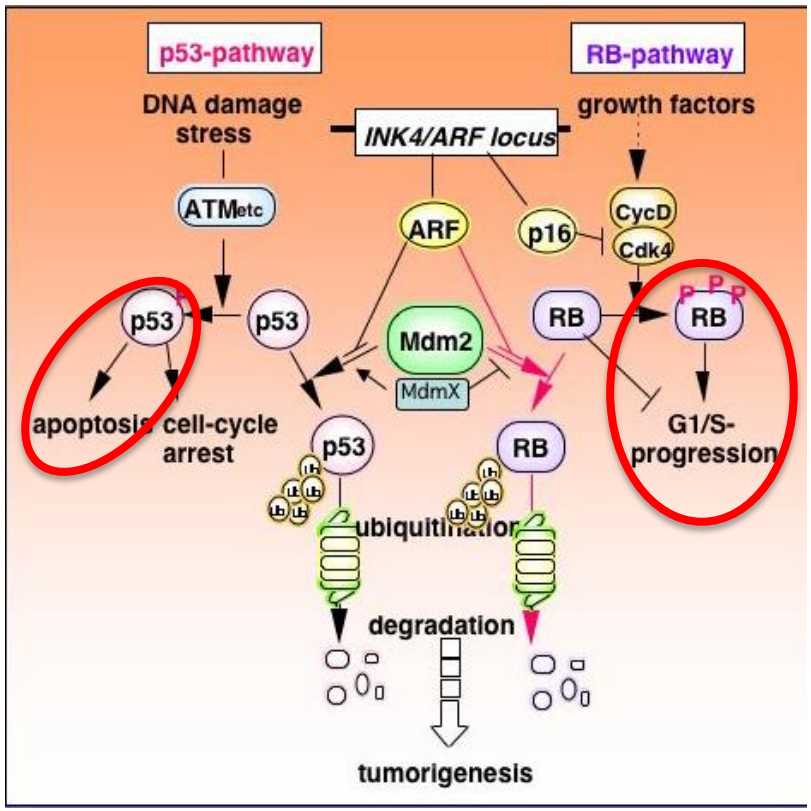
miRNAtarget

- miRNA targets database

TargetScanHuman
Prediction of microRNA targets
Release 6.0: November 2011

miRBase

- **miR-125b**: **P53, BCL-2 Family**
  - Bak1 (apoptosis)
  - TP53 (apoptosis)
  - PUMA (apoptosis)



- **miR-100**: **Rb Family**
  - CTDSPL (cell cycle）

Conclusion and Next Steps

- We identified the miRNAs as predictive biomarker of chemo-response in osteosarcoma.
- miR-125b and miR-100 were up-regulated in non-responders.
- Cytotoxicity assay suggested these miRNAs may contribute to a broad spectrum of chemo-resistance mechanism.
- miR-125b and miR-100 targeted p53 and Rb pathway. These miRNAs may promote cell proliferation, and inhibit drug-induced apoptosis.
- ROC curve analysis revealed the high predictive ability of these miRNAs.

- Further miRNAs identified in OS
- May have role as a **Predictive Biomarker**
- Single vs multiple miRNAs?
- Identified through functional screens, and then validated clinically and preclinicically

Future Studies

- Prospective validation in large clinical trials
- ?role in modifying response to all 3 agents
- ?other measures of miRNAs eg circulating levels

A Whole Genome Approach to Better Understand the Link Between Kaposi's Sarcoma-Associated Herpesvirus and Human Cancers

Abstract 3590

ESMO Asia – Dec 19th 2015

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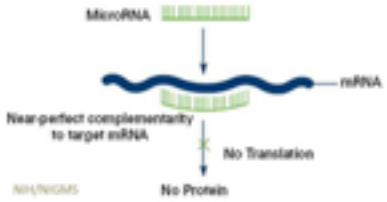
Overview

KSHV and Hypoxia

- KSHV-associated malignancies, KS and PEL, arise in settings of relatively low oxygen concentrations (hypoxia)
- Hypoxia can activate KSHV production via a transcription factor called HIF (Hypoxia-inducible factor)



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KSHV Infected Cells:

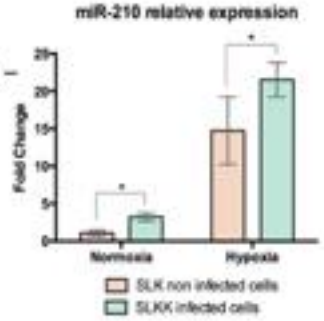
Whole genome approach to explore genes affected by hypoxia

Results

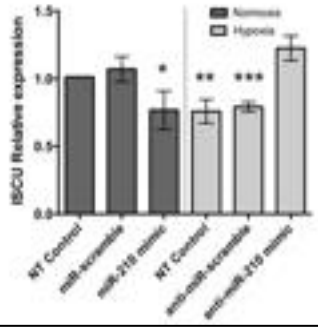
miR-210, a microRNA involved in hypoxia and cancer, was increased by both hypoxia and KSHV infection

- miR-210 is a predominant microRNA up-regulated by hypoxia in a variety of cell lines
- By knocking down a variety of repressors, miR-210 induces angiogenesis, cell survival and cell proliferation
- miR-210 known targets are ISCU (mitochondrial metabolism) and EFNA3 (angiogenesis inhibitor)

- miR-210 is up-regulated by hypoxia, but also by KSHV infection – even in normoxic conditions



- miR-210 expression is inversely correlated to its target expression (ISCU)



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- Hypoxia drastically changes expression profile of KSHV-infected cells
- KSHV infection induces miR-210, a key hypoxia-regulated miRNA involved in cancer
- However, viral miRNAs don't change in response to hyoxia

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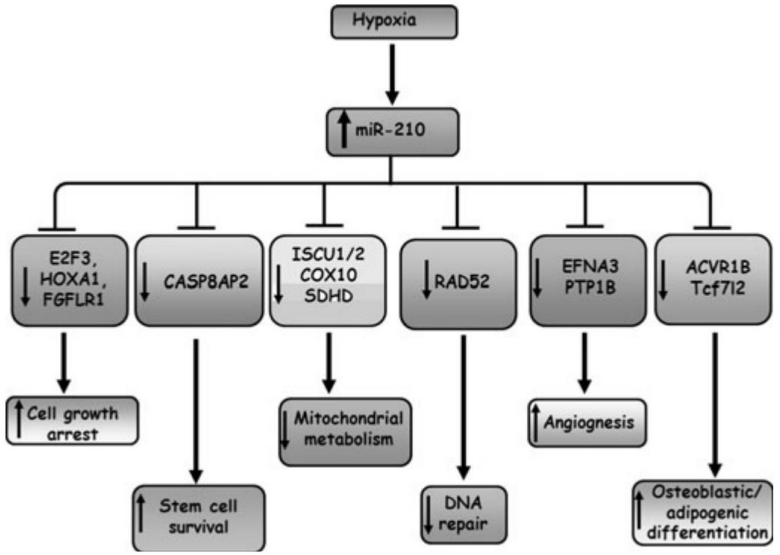
Additional information

miRNA-210

- miR-210 targets and their biological functions:
  - miR-210 induces cell survival and increases cell proliferation
  - miR-210 induces angiogenesis
  - miR-210 represses mitochondrial metabolism
  - miR-210 stalls DNA repair



miR-210: the Master Hypoxamir, Chan et al. 2011

Conclusions Abstracts 3580 and 3590

- Potential value in using miRNAs to better understand the complexities of tumorigenesis
- Explore Utility of miRNAs as both a biomarker (predictive and prognostic) and in understanding pathogenic links to disease
- Potential value as a circulating biomarker
- Challenges will be in understanding their context and functional significance in individual tumour types

Clinicopathological and functional analyses of protein phosphatase 2, regulatory subunit A, alpha mutations in gastrointestinal stromal tumors

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Abstract 3600

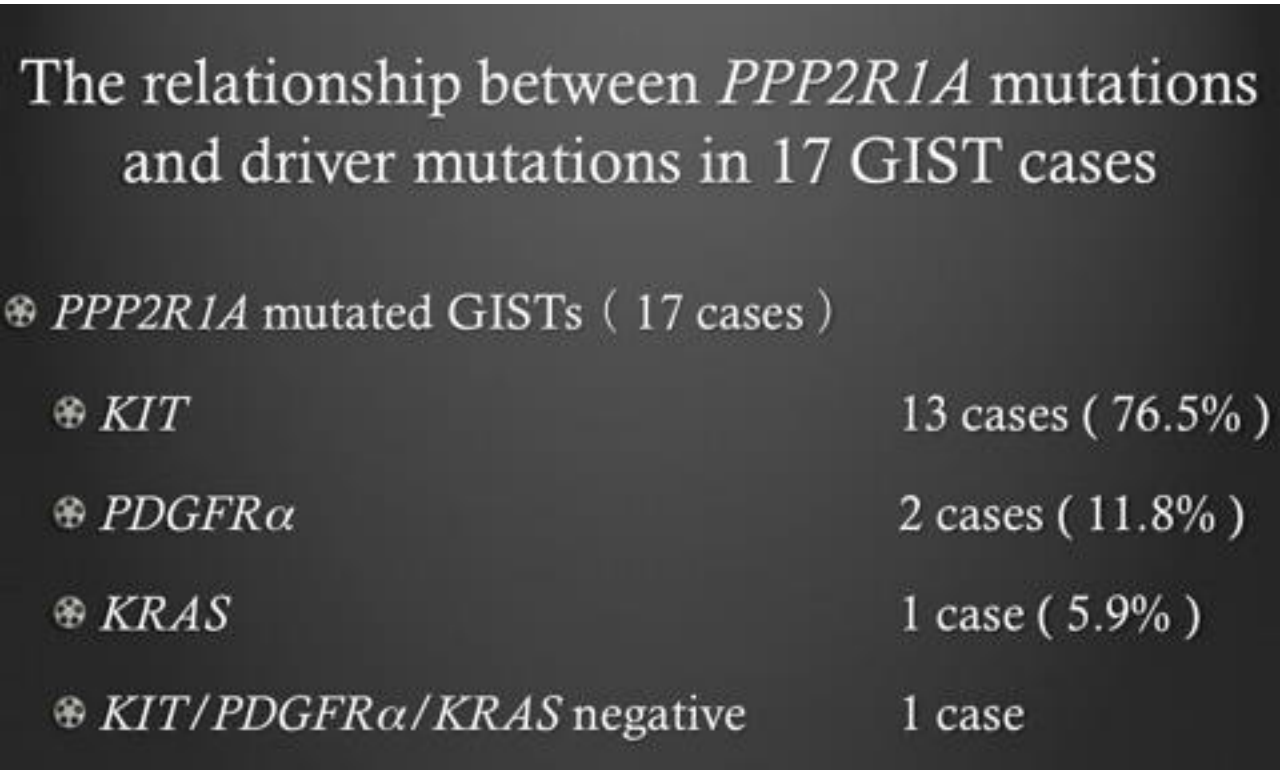
JUNTENDO UNIVERSITY TOKYO 1838

Overview

- Mutations in *PPP2R1A* only recently described (2007)
  - Most commonly reported in Ovarian and Uterine Ca
  - Only 169 cases in Cosmic database
  - Reports in other tumours, eg. prostate

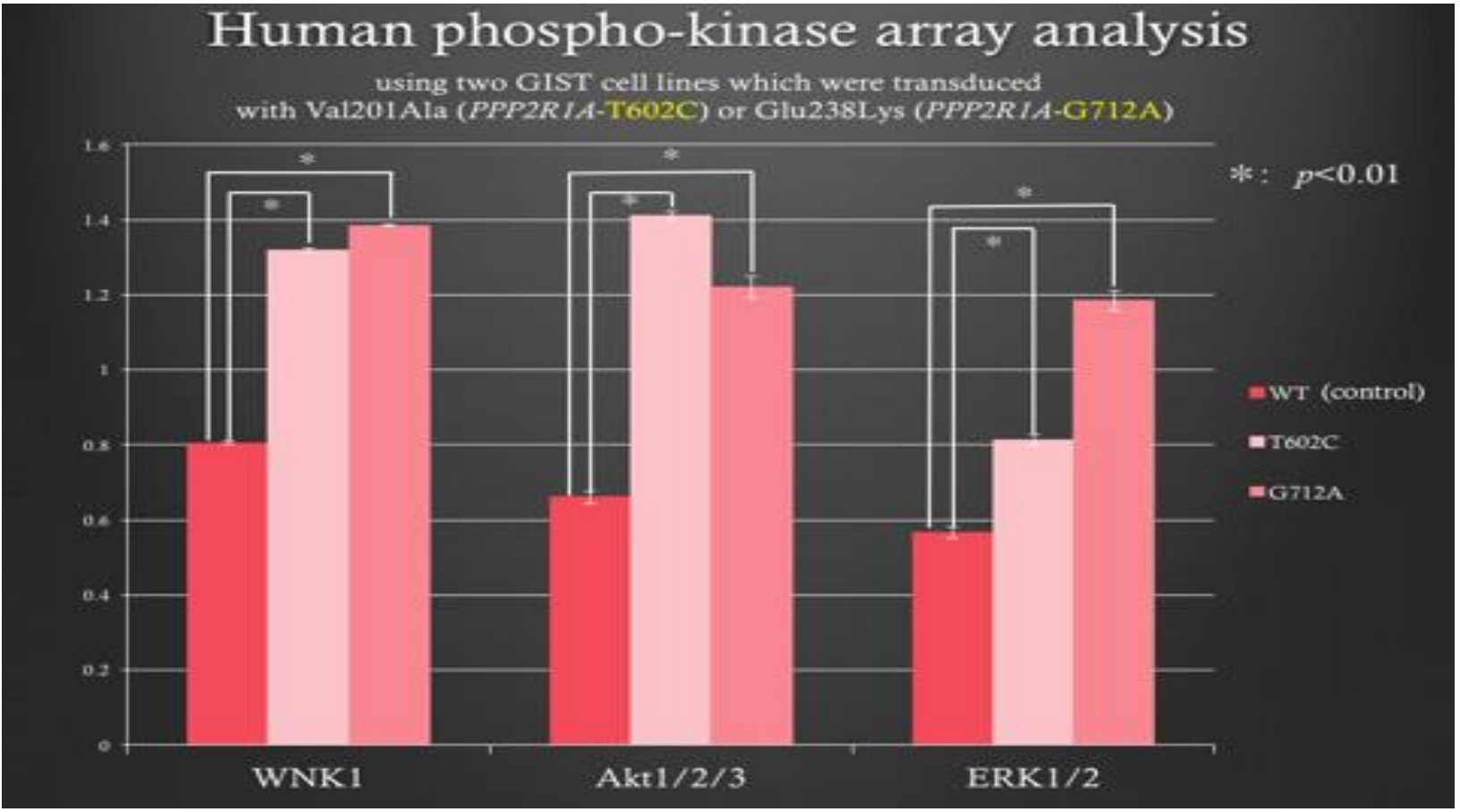
- Aimed to explore PPP2R1A in GIST
  - 94 Patients
  - All primary tumours, i.e.pre-treatment
  - Why?

RESULTS



- 17 (18.1%) of 94 GIST cases harbored PPP2R1A mutations.
- Not isolated to WT patients
- Univariate analysis: Correlated with tumour grade/agressiveness, and overall outcomes
- Multivariate analysis with larger numbers would be very useful

RESULTS: Functional Significance



- Limited data in gynae cancer models suggesting function through AKT
- Transduced GIST cell lines
  - ?unsure how extensive their phospo-protein analysis was

Conclusions and Next Steps

- Novel and very interesting study
- Co-existing mutations in reasonable percentage of GIST cases, co-existing with other key drivers
- Value in
  - Better understanding the utility of PPP2R1A as a biomarker
  - Exploring patient cohorts post-TKI therapy
  - Understanding functional effects in more detail
  - Exploring mechanisms to target these changes