CANCER SCIENCE
INSTITUTE OF SINGAPORE

RESEARCH MEETINGS

7 July 2017, Friday I 12pm – 1pm

LT36, Level 3, Centre for Translational Medicine (MD6)
14 Medical Drive, Singapore 117599

Avinash Govind Bahirvani I Research Fellow, A/Prof Motomi Osato's Group (L12)

Enhancer for Runx1, eR1: A Powerful Tool in Stem Cell and Cancer Biology

A cis–regulatory genetic element which targets gene expression to stem cells, termed stem cell enhancer, serves as a molecular handle for stem cell-specific genetic engineering. Here we show the generation and characterization of a tamoxifen (TM)-inducible CreERT2 transgenic (Tg) mouse employing previously identified hematopoietic stem cell (HSC) enhancer for Runx1, eR1 (+24m). Kinetics analysis of labeled cells after TM injection and transplantation assays revealed that eR1-driven CreERT2 activity marks dormant adult HSCs which slowly but steadily contribute to unperturbed hematopoiesis. Fetal and child HSCs which are uniformly or intermediately active were also efficiently targeted. Notably, a gene ablation at distinct developmental stages, enabled by this system, resulted in different phenotypes. Similarly, an oncogenic Kras induction at distinct ages caused different spectrums of malignant diseases. These results demonstrate that the eR1-CreERT2 Tg mouse serves as a powerful resource for the analyses of both normal and malignant HSCs at all developmental stages.

Vinod Vijay Subhash I Research Fellow, Dr Yong Wei Peng's Group (L13)

Oncogenic Roles of Maternal Embryonic Leucine Zipper Kinase (MELK) in Gastric Cancer and its Therapeutic Targeting using Small Molecule Inhibitor OTS 167

Maternal Embryonic Leucine Zipper Kinase (MELK) belongs to the subfamily of AMP-activated Ser/Thr protein kinases. It's expression is up regulated in various cancers and is known to be associated with cancer progression, maintenance of stemness and poor prognosis. The present study investigates the tumorogenic role and biological functions of MELK in gastric cancer using OTS167, a novel and selective small molecule inhibitor. MELK was found to be up regulated in clinical samples of gastric cancer that correlated with distant metastasis and poor survival outcomes. Strikingly, MELK inhibition caused a senescence like phenotype in gastric cancer cells with an increase in replication stress, DNA double stranded breaks and reduced expression of stem cell markers. Absence of MELK expression led to the arrest of cell cycle at G2M phase with an increase in epithelial characteristics and cellular apoptosis. On the other hand, a decrease in cellular invasion and proliferation was also observed. Moreover, OTS167 treatment of mouse models bearing gastric cancer PDX's resulted in a significant inhibition of tumor growth. Taken together, our study highlights the potential of MELK as a therapeutic target in gastric cancer and underscores the clinical benefits of its pharmacological inhibition using OTS167. Further studies are underway to identify the regulatory mechanism of MELK expression and to characterize its function in greater detail.