CANCER SCIENCE INSTITUTE OF SINGAPORE

RESEARCH MEETINGS

23 Sep 2016, Friday I 12pm – 1pm

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

Dennis Kappei I Special Fellow (L11)

48 – The Answer to Cells, Telomeres and Everything

Telomeres are the molecular caps of chromosomes and in most vertebrates they consist of TTAGGG repeats. Due to the end replication problem and active end processing telomeres shorten with every cell division, ultimately leading to cellular senescence. Cancer cells would eventually share this fate. However, they developed two mechanisms to defy telomere shortening: 85% of all tumors reactivate the reverse transcriptase telomerase which adds telomeric repeats *de novo*, while the other 15 % use the recombination-based Alternative Lengthening of Telomeres (ALT) pathway. We have recently identified novel telomere-binding proteins through a functional 'phylointeractomics' screen by interrogating a telomeric DNA bait with the proteome of 16 vertebrate species. We reasoned that proteins that are functionally conserved throughout evolution are likely to be key regulators for these fundamental telomere maintenance mechanisms. Here, we focus on the functional characterization of one of these novel factors: ZBTB48 is a direct telomere-binding protein, it is found at telomeres of human cancer cells regardless of the mode of telomere maintenance and it acts as a negative regulator of telomere length. Furthermore, the combined omics analyses of ChIPseq, RNAseq and proteomics expression profiling reveals that ZBTB48 has transcription factor activity, connecting its telomere functions to mitochondrial metabolism.

Lau Wen Min I Senior Research Scientist, Dr Chan Shing Leng's Group (L12)

Diffuse-type Gastric Cancer: Pre-clinical Models which Provide Insight into Drug Sensitivity, Acquired Resistance Mechanisms and Reveal Opportunities for Therapeutic Intervention

Diffuse-type gastric cancer (DGC) is histologically and clinically distinct from intestinal gastric cancer with a poorer prognosis and lower 5-year survival rates. Pre-clinical models of DGC which reliably predict responses to therapeutic compounds are lacking, and molecular analyses of DGC have been hampered by difficulty in obtaining primary tumors of sufficient tumor cellularity without contaminating stroma. To circumvent this, we isolated cancer cells from malignant ascites of DGC patients for exome sequencing analysis and generation of patient-derived xenograft (PDX) models. Further characterization of our DGC PDX models identified key pathways and novel mutations which revealed potential avenues for therapeutic intervention. Proof-of-concept drug treatments on various PDX tumors were performed to predict the sensitivity of gastric tumors to targeted therapeutics. Further investigation into drug resistance mechanisms in our models revealed the development of compensatory signaling pathways which are independent of gatekeeper mutations. We are also interested in targeting the DNA damage repair (DDR) pathways for cancer treatment using the concept of synthetic lethality. By exploiting vulnerabilities in DNA damage repair mechanisms, we aim to identify a subset of gastric tumors which can be targeted using PARP inhibitors.

Md Zakir Hossain I Facility Head, Transgenic and Gene Targeting Facility (L13)

Animal Model for Human Disease and Physiology

Animals play indispensable role in life science in many ways. We exploit mouse embryogenesis to generate genetically engineered mouse model. Previously, we've shown that CRISPR/Cas9 technology has been successfully used to create indel and nucleotide editing in C57Bl/6 mice and rats respectively at our in-house trans-core facility in CSI/NUS. In this talk, I'll present further progress and refinement in genotyping and complex targeting approaches in mice using CRISPR/Cas9. Despite much complications with genotyping, germline transmission and off-target issues, we encourage researchers to consider CRISPR/Cas9 technology to generate animal model, especially when C57Bl/6 strain is crucial for study. As part of our interest in disease model, I'll also present a genetic mouse model for male subfertility associated with loss of Y-box protein 3 (*Msy3*). *Msy3* is thought to play an important role as a translational repressor in spermatogenesis. In the testis, *Msy3* is not expressed in sertoli cells but expressed in germ cells, where it is predominantly found in spermatogonia. The lack of *Msy3* function in Msy3-knockout mice caused prominent histological abnormalities in testis and multiple defects in sperm morphology, a reminiscent clinical feature of teratospermia in man, which was attributed for subfertility in Msy3-knockout male mice. This study suggests that function of *Msy3* is essential for male fertility.