Cancer Science Institute of Singapore

SEMINAR SERIES

Date: Wednesday, 2 Nov 2016
Time: 9.30am – 1pm
Venue: LT36, Level 3 Auditorium, CeTM
(14 Medical Drive, Singapore 117599)

Judy Lieberman (9.30am-10.30am)

Chair in Cellular and Molecular Medicine, Boston Children's Hospital
Professor, Department of Pediatrics, Harvard Medical School



Knocking Down Disease: A Progress Report on siRNA Therapeutics

The discovery of the role of RNA interference (RNAi) in inhibiting gene expression spurred intensive efforts to develop small interfering (si)RNA-based therapeutics to knock down disease-causing genes. The main obstacle is delivering small RNAs across cell membranes to the RNAi machinery in the cytosol of target cells. This problem has been solved for targeting the liver as clinically acceptable methods to deliver siRNAs into hepatocytes have been developed. Lipid based nanoparticles (LNPs) that carry siRNA payloads or GalNAc-conjugated siRNAs that are taken up by the asialoglycoprotein receptor on hepatocytes are showing impressive and durable gene knockdown in the liver and suggestions of clinical benefit in advanced phase clinical trials with acceptable toxicity. However, designing clinically useful strategies for delivering siRNAs to tissues outside the liver has proven difficult. Such strategies are needed to harness RNA interference for treating most diseases, including cancer. Delivery to other tissues requires development of a targeted delivery carrier. I will describe a flexible platform for targeted delivery that use RNA aptamers for selective cell uptake in vivo and gene knockdown, using difficult-to-transfect immune cells and disseminated cancer cells as models.

Morning Refreshments (10.30am – 11am)

Lee Grimes (11am – 12pm)

Director, Cancer Pathology Program
Division of Experimental Hematology & Division of Pathology
Cincinnati Children's Hospital Medical Center

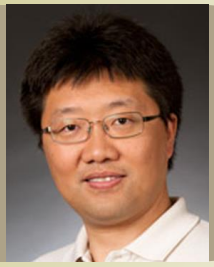


Single Cell Analyses of Normal and Malignant Hematopoiesis

We have used scRNA-Seq, coupled with a new analytic tool, ICGS and clonogenic assays to delineate hierarchical genomic and regulatory states culminating in neutrophil or macrophage specification. From our analyses, we propose that mixed-lineage states are obligatory during cell-fate specification and manifest differing frequencies because of their "dynamic instability", dictated by counteracting gene-regulatory networks. Separately, we demonstrated that mice with Flt3-internal-tandem duplication (Flt3ITD) and inducible deletion of Dnmt3a spontaneously develop a rapidly-lethal, completely-penetrant, and transplantable AML of normal karyotype. Moreover, dissection of the cellular architecture of the AML model using single-cell RNA-Seq, flow cytometry and colony assays identified clonogenic subpopulations that differentially express genes that are sensitive to the methylation of nearby genomic loci, and varied in response to Dnmt3a levels. The two projects illustrate the utility of single cell analyses in dissecting complex biological problems.

Huang Gang (12pm – 1pm)

Associate Professor of Pathology and Laboratory Medicine
Divisions of Pathology and Experimental Hematology & Cancer Biology
Cincinnati Children's Hospital Medical Center



HIF-1α Signaling is a Central Pathobiologic Mediator of Myelodysplastic Syndromes (12pm – 1pm)

Myelodysplastic syndromes (MDS) are heterogeneous haematopoietic disorders that are incurable with conventional therapy. The incidence is increasing with global population ageing. Although many genetic, epigenetic, splicing, cohesin, and metabolic aberrations have been identified in MDS patients, their clinical features are quite similar. Here we show that hypoxia-inducible factor 1α (HIF-1α) signaling is both necessary and sufficient to induce dysplastic and cytopenic MDS phenotypes. The HIF-1α transcriptional signature is generally activated in MDS-patient bone-marrow stem/progenitors. Mouse modeling of mutations frequently found in human MDS (Dnmt3a, Tet2, Asxl1, Runx1, and Mll1) activates the HIF-1α signature. While inducible activation of HIF-1α signaling in haematopoietic cells is sufficient to induce MDS phenotypes, both genetic and chemical inhibition of HIF-1α signaling rescues MDS phenotypes in a mouse model of MDS. These findings suggest a common underlying pathophysiology in MDS, and identify a novel effective therapeutic target for a broad spectrum of MDS patients.