Institute of Medical Biology
A*STAR

Seminar Announcement

- All Are Welcome -



Speaker: **Prof Tariq Enver**
UCL Cancer Institute, London

Title : **"Origins and clonal evolution of childhood leukaemia"**

Date : 3 Mar 2016 (Thursday)
Time : 2.00pm – 3.00pm
Venue : Creation Theatrette, Matrix Level 4, Biopolis
Host : Dr Ray Dunn
(Tel: 64070164, e-mail: ray.dunn@imb.a-star.edu.sg)

Abstract of the Seminar:

Childhood acute lymphoblastic leukaemia is thought in many cases to initiate in utero. The factors that influence the formation of the initiating lesions are not well understood although the nature of these genetic aberrations is well documented and include in approximately a quarter of children the presence of the t12;21 chromosomal translocation that fuses the transcription factors Tel (ETV6) and Aml1 (RUNX1). The Tel-Aml1 fusion gene produces a pre-leukaemic clone but in and of itself is insufficient to produce frank leukaemic transformation. For this, additional mutations are required and it remains unclear what factors influence their acquisition. These additional mutations tend to arise in loci that are normally involved in cell fate control in the B lineage. Cell fate regulators act in a context dependent manner and thus understanding the nature of the target cell or cells in which the initiating and subsequent mutations arise is of importance.

Leukaemic clones appear to evolve in a branching manner such that at presentation the marrow is replete with multiple variegated subtypes proving a diverse substrate for selection in response to therapy. Beyond genetic heterogeneity, leukaemic cells exhibit epigenetic heterogeneity in respect of their immunophenotypes and functional properties including cell cycle status and niche residence. Despite the extensive nature of genetic and epigenetic variation in childhood ALL, all leukaemic cells remain dependent on continued expression of TEL-AML1.

This places emphasis on understanding the scope of TEL-AML1 target genes as well as the nature of the cells initially targeted by TEL-AML1. In respect of the latter we have explored lymphopoiesis in the emerging human embryo and recapitulated aspects of it using pluripotent human stem cells in vitro. These studies have tabled a candidate target cell for the in utero impact of TEL-AML1. Through CRISPR-directed homologous recombination we have introduced TEL-AML1 into the endogenous TEL-locus and consequently gained insight into the mechanisms by which TEL-AML1 initiates leukaemogenesis in utero.

TEL-AML1 hPSCs will afford the systematic evaluation of the contribution of additional mutations seen in cALL and may offer a tractable platform for drug screening.

About the Speaker:

Tariq Enver is Professor of Stem Cell Biology and Director of the UCL Cancer Institute. He is a Visiting Professor at Lund University and part of the Hemato-Linné Program. He is also a member of the 1000 Talents Programme in China, hosted by the Jiao Tong University in Shanghai. Tariq Enver leads the Cancer theme of the UCL Partners Academic Health Sciences Centre and is a member of the European Molecular Biology Organization.

His research career has been principally concerned with understanding the mechanisms by which stage specific gene expression is achieved and how it influences cell fate decisions. This has led to new insights into how blood stem cells are configured in molecular terms; knowledge which informs strategies for stem and progenitor cell amplification and functionalization for therapeutic use in stem cell transplantation. In parallel, he explores how chimeric transcriptional regulators associated with leukaemia corrupt cell fate decisions particularly in the context of childhood leukaemia. This work led to the concept of pre-leukaemic stem cells as well as the notion that leukaemic stem cells evolve through branching or polytypic evolution. More recently, his studies on childhood leukaemia emphasise epigenetic heterogeneity in stem cells as a source of therapy resistance.