Cancer Science Institute of Singapore

Distinguished Speakers' Series 2016

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Central Role for Super-Enhancers in T-Cell Acute Leukemia

Date: Monday, 10 October 2016
Time: 10am – 11am
Venue: LT35, Level 1, Centre for Translational Medicine (MD6)
(14 Medical Drive, Singapore 117599)
Chair: Dr Takaomi Sanda

Abstract:
Super-enhancers are regulatory elements that are normally found at genes that determine unique aspects of cell identity in diverse tissues during embryonic development. In T-cell acute lymphoblastic leukemia (T-ALL), the TAL1 oncogene is often aberrantly overexpressed due to somatically acquired chromosomal translocations or intra-chromosomal deletions. We have discovered a new mechanism mediating overexpression of TAL1, in which small somatic insertions are acquired that introduce binding motifs for the MYB transcription factor in a precise noncoding site, which creates a super-enhancer upstream of the TAL1 oncogene. MYB binds to this new site and recruits its binding partner CBP, which has H3K27 acetylase activity, as well as core components of a major leukemogenic transcriptional complex that contains RUNX1, GATA-3, and TAL1 itself. We have shown that MYB is responsible for initiating this super-enhancer by employing CRISPR/Cas9 technology to delete the insertion that forms the MYB binding site, and showing that this causes the super-enhancer to melt away. Our findings raise the possibility that acquisition of such enhancer mutations constitutes a general mechanism in the molecular pathogenesis of cancer, implicating enhancer elements within the non-coding genome as sites for discovery of somatic mutations that aberrantly upregulate oncogene expression. Drugs that target key components of the transcriptional machinery, such as BRD4 and CDK7, preferentially target tumor-specific super-enhancers at oncogenes essential for cancer cell growth and survival. Thus, super-enhancers, with the high levels of transcriptional machinery that they preferentially recruit, provide new targets for drug development to improve cancer therapy.

Biography:
A. Thomas Look, M.D., is a Professor of Pediatrics at Harvard Medical School and a member of the Department of Pediatric Oncology at the Dana-Farber Cancer Institute, as well as a co-Leader of the Dana-Farber/Harvard Cancer Center's Leukemia Program. He is the principal investigator on several NIH-funded grants, including a program project focusing on T-ALL pathogenesis. Over the past three decades, Look has published multiple peer-reviewed papers about the molecular basis of apoptosis and cancer and the application of molecular genetic findings to improve the treatment of childhood malignancies, particularly T-cell acute leukemia and neuroblastoma. He moved from St. Jude Children's Research Hospital to Dana-Farber Cancer Institute in 1999 specifically to establish a research program in the zebrafish model. He used this research to conduct genetic studies aimed at the identification of novel targets for cancer therapy, and he is now internationally recognized as a leader in this field. His laboratory has developed the first zebrafish transgenic model of T-cell acute lymphoblastic leukemia and childhood neuroblastoma, opening up the opportunity to apply the powerful genetic technology available in the zebrafish to identify new molecular targets for therapy in these childhood cancers. Look received his M.D. degree and postgraduate training in Pediatrics from the University of Michigan and his fellowship training in Pediatric Oncology at St. Jude Children's Research Hospital. Prior to his appointment at Harvard, he was a professor at the University of Tennessee College of Medicine.