Cancer Science Institute of Singapore

SEMINAR ANNOUNCEMENT

Ross LEVINE

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Genetics and Therapy of Myeloid Malignancies

Date: Monday, 16 January 2017
Time: 10.30am – 11.30am
Venue: LT36, Level 3, CeTM (MD6) (14 Medical Drive, S117599)
Host: Prof Daniel Tenen

Abstract:

Clinical, cytogenetic, and gene-based studies have been used to inform biology and improve prognostication for patients with acute myeloid leukemia (AML), myelodysplasia (MDS), and myeloroliferative neoplasms (MPN). Most recently, a series of candidate gene and whole genome studies have identified recurrent somatic mutations in AML patients including TET2, ASXL1, DNMT3A, and cohesin complex mutations. Moreover, these mutations can be used to improve risk stratification in AML independent of established clinical parameters. Integrating mutational data with dose-intensity revealed that high-dose daunorubicin improved survival in patients with DNMT3A/NPM1 mutations or MLL translocations relative to treatment with standard dose daunorubicin, but not in patients wild-type for these alterations. These data provide important clinical implications of genetic alterations in AML by delineating mutation combination genotypes that predict outcome in AML and improve AML risk stratification. Of biologic importance, the TET family of proteins have been shown to place a hydroxyl mark on methylated DNA and lead to DNA demethylation. We and others have found that TET2/IDH mutations leads to loss of DNA hydroxymethylation and a hypermethylation phenotype in leukemia patients. In addition, in vitro and in vivo studies show that TET2 loss or neomorphic IDH1/2 mutations leads to impaired hematopoietic differentiation, increased stem cell self-renewal, and myeloid transformation *in vivo*. We have also investigated the role of mutant DNMT3A in AML pathogenesis, and shown these mutations cooperate with other disease alleles to induce leukemic transformation and to confer chemoresistance due to impaired DNA damage sensing. We will present novel data showing how these mutations coopt the epigenetic state of hematopoietic stem/progenitor cells in order to contribute to transformation and that these mutations have biologic and prognostic relevance.

Biography:

Ross Levine, MD, is a Member of the Human Oncology and Pathogenesis Program and an Attending Physician on the Leukemia Service, Department of Medicine and is the Laurence Joseph Dineen Chair in Leukemia Research and the director of the MSK Center for Hematologic Malignancies and a Professor of Medicine at Weill Cornell Medical College. Dr. Levine received his AB from Harvard College and a M.D. from Johns Hopkins. Dr. Levine served as a Resident in Internal Medicine at the MGH and subsequently as a Hematology-Oncology Fellow at DFCI. He then joined Gary Gilliland's laboratory as a postdoctoral fellow and performed kinome sequencing at the Broad Institute to identify JAK2V617F and MPL mutations in MPN patients. In September 2007 he was recruited to MSK to the Human Oncology and Pathogenesis Program while he sees patients on the Leukmia Service. His laboratory has identified MPN predisposition alleles and characterized somatic genetic alterations in MPN patients, which has improved our understanding of the genetic basis of MPNs. His lab also investigates the role of somatic mutations in epigenetic modifiers in MPN and in AML.