

## **Postdoctoral - Pediatric Oncology - role of PASG (HELLS) in leukemia, embryogenesis and aging**

A funded **POSTDOCTORAL POSITION** is available to study epigenetic mechanisms controlling normal development and in high risk pediatric cancers, with an emphasis on the role of PASG (HELLS) in leukemia, embryogenesis and aging.

**Please submit a curriculum vitae and names and contact information for three references by mail and/or email to: Dr. Robert J. Arceci, 1650 Orleans Street, CRB Room 207, Kimmel Comprehensive Cancer Center at Johns Hopkins E-mail: arcecro@jhmi.edu**

Our laboratory is focused on the elucidation of fundamental mechanisms of cell growth, survival and senescence during normal and neoplastic development with the overall goal of identifying novel pathways for epigenetic, signal transduction pathways and immunologic therapeutic targeting of leukemia and solid tumors. A primary focus area of our laboratory involves the analysis of epigenetic mechanisms during development, cancer pathogenesis and senescence/premature ageing. Our work on understanding of the molecular pathways contributing to leukemia cell survival and stem cell expansion resulted in the identification of a novel chromatin remodeling factor, which we termed PASG, for Proliferation Associated SNF2-like Gene.

The generation of a knock-out mouse model of PASG demonstrated that this gene product is a facilitator of DNA methylation and epigenetic patterning during development. Without PASG, mice develop genomic hypomethylation and premature aging due to altered gene expression and replicative senescence that in turn lead to a defective ability to expand hematopoietic and other types of stem cells. Because PASG was identified from a human leukemia cell line from which Stem Cell Factor had been withdrawn, we examined acute leukemia samples for mutations in PASG and identified an in-frame deletion of a conserved functional domain in a high percentage of leukemia samples. This in-frame deletion variant lacks the ability to facilitate DNA methylation and interact with DNA methyltransferases. In addition, the PASG variant is associated with complex karyotypes, distinct alterations in gene expression patterns, decreased genomic methylation and poor outcome in AML. We are currently pursuing these findings to better understand epigenetic patterning in leukemic stem cells as well as developing approaches to identify treatment approaches that induce replicative senescence in leukemia. In addition, these studies are being extended to do genome-wide mapping of transcriptional profiles, DNA losses and gains, epigenetic mapping as well as small molecular and siRNA screening of potential therapeutic pathways for pediatric high risk sarcomas and leukemia.

Another area of work in the laboratory concerns the analysis of the role of altered ribosome biogenesis in bone marrow failure and cancer predisposition. This work is based in part on our identification of a mutated large ribosomal protein as the basis for Diamond Blackfan anemia. A third area of work is focused on the further development of a human anti-CD1a monoclonal antibody for immunotherapeutic targeting of leukemia and Langerhans cell Histiocytosis as well as in graft versus host disease prevention and the augmentation of anti-cancer vaccines.