"Large-scale Studies of the Epigenetics of Human Leukemia"

Principal Investigator:
- Bradley Bernstein, MD, PhD, Broad Institute of MIT and Harvard

Co-Principal Investigators:
- Alexander Meissner, PhD, Broad Institute of MIT and Harvard
- Ross Levine, MD, Memorial Sloan-Kettering Cancer Center

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Abstract: Malignant transformation is associated with widespread changes in cell signaling and gene expression. These changes can result from genetic alterations and, accordingly, many pathogenetic mutations have been identified in human cancers. Alternatively, they can reflect aberrant epigenetic mechanisms that, for example, confer stable silencing of tumor suppressor genes. Yet in stark contrast to high-throughput characterizations of genetic mutations in cancer, the study of cancer epigenetics has largely consisted of *ad hoc* analysis of individual candidate genes.

Over the past year, we developed two complementary methods that have transformed our ability to study human epigenetics. These methods leverage state-of-the-art sequencing technology to efficiently acquire genomewide maps of histone modifications and DNA methylation. The goal of this project is to apply these tools towards comprehensive characterization of the epigenetics of human leukemia. We hypothesize that genetic aberrations known to underlie leukemogenesis co-exist and synergize with specific epigenetic changes. We propose to characterize the epigenetic landscapes of acute leukemias with defined genetic aberrations by systematically profiling histone modifications and DNA methylation in cell lines and primary samples (Aims 1 and 2). To gain insight into the mechanistic relationships and causality among the genetic and epigenetic alterations, we will study how phenotypes are altered by shRNA knockdown or small-molecule modulation of implicated genetic and epigenetic factors (Aim 3). The proposed studies would represent the first comprehensive characterization of any cancer epigenome, and should provide essential insight into how genetic and epigenetic mechanisms synergize in hematopoietic transformation.