Abrogating clonal evolution and myeloid transformation by targeting epigenetic plasticity

Principal Investigator:
- Vijay Sankaran, MD, PhD - The Broad Institute of MIT and Harvard

Co-Principal Investigators:
- Peter van Galen, PhD - The Broad Institute of MIT and Harvard
- Ross Levine, MD - Memorial Sloan Kettering Cancer Center

Abstract: Approximately 20,000 people are diagnosed with acute myeloid leukemia (AML) in the US each year. This disease is preceded by the acquisition of leukemia-associated mutations in hematopoietic stem cells (HSCs), leading to clonal expansion of blood stem/progenitor cells. This pre-malignant state, termed clonal hematopoiesis (CH), is common in aged individuals and can often be detected years before the diagnosis of AML. The most common pathogenic mutations in CH impair DNMT3A, an epigenetic enzyme that regulates differentiation through its DNA methyltransferase activity. However, the specific molecular machinery that is altered as a consequence of DNMT3A inactivation remains poorly understood. Our objectives are to discover features associated with the expansion of DNMT3A-mutated subclones at premalignant and malignant disease stages, and to test if restoring wild type enzymatic activity can reinstate epigenetic constraints. Towards these goals, we will compare human DNMT3A wild type and mutated cells from the same bone marrow environment in two contexts, CH and AML, leveraging single cell genomic tools we developed to track epigenomic and transcriptomic states in specific clones. We will also determine the reversibility of Dnmt3a-mediated clonal expansion using an innovative inducible/reversible mouse model that allows restoration of wild-type Dnmt3a expression. Together, these studies will establish whether DNMT3A-mutated clones exhibit features that render them vulnerable to therapeutic targeting to prevent the progression of CH to AML. Our approach will lead the way to broader studies of the mechanisms driving clonal expansion in different tissue contexts and advance the concept of targeting pre-malignant cells for cancer prevention.