**Discovery of AID-dependent Epigenetic Mechanisms in Hematological Malignancies**

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**Abstract:** Our goal is to discover and target epigenetic mechanisms that contribute to hematological malignancies. Our focus is activation-induced cytidine deaminase (AID), a gene that regulates cytosine methylation patterns. We hypothesize that AID controls the epigenetic landscape of hematopoietic stem/progenitor cells, and can impact cancer by regulating DNA methylation patterns, irrespective of mutator activity. Our preliminary data suggest that AID functions as a tumor promoter in lymphoma, and as a tumor suppressor in myeloid leukemia. Using mouse models of lymphoma and leukemia we will 1) Determine whether AID is required to maintain self-renewal and tumor repopulating properties of DLBCL and how this is linked to its effects on cytosine methylation, and 2) Discover mechanisms by which AID functions as a tumor suppressor through resistance to a leukemia stem cell phenotype. We have also developed a novel reprogramming assay using AID-null fibroblasts that revealed AID-dependent functions at two distinct transitional stages: first for maintaining a committed state, and secondarily for stabilizing a stem cell phenotype. We propose to use this tightly controlled *in vitro* system to model both the putative tumor promoter and tumor suppressor capacities of AID. Our experiments will map AID-dependent epigenetic programs and use enhanced computational methods to discover targetable pathways. To achieve our goals, we built a consortium of collaborative investigators with expertise in AID, lymphoma, leukemia, epigenetics, stem cell biology, and computational genomics. This project will reveal at the genome-wide level AID-dependent epigenetic mechanisms that impact lymphoma and leukemia and thereby identify novel therapeutic targets.