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Diffuse large B-cell lymphoma (DLCL) is the most common type of lymphoma affecting ~30,000 patients annually. Recent insights into the molecular pathogenesis of DLBCL has divided this disease into two molecular subtypes: germinal center (GC) and ABC subtypes. Targeting molecular features of ABC-DLCL are in the final stages of development, but such success has not been realized for the more common GC-DLCL. The GC is a compartment of the lymph node responsible for generating high affinity antibodies via somatic hyper-mutation and class switch recombination. Epigenetic modifiers such as EZH2, histone acetyltransferases (HATs), and the transcriptional repressor, Bcl6, are essential to B-cell development allowing for requisite mutagenesis and silencing of tumor suppressors necessary for somatic hypermutation. This physiologic state is partly achieved by decreased acetylation and increased methylation of histones enforcing a transcriptionally repressed state. Mutations affecting these epigenetic and transcriptional modifiers, HATs, EZH2 and Bcl6, have been identified as driving events in GC-derived lymphomas.

Given the critical importance of epigenetic dysfunction in the pathogenesis of GC-derived B-cell lymphomas, we hypothesize that if inactivating mutations in HAT alleles are crucial to GC-DLCL then drugs activating the wild-type enzyme should demonstrate therapeutic effect. In addition, we believe that combined targeting of epigenetic machinery with HAT activators and other epigenetic modifying agents (HDAC and EZH2 inhibitors) may induce profound epigenetic modification leading to synergistic induction of programmed cell death. Finally, if mutational status and expression levels of specific genes such as EP300 correlate with response to HAT activators or combined epigenetic therapy, then a NanoString expression panel may be developed as a biomarker for response.

The objectives of this proposal will be evaluated by addressing the following specific aims: (1) Characterize the HAT activator YF2 by determining binding to HAT enzymes and its functional effects on acetylation in cell-free assays. (2) Determine the effects of HAT activators in combination with clinically available epigenetic modifying agents in cell lines and mice. Epigenetic modifying agents will include HDAC and EZH2 inhibitors. The effects of HAT activators in combination with epigenetic modifying agents on post-translational modifications (methylation, acetylation), and gene expression of downstream targets will be determined. (3) Interrogate the mutational status of EP300 and epigenetic gene signatures of lymphoma cell lines to inform precision targeting with HAT activators. Basal gene mutation and expression profiles will be determined for candidate epigenetic and transcriptional modifiers in lymphoma cell lines and will be correlated to the IC50 of HAT activators and the synergy coefficients of combined epigenetic therapy. Should we accept these hypotheses, this would represent an opportunity to directly target mutations, such as HAT and EZH2, which drive GC-DLCL.