Targeting the Chromatin Reader Protein TRIM33 as Epigenetic Therapy in B Cell Neoplasms

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Abstract: Therapeutic targeting of lineage-specific dependencies has shown significant clinical benefit in patients with B cell malignancies, since reversible inhibition of normal B cell production and function is well tolerated in most individuals. Using an shRNA screening approach, we have identified the chromatin reader protein TRIM33 as a lineage dependency in cancers of B cell origin. The proposed research seeks to develop TRIM33 as a novel drug target in B lymphoid cancers, including B-ALL, B cell lymphomas, and multiple myeloma. This will be accomplished by first defining the spectrum of B cell neoplasms that are dependent on the chromatin reader functionality of TRIM33, using human cancer cell lines and primary patient-derived samples. The goal of such studies will be to identify patient populations that would be most suitable for evaluating TRIM33-inhibition as a therapeutic strategy. Furthermore, we will perform detailed biochemical studies of TRIM33 function to define its key downstream target genes that are relevant for cancer maintenance. Finally, we will develop small-molecule inhibitors of the PHD-Bromodomain functionality of TRIM33 for mechanistic study and for development as novel therapeutics. This innovative research plan will integrate epigenomics, shRNA mouse transgenics, genome editing, discovery chemistry, and structural biology approaches to develop a novel epigenetic therapy. It is anticipated that these studies will lead to detailed molecular insight into a novel therapeutic target in oncology and provide a strong foundation for future drug discovery campaigns.