Discovery of Epigenetic Drivers of Tumor Evolution

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Abstract: Intra-leukemic genetic heterogeneity in chronic lymphocytic leukemia (CLL) impacts clonal evolution and clinical outcome (Landau et al., Cell, 2013, Nature, 2015; Burger et al., Nature Communications, 2016). Nevertheless, as cellular phenotypes result from both genetic and epigenetic alterations (Landau et al., Cancer Cell, 2014), we seek to develop methods for unbiased discovery and high-throughput validation of epigenetic drivers (epi-drivers) of CLL progression and relapse. First, to identify candidate epidrivers of CLL progression and relapse, we will perform bulk and single cell bisulfite sequencing on large cohorts of longitudinally sampled patients treated with chemoimmunotherapy or targeted therapy. We will utilize newly developed statistical inference methods, to identify recurrently differentially methylated regions. These methods improves on existing approaches, by taking into account the background stochastic methylation variation and use principles of genetic driver inference algorithms. Second, to enable scalable validation of epidrivers, we will apply an innovative epigenetic editing approach using Cas9 coupled with a methylase, to screen hundreds of putative epidrivers in vitro for impact on growth and drug response. Collectively, these studies are anticipated to propel the field of epidriver discovery forward generating novel tools for statistical inference to replace current approaches that are based on naive background models. Furthermore, we will develop robust and scalable methods to screen and validate these epidrivers. Thus, we anticipate that these studies will catalyze a new field of exploration with vast potential akin to the tremendous impact of statistical inference and functional screen tools on genetic drivers of cancer.