Thesis Abstract:

Human hematopoietic stem cells (HSCs) are responsible for meeting enormous daily demands for blood production. Adaptations to stress over a lifetime, together with the acquisition of somatic mutations, contribute to heterogeneity within the HSC pool with downstream implications for human disease. In leukemia, variation within disease-driving leukemia stem cells (LSCs) contributes to both intra-patient and inter-patient disease heterogeneity. In this thesis, I consider stem cell heterogeneity in the context of both normal and malignant hematopoiesis.

First, I have co-discovered a novel human HSC state termed the Inflammatory Memory HSC (HSC-iM). HSC-iM retains transcriptional and epigenetic memory of prior inflammatory stress and transmits these inflammatory programs to downstream progeny. HSC-iM-specific molecular programs are up-regulated within human HSCs after recovery from severe COVID-19 infection and accumulate within the HSC pool in older age. Somatic mutations in DNMT3A and TET2 preferentially impact gene expression within HSC-iM compared to other HSC subsets, and the impact of these mutations on HSC-iM may provide a new mechanism for understanding the age-related expansion of mutant clones in clonal hematopoiesis.

Second, my studies of heterogeneity within disease-driving LSCs in acute myeloid leukemia (AML) and the cellular hierarchies that they sustain has resulted in a new framework for understanding inter-patient heterogeneity in AML. Variation in AML cell hierarchy composition along the Primitive vs Granulocyte-Monocyte Progenitor (GMP) axis predicts patient survival while variation along the Primitive vs Mature axis predicts sensitivity to biologically targeted therapies. I demonstrate that gene expression scores capturing AML hierarchy composition predict response to investigational drugs in vitro, in vivo, and within clinical trials.

Third, I have constructed single-cell transcriptomic atlases of human hematopoietic differentiation to better understand cellular heterogeneity in acute leukemia. I used these reference atlases to map millions of single-cell transcriptomes in the context of AML and B-cell acute lymphoblastic leukemia (B-ALL), capturing the differentiation landscapes of hundreds of acute leukemia patients. This has linked genetic driver alterations to specific differentiation phenotypes and provided insight into the cellular origins of each patient's disease. In B-ALL, quantification of cell states with multipotent lineage potential has led to the development of a novel prognostic signature.