Modulating inflammation to eradicate clonal stem cells

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Abstract**:** Inflammatory signaling accelerates clonal evolution in clonal hematopoiesis (CH) and myeloid neoplasms. However, we currently have limited understanding of how inflammatory cues modulate clonal fitness. To fill this gap, we have identified pathways by which type 1 interferon (IFN) curates the hematopoietic stem cell (HSC) pool via single-cell lineage tracing methods in zebrafish and human. We had previously identified in zebrafish that surface expression of CALR on HSCs mediates interactions with macrophages that lead to phagocytosis of HSCs with elevated reactive oxygen species (ROS), resulting in 'dooming'. However, IFN signaling induced by endogenous retroviruses (ERVs) blocked phagocytosis via the 'don't eat me' signal B2m, leading to 'grooming'. In human, we identified that IFN treatment led to a precipitous activation of a subset of HSCs into an alternate differentiation pathway via the inflammatory granulocytic progenitors (IGP), thereby depleting HSC clones. We will manipulate these three modes of stem cell curation, by selectively inducing CALR and ROS to cause dooming of the clonal stem cells (Aim 1), identifying ERVs that regulate B2m expression and grooming in mutated clones (Aim 2), and inducing differentiation of the mutated stem cells into the alternate differentiation pathway (Aim 3). We will achieve these aims via advanced single-cell multi-omics and cellular barcoding models, combined with high-throughput screens, to preferentially target the mutated clones in CH and myeloid neoplasms.