Project Proposal Abstract to NIH

The transcription factor FOXP3 is critical to the regulation of numerous debilitating human immune-mediated diseases. Very recently, the essential role for the histone methyltransferase (HMT) EZH2 in the epigenetic regulation and function of FOXP3 has been described. Inflammatory pathways modify EZH2 activity, and inflammatory signaling impairs Treg function in vivo and in vitro. The biological impact of the FOXP3-EZH2 pathway to IBD is unknown. Our long-term goal is to dissect epigenetic mechanisms regulating Treg cellular differentiation and function, particularly within the setting of GI inflammatory diseases. These discoveries will facilitate design of human cell therapy trials for IBD.

The objective of this grant is to characterize the role for EZH2 in Treg suppressive function. The central hypothesis is that EZH2 plays a critical role in the homeostasis of Treg cells, and the disruption of EZH2 function by inflammatory signaling pathways contributes to IBD. Our rationale is that identification of the mechanism(s) to restore Treg suppressive function in the setting of intestinal inflammation will offer new therapeutic opportunities. Our specific aims will test the following hypotheses: (Aim1) Repression of immunoregulatory gene networks by FOXP3 requires the formation of a complex between this transcription factor and EZH2; (Aim 2) Inflammatory stimuli, such as IL6 lead to EZH2 phosphorylation and thereby disrupt the enzymatic activity of this epigenomic regulator; (Aim 3) Inhibition of the IL6 to EZH2 signaling pathway permits sustained Treg suppressive function in the setting of intestinal inflammation. Upon conclusion, we will understand the role for EZH2 in Treg loss of function in the setting of active inflammation. This contribution is significant since it will establish that several pathways targeted by available therapies (ie IL1β, IL6, TNFα) have the potential to regulate EZH2 HMT activity through post- translational modifications. Furthermore, current Treg cell therapy trials, while promising have not addressed the key issue of in vivo inflammation-induced disruption of Treg function.

The proposed research is innovative because we investigate the effect of inflammatory signaling pathways on epigenetic complexes in Treg cells, a heretofore-unexamined process. Insight into epigenetic mechanisms is impactful as T cell progenitor cells inherit the parent transcriptional profile and unlike genetic change, they are modifiable by currently available therapy.