DESCRIPTION: My career goal is to direct an independent research group studying the nature and function of chromatin factors that control hematopoietic cell fate. My research background in epigenetic gene regulation plus my developing expertise in zebrafish genetics and hematopoiesis provide me with the knowledge to perform the proposed research. The training program in the hematology/oncology division at Children’s Hospital and Harvard Medical School provides an outstanding environment for the completion of training during the mentored phase. This will greatly facilitate my smooth transition to independence.

Hematopoiesis is controlled by complicated genetic programs involving tissue-specific transcription factors and chromatin remodeling factors. Understanding the regulatory mechanism of hematopoiesis provides significant insight into the pathophysiology of human blood malignancies such as leukemia. The transcription intermediary factor $TIF1y$ is a critical factor for hematopoiesis yet the mechanism is not well understood. Through a large-scale genetic suppressor screen using the zebrafish $T/F1r$ mutant, I identified two suppressor mutants that can bypass the requirement of $T/F1r$ and restore blood in $TIF1y$-deficient animals. Initial characterizations of these mutants suggest a fundamental role of $TIF1y$ in regulating transcriptional elongation and chromatin remodeling during hematopoiesis. The research described in this proposal is designed to elucidate the mechanism by which $TIF1y$ regulates these processes. Aim1 will use chromatin immunoprecipitation (ChiP) analyses to thoroughly examine the distribution of RNA polymerase II and associated histone markers on blood genes in $TIF1y$-deficient cells. Aim2 will use the available conditional knockout mice to investigate the function of $TIF1r$ and its suppressors in mammalian hematopoiesis. Aim3 will focus on the in-depth characterization of the interaction between $TIF1r$ and the cohesin chromatin remodeling complex using genetic and biochemical approaches. Completion of these aims will reveal the interplay among transcription factors, elongation factors and chromatin remodelers during hematopoiesis. Given the involvement of transcriptional elongation and chromatin modification in a variety of human disorders, these studies will advance our understanding of their roles in the pathogenesis and progression of these maladies and may also identify candidate genes or pathways that can be used for developing novel targeted treatment strategies.