Project Summary

Background: Pulmonary hypertension (PH) is a deadly disease of the lung vasculature with a complex pathophysiology that remains largely undefined. My mentor's laboratory established the microRNA-130/301 family as a mediator of PH development and defined a separate mechanism by which iron-sulfur (Fe-S) cluster deficiency promotes PH. Fe-S clusters are bioinorganic cofactors essential to mitochondrial and cellular function. Frataxin (FXN) is a mitochondrial protein crucial to Fe-S biogenesis. Loss of FXN due to a trinucleotide repeat mutation causes Friedreich's ataxia (FRDA), a disease characterized by neurologic dysfunction and hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy is often accompanied by PH, thought to be the result of left ventricular stiffening rather than direct dysfunction of the pulmonary vessels. However, I have found that hypoxia, a key trigger of PH, down-regulated FXN expression in pulmonary arterial endothelial cells. FXN was also decreased in the pulmonary vasculature of mice and humans with PH. Consequently, such FXN deficiency altered endothelial mitochondrial, vasomotor, apoptotic indices, thus leading to preliminary data regarding the alteration of PH *in vivo*. Taken together, there may be a direct role for FXN in PH. **Hypothesis: FXN deficiency, induced by hypoxia or genetic mutation, disrupts endothelial metabolism and function to promote PH.**

Specific Aims: **1) Determine whether hypoxic down-regulation of FXN is controlled by miR-130b.** I have found that the FXN transcript contains a possible binding site for the PH-relevant miR-130b. By gain- and loss-of-function methods in pulmonary arterial endothelial cells, I will determine whether hypoxia-induced miR-130b decreases FXN expression, thus defining a causative relationship among miR-130b, FXN, and Fe-S biogenesis.

2) Determine whether FXN loss attenuates mitochondrial respiration and endothelial function. In primary endothelial cells and inducible pluripotent stem cell-derived endothelial cells (iPSC-ECs) from FRDA patients, I will test the hypothesis that FXN deficiency induces Fe-S cluster-dependent mitochondrial dysfunction, resulting in endothelial phenotypic changes (*e.g.*, apoptosis, proliferation). If successful, findings could establish a key link between hypoxia- or genetically-driven FXN loss and endothelial dysfunction consistent with PH.

3) Establish whether FXN loss and resulting mitochondrial dysfunction predisposes to PH *in vivo*. In a tamoxifen-dependent endothelial cell FXN knockout mouse model, I will test the hypothesis that FXN deficiency in the pulmonary endothelium promotes molecular, histologic, and hemodynamic changes consistent with PH. If successful, these results will validate an integral and direct role for FXN in the development of PH.

Significance: This project is ideally structured to train me as a physician-scientist and bridge the gap between basic science and clinical medicine. I aim to contribute to the currently deficient understanding of Fe-S assembly proteins in endothelial function. I could also identify FXN as a key pathogenic factor in PH, offering the potential of diagnosing FRDA patients at risk for PH and defining FXN as a new drug target to benefit all PH patients.