MEDICAL SCIENTIST TRAINING PROGRAM

University of Pittsburgh & Carnegie Mellon University

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The Division of Receipt and Referral
Center for Scientific Review
6701 Rockledge Drive MSC 7720
Bethesda, MD 20892-7720

NIH Research Grant Program: **Ruth L. Kirschstein Individual Predoctoral NRSA for MD/PhD Fellowships**

Dear Scientific Review Committee Members:

I am pleased to submit the grant proposal entitled "**Frataxin loss induces endothelial dysfunction to promote pulmonary hypertension**" for consideration under the Ruth L. Kirschstein Individual Predoctoral NRSA for MD/PhD Fellowships program with PA number PA-16-305, as discussed with Drew E. Carlson, Ph.D.

Please assign this application to the following:

Institute: **National Heart, Lung, and Blood Institute – NHLBI**

Study Section: **Physiology and Pathobiology of Cardiovascular and Respiratory Systems – F10A**

Pulmonary hypertension is a progressive disease of the lung vasculature with a complex pathophysiology that remains largely undefined. Recent discoveries illustrated that iron-sulfur cluster deficiency results in the development of pulmonary hypertension. Iron-sulfur clusters are bioinorganic cofactors required for a wide range of metabolic and cellular processes. Frataxin is a mitochondrial protein essential to iron-sulfur cluster assembly. Interestingly, frataxin deficiency, driven by a trinucleotide repeat mutation, causes the neurologic disease Friedreich's ataxia. Patient mortality is driven by hypertrophic cardiomyopathy, which is often accompanied by pulmonary hypertension thought to be the result of left ventricular stiffening and hypertrophy. However, my preliminary data demonstrated frataxin expression is down-regulated in human pulmonary arterial endothelial exposed to hypoxic conditions as well as in the pulmonary arteries of mice and humans with PH, suggesting a direct role for frataxin in pulmonary hypertension. **Therefore, I hypothesize that frataxin deficiency, driven by genetic or acquired triggers, induces endothelial metabolic dysfunction to promote pulmonary hypertension.** In this proposal, I will purse three aims: 1) Determine whether hypoxic down-regulation of FXN is controlled by miR-130b, 2) determine whether FXN loss attenuates mitochondrial respiration and endothelial function, and 3) establish whether FXN loss and resulting mitochondrial dysfunction predisposes to PH *in vivo*.

My proposal seeks to define a novel mechanism centered on the direct role of frataxin in the development of pulmonary hypertension. If successful, my results will support the critical role of iron-sulfur clusters and their assembly proteins in acquired human disease. More specifically, the

proposal could improve the management of a cohort of Friedreich's ataxia patients and illuminate novel drug targets for the treatment of pulmonary hypertension. Taken together, this proposal employs unique *in vitro* and *in vivo* models to interrogate a key pathogenic mechanism of metabolic dysfunction in the pulmonary vasculature. Therefore, this project aligns with the mission of the National Heart, Lung, and Blood Institute and should be reviewed by the Physiology and Pathobiology of Cardiovascular and Respiratory Systems study section.

List of Referees	**Affiliations**
Stanley L. Hazen, M.D.,Ph.D.	Department of Cellular and Molecular Medicine, Center for Cardiovascular Diagnostics and Prevention, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH
Mark T. Gladwin, M.D.	Vascular Medicine Institute, Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA
Richard A. Steinman, M.D.,Ph.D.	Department of Medicine, University of Pittsburgh Cancer Institute, Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA

Thank you very much for your consideration.

Regards,

Miranda K. Culley
MD/PhD Candidate
Medical Scientist Training Program
University of Pittsburgh School of Medicine