**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Miranda Culley

eRA COMMONS USER NAME (credential, e.g., agency login): MIRANDACULLEY

POSITION TITLE: MSTP Trainee

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | Start Date MM/YYYY | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|---|
| Case Western Reserve University, Cleveland, OH | B.A. | 08/2010 | 05/2014 | Biochemistry, Classics |
| University of Pittsburgh School of Medicine, Pittsburgh, PA | M.D., Ph.D. | 06/2014 | 05/2022 | Medicine, Cellular and Molecular Pathology |

**A. Personal Statement**

I am a first-year graduate student pursuing combined MD/PhD training at the University of Pittsburgh-Carnegie Mellon Medical Scientist Training Program (MSTP). I have chosen a dual-degree program with the goal to become an independently funded physician scientist at a large academic medical institution. I envision a dynamic career in translational cardiovascular research in which I merge both clinical medicine and basic research to identify novel diagnostic and therapeutic markers of disease. I will complete my thesis work in the laboratory of Dr. Stephen Y. Chan studying how frataxin deficiency promotes the development of pulmonary hypertension by attenuating iron-sulfur biogenesis, mitochondrial respiration, and pulmonary endothelial function. My work leverages cutting-edge technologies in molecular biology and unique *in vitro* and *in vivo* models to define a novel mechanism of pulmonary hypertension development converging on frataxin. My results will support an emerging role for iron-sulfur biology in complex acquired diseases like PH, improve the management of a new cohort of Friedreich's ataxia patients, and identify important drug targets for future PH therapy. My scientific pursuits will be complemented by the constant mentorship of Dr. Chan. The Chan laboratory and the Vascular Medicine Institute as a whole provide a collaborative, innovative environment for both intellectual and professional development. Coupled with the supportive environment of the Cellular and Molecular Pathology graduate program and the MSTP, I am confident that I am well-positioned to successfully complete my project proposal and receive the scientific, technical, and ethical training to propel my career as a physician scientist.

I believe my past research experiences and accomplishments provide a solid foundation for these pursuits. Notably, my time as an undergraduate research student at the Center for Preventative Cardiology in the Lerner Research Institute inspired my choice for a dual-degree and guided the evolution of my career goal. There I had the privilege of working within Dr. Stanley L. Hazen's laboratory where we sought to characterize the link between high dietary lipid intake, the gut microbiome, and atherosclerosis. This opportunity provided me with applicable laboratory skills in molecular genetics, mass spectrometry, organic synthesis, and the use of *in vivo* models. I was able to make productive contributions to several ongoing lab projects, as reflected by the peer-reviewed co-authorships in *Cell Metabolism, Cell,* and *Nature Medicine*. Most importantly, I had the great fortune of working with dedicated, innovative mentors. Since joining the MSTP in June 2014, I have successfully completed my first two years of medical school, the USLME Step 1 examination, and one clinical clerkship in Neurology and Psychiatry as well as three graduate research rotations that broadened my scientific understanding and technical skill set. Together, these opportunities have strengthened my desire to become a physician scientist with a focus in translational cardiovascular medicine. Combined with the "Training Plan" outlined in the proposal, I believe

this fellowship would be instrumental in developing the scientific, technical, and ethical skills necessary for a future role as an independent physician-scientist.

**B. Positions and Honors**

| ACTIVITY/ OCCUPATION | START DATE (mm/yy) | ENDING DATE (mm/yy) | FIELD | INSTITUTION/ COMPANY | SUPERVISOR/ EMPLOYER |
|---|---|---|---|---|---|
| Undergraduate Research Student | 01/2011 | 05/2015 | Preventative Cardiology | Lerner Research Institute, Cleveland Clinic | Stanley L. Hazen, M.D., Ph.D |
| Graduate Student Rotation I | 06/2014 | 08/2014 | Pathology, Surgery | UPMC | Timothy R. Billiar, M.D. |
| Medical Student | 06/2014 | Present | Medicine | University of Pittsburgh School of Medicine | |
| Graduate Student Rotation II | 06/2015 | 08/2015 | Cell Biology and Molecular Physiology, PACCM | UPMC | Rama K. Mallampalli, M.D. |
| Graduate Student | 07/2016 | present | Pathology, Medicine | UPMC | Stephen Y. Chan, M.D., Ph.D. |

**Selected Honors**

| | |
|---|---|
| 2010-2014 | Provost Merit Scholarship Recipient 2010-2011 |
| 2011-2014 | Dean's High Honors, August 2010 – May 2014 |
| 2014 | Flora Stone Mather Memorial Award, *for an outstanding student in the humanities* |
| 2014 | Utter Prize Recipient, *for an outstanding biochemistry undergraduate* |
| 2014 | Summa cum laude, Case Western Reserve University |
| 2014-present | Phi Beta Kappa Society |
| 2016-present | Angiopathy Training Program |

**C. Contributions to Science**

**Understanding the role of the intestinal microbiome in cardiovascular disease**

(Mentors: Stanley L. Hazen, M.D., Ph.D., Joseph Didonato, Ph.D., Robert A. Koeth, M.D., Ph.D.)

The Hazen laboratory demonstrated that the gut microbiota-mediated metabolism of two trimethylamine-containing dietary lipids – phosphatidylcholine and *L*-carnitine – promotes atherosclerosis. Ingested lipids are metabolized to an intermediate compound, trimethylamine (TMA), that is further oxidized by the liver to trimethylamine-*N*-oxide (TMAO). TMAO is an independent predictor of major adverse cardiovascular events in humans. Specifically, TMAO promotes cholesterol accumulation as well as platelet aggregation and risk of thrombosis. First, I helped characterize a dominant product of *L*-carnitine, *Gammabutyrobetaine (γBB*), which is also converted to TMA in a gut-microbiome-dependent manner. Chronic dietary exposure to *L*-carnitine or γBB promotes development of functionally distinct microbial communities optimized for the metabolism of L-carnitine or γBB, thereby linking lipid intake with a pro-atherogenic microbiome. As a co-author, my contributions included performing or assisting in all animal studies, proteomic mass spectrometry analysis, and organic synthesis in addition to data analysis, creating figures, and aiding in the drafting of the manuscript (a). Separately, the laboratory investigated the impact of targeted inhibition of commensal microbial TMA production with 3,3-dimethyl-1-butanol (DMB) on diet-induced atherosclerosis. Results showed decreased TMAO blood levels and atherosclerotic lesion development in *ApoE-/-* mice fed these lipids. As a co-author, I assisted with animal diet-challenges and harvest as well as the aortic tissue sectioning, staining, and quantification (b).

a. Koeth RA, Levison BS, **Culley MK**, Buffa JA, Wang Z, Gregory JC, Org E, Wu Y, Li L, Smith JD, Tang WH, DiDonato JA, Lusis AJ, Hazen SL. γButyrobetaine is a proatherogenic intermediate in gut microbial metabolism of *L*-carnitine to TMAO. *Cell Metab*. **20**, 799-812 (2014). PMCID: PMC4255476
b. Wang Z, Roberts AB, Buffa JA, Levison BS, Zhu W, Org E, Gu X, Huang Y, Zamanian-Daryoush M, **Culley MK**, DiDonato AJ, Fu X, Hazen JE, Krajcik D, Didonato JA, Lusis AJ, Hazen SL. Non-lethal