NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT

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Genetic Contribution to HET3 Aging Mice Variation in Exercise Capacity Trainability

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How did you become interested in aging?

I became interested in aging research while completing my postdoctoral fellowship at the National Institute of Environmental Health Sciences. My postdoctoral mentor – Dr. Steven Kleeberger – had just started considering the role of mitochondria and mitochondrial genetics in pulmonary diseases. I joined his lab as a postdoctoral fellow to gain knowledge and expertise in mitochondrial biology and genetics, combined with expertise in exercise physiology. Endurance or aerobic exercise training is the most effective modality for enhancing mitochondrial function, which we know declines with biological aging, and their dysfunction is linked to a host of age-related diseases. Given both endurance trainability and biological aging are, in part, influenced by genetic background, determining the role of mitochondria, and their genome drew my interest in this field in developing my independent research agenda.

Briefly describe your project in non-scientific terms. What questions are you trying to answer?

This project aims to determine how genetic background influences endurance trainability in an aging mouse model. We suspect the diverse genetic background in these aging mice influences how the major cellular energy producers – mitochondria – adapt with training. We suspect mitochondria in the muscle of mice that do not increase their fitness with treadmill training is one potential reason explaining these differences. Thus, this project seeks to identify gene candidates and changes in mitochondrial function with training.

What previous research or experience informed the development of this proposal?

First and foremost, when I was a graduate student, my Ph.D. mentor, Dr. Tim Lightfoot, took the time to develop and implement a grant writing course targeted at NIH applications. I have treasured the tools I learned from taking that course and receiving his feedback regarding idea development and writing the proposal. Without taking that course or receiving his mentorship, I could not have developed or written a successful proposal. Thus, his guidance significantly informed the development of this current work, for which I am truly grateful.

For the idea, in 2020, I received a New Investigator Pilot from the San Antonio Nathan Shock Center. We trained HET3 male mice on a standardized treadmill endurance training program in this work. Interestingly, we found significant intrastrain variability when comparing the change in exercise capacity measured from pre to post-training. Because HET3 mice are a heterogeneous strain, this finding led us to question the genetic contribution to the intra-strain variation in endurance trainability and if the exercise trainability phenotypes correlated with mitochondrial and/or oxidative stress markers known to change with training.

What's exciting about your project's potential impact?

I am most excited about this project's potential impact on **establishing personalized endurance exercise programming**. The widely familiar *Physical Activity Guidelines* have been around since the mid-1970s, which were developed and implemented as an important lifestyle component for overall health and well-being of the individual. However, with these guidelines, it's also known that not all individuals increase their cardiorespiratory fitness after following a standardized exercise program meeting these recommendations. Recent work from my lab and collaboration with Drs. Claude Bouchard and Mark Sarzynski have identified nuclear and mitochondrial genetic contributions to the interindividual variation in endurance trainability in humans. Based on the methods we used in those previous studies, I plan to use in this current line of aging research to establish precision-based exercise programming targeted to enhance mitochondrial function and enhance an individual's healthspan. Of course, genetics is only one component of precision-based exercise programming; however, the HET3 aging mice are an excellent model for uncovering other factors contributing to their strain variation in endurance exercise trainability.

If your project is successful, what is the next step?

The next step is to use our findings for a K01 application, planned for a February 2022 submission. In this proposal, future work will include **1)** increasing our sample size, **2)** assessing for biological sex differences, and **3)** aligning skeletal mitochondrial function with exercise capacity trainability based on genetic background. Ultimately, the goal is to translate these findings to humans and establish individualized exercise programming that improves mitochondrial function and healthspan (i.e., precision-based medicine).

How has support from and collaboration with the NSCs helped further this project and/or your research overall?

I believe that the research support in having access to study the HET3 aging mouse model and resources to complete time-intensive experiments greatly boosted this project's potential and my research overall. However, of equal importance is connecting and now collaborating with the leaders in biological aging research. I have had and continue to have wonderful mentoring from the San Antonio Nathan Shock Center investigators (Drs. Peter Hornsby, Nicolas Musi, and Adam Salmon) and the Oklahoma Nathan Shock Center (Drs. Benjamin Miller, William Freeman, Michael Kinter, and Arlan Richardson), who have significantly supported me.