NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT

Mark A. Phillips, PhD

Assistant Professor
Department of Integrative Biology
Oregon State University

2022 UW NSC Pilot Award

Metabolomic characterization of experimentally evolved D. melanogaster populations with distinct life-history patterns as they age

---

How did you become interested in aging?

My interest in aging research was sparked during an evolutionary biology course I took as an undergraduate. Although I had a fair amount of exposure to the molecular biology of aging by this time, delving into the "whys" of aging was a new concept. Questions like "why did aging evolve?" and "why is there so much variation in longevity and aging between and within species?" instantly drew my interest. And the fact that these questions could be largely explained by how the force of natural selection acting on initials varies over time (e.g. selection is more effective at removing mutations that negatively impact survival prior to the start of reproduction than after) completely changed the way I viewed aging. My interest in this topic eventually grew to the point where I made the decision to shift my career focus from biotechnology and engineering to pursuing a PhD studying evolutionary biology and aging.

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

Understanding why some individuals live longer and "age better" than others is at the core of this project. To address this question, my lab makes use of laboratory evolved fruit fly populations with radically different aging and longevity patterns. Specifically, we have large genetically diverse populations where hundreds of generations of selection for early reproduction has produced individuals that develop quickly and die young relative to longer lived control groups. In essence, we have used evolution to produce entire populations of flies genetically predisposed to "aging badly". By studying differences between these populations and their controls, we aim to better understand the mechanisms that drive aging and longevity differences between individuals. We hope that in the long term this knowledge can contribute to broader efforts to improve human health and longevity.

With respects to this particular project, our focus is on characterizing differences in metabolomic profiles between individuals from our accelerated aging groups and their controls. By studying how profiles change in cohorts from these groups as individuals age, we hope to identify patterns associated with unhealthy aging. For instance, is it the case that accelerated aging has a distinct metabolomic profile from normal aging? Or is it the case overall metabolic trajectories are similar but transitions are occurring at different rates? In effect, we are trying to determine if unhealthy aging is caused by distinct patterns of metabolic degeneration or simply by the acceleration of a more universal process. In both cases, we will also be able to determine what specific patterns are the best predictors of aged related physiological declines in our system.

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

In the past, I have led and contributed to several projects aiming to parse the genetics of aging and correlated stress resistances by combining experimental evolution and DNA/RNA sequencing. However,

despite increasingly powerful data sets and sophisticated statistical methods, findings have largely been limited to “aging is a complex trait involving many genes”. As a result, I am now working to incorporate data from higher levels of the omic hierarchy (e.g. metabolomics and proteomics) into the experimental evolution framework in the hopes of generating deeper biological insights into the aging process. This project is a direct result of this thinking.

What’s exciting about your project’s potential impact?
Based on previous work, we have some indication that there are general patterns and mechanism associated with accelerated aging. When we ran metabolomic data from 21-day old flies through a metabolomic clock program, flies from the accelerated aging group were predicted to be ~50 days old while their controls were accurate predicted to be ~20 days. Given this clock was developed and trained using related flies, this finding suggests some core reality is being captured and biological and chronological age have been disconnected in our system. The present trajectory-based study will allow us to explore this idea more definitively and determine if there are indeed some general patterns and mechanism associated with accelerated aging. If this is shown in the affirmative, it could point to general strategies to promote healthy aging and increased longevity.

If your project is successful, what is the next step?
If successful, a major outcome of this project would be the identification of metabolites and metabolic pathways associated with unhealthy aging in my experimental system. A natural next step would be manipulative studies targeting these pathways through dietary interventions or changes to environmental conditions to see if we can recover normal life-history patterns in our accelerated aging populations.

How has support from and collaboration with the NSCs helped further this project and/or your research overall?
While I have worked extensively with fruit fly populations with different aging and life-history patterns, my specific questions and hypotheses tend to be more generally concerned with the genetics of adaptation. As such, work directly investigating the biology of aging is a new research direction for my lab. This project represents the first major effort my lab as developed from the ground up in this arena and would not have been possible in its current form without the support of the Nathan Shock Center at UW. As much as funding, their feedback and suggestions when finalizing my experimental design has been an invaluable asset given my own limited experience working with metabolomic data.

In terms of my overall research objects, successfully completing this project will almost certainly put me in a better position to continuing studying the mechanisms underlying differences in rates of senescence between individuals. The success of this project could also have implications for my work unrelated to aging. For instance, developing approaches to predict whether populations will adapt or extinct when faced with major shift in environmental conditions is a major area of interest in my lab. Here I believe metabolomics might offer a way to identify markers of population health that can be used to predict persistence in shifting environments. While not directly relevant to human health and aging, approaches in this vein could be immensely valuable as we determine how to best contend with the reality that many species all over the world are increasingly at risk of extinction due to climate change.