NATHAN SHOCK CENTERS OF EXCELLENCE IN THE BASIC BIOLOGY OF AGING

PILOT AWARDEE SPOTLIGHT

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Hiding in plain sight: the ubiquitous actin as a target for aging

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How did you become interested in aging?

As someone who worked in the hustle and bustle restaurant environment of New York City, high stress was an everyday phenomenon. We always hear the dogma of “stress is bad for aging”, and thus as someone who was constantly in high stress environments, I was very curious about what actually happened on the cell biological level when one was constantly inundated with stress, and ultimately how this impacted aging. Through my research experience, I was able to slowly begin to understand how stress impacts aging by understanding the concept of stress resilience – our capacity to respond to stress. Now, the Sanabria Lab investigates how stress resilience declines during aging, and what we can do to maintain high stress resilience as a means to combat age-related decline in health.

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

The Sanabria lab studies the intersection between stress and aging, trying to understand how stress impacts the aging process and how aging alters an organism’s capacity to deal with stress. We use diverse genetic tools to identify mechanisms that impact stress resilience: that is, an organisms capacity to return to normal health after exposure to stress. We have identified a unique and novel stress response that protects the actin cytoskeleton, which makes up the highway of the cell that allows for transport and trafficking of cell components. Specifically, protecting the actin cytoskeleton from stress can mitigate damage associated with aging, similar to how protecting highways from stress (e.g., anti-weather coating to prevent erosion from water) can preserve roads and result in higher efficiency in cities. In conjunction with the health and retirement study performed by Eileen Crimmins and Em Arpawong, we investigated how genetic variations in actin regulatory genes could be associated with age-related phenotypes. Importantly, we find in model organisms that increasing protection of the actin cytoskeleton to stress can promote lifespan and we aimed to translate these findings into human health and aging.

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

My lab’s research focused on studying the decline in stress resilience during aging. That is, we aimed to understand how older individuals have a lower capacity to deal with stress, and thus stress exposure at late age can be more damaging. We specifically focused on how organisms mitigate damage associated with exposure to heat stress and stress to the specific organelles, the mitochondria (the energy producer of the cell) and endoplasmic reticulum (the factory of the cell, which produces important proteins and fats). These previous experiences poised us in a great position to investigate a completely new stress response, one that protects the actin cytoskeleton, the highways of the cell.

What's exciting about your project's potential impact?
What is exciting about our work is that we directly translate our work in model organisms to human health and aging. Specifically, we find mechanisms in model organisms that directly impinge on organismal health and lifespan. These studies would be impossible to perform in humans due to the long lifespan of humans and inability to alter genes. Upon identifying genetic mechanisms that can impact lifespan, we can determine whether these genes also influence age-related phenotypes. Specifically, we found that actin regulatory genes directly impact muscle health during aging, and people with specific genetic variations in these genes can be at higher risk for muscle failure at older age. These genetic variations are quite easy to identify through sequencing, and thus early interventions can be applied to these individuals to prevent muscle failure at old age.

If your project is successful, what is the next step?
While our studies presented here help us identify genetic variations that can be associated with specific phenotypic outcomes at late age (i.e., muscle function in this proposal), further research needs to be done to determine the cause of these outcomes so that a proper intervention can be applied. Thus, with the information gleaned from these studies, we can take the genetic variations back to the bench and determine the molecular mechanism whereby these genetic variations can result in increased risk for muscle failure. The identification of mechanisms allows for identification of druggable targets, which can then be utilized in the clinic.

How has support from and collaboration with the NSCs helped further this project and/or your research overall?
The collaboration with the USC-Buck NSC was instrumental in translating our fundamental biology work into the human biology of aging. While it is inarguable that exposure to stress can be detrimental to aging, the rationale for why stress exposure can be damaging on the cellular level is more poorly understood. On the opposite spectrum, the Sanabria lab has expertise in understanding the fundamental mechanisms that govern stress resilience in cells, but to apply these findings back to the human biology is a truly unique and important opportunity that would have been impossible without our collaboration with the USC NSC.