2022 Buck Summer Scholar: Theresa FitzGibbon

Hi! My name is Theresa FitzGibbon. I am a recent graduate from Marist College, a small private school located in Poughkeepsie, New York. I graduated with a B.S. in Biological Sciences and a minor in Political Science. As an undergraduate, I had the opportunity to work briefly under the direction of Dr. Paula Checchi. Dr. Checchi ran a *Caenorhabditis elegans* lab committed to understanding the dynamics of chromosomal repair as it relates to embryonic viability and reproductive health. In other words, Dr. Checchi used microscopic nematodes (worms) to understand how different molecular components work to repair damaged DNA and how that repair contributes to fertility. At the time of my participation Dr. Checchi's lab was focused on understanding the role and importance of the Nucleosome Remodeling Deacetylase Complex (NuRD). This highly conserved complex is responsible for chromosomal remodeling, or changing the degree to which DNA is packed together. Prior to my involvement, Dr. Checchi and her students discovered that NuRD is required for DNA repair during *meiosis* and embryonic viability is contingent upon the proper functioning of NuRD. The project I took part in was designed to understand NuRD's role in *mitotically* dividing reproductive cells. My role in the project was simple: observe what happened to chromosomal number and structure when NuRD was malfunctioning. To quantify chromosomal number within reproductive cells, I spent many hours at a fluorescent microscope taking what I thought were beautiful pictures of fluorescing *C. elegan* germlines!

Continuing my journey with the little 1 mm nematode, this summer I had the opportunity to intern in the *C. elegans* lab of Dr. Gordon Lithgow at the Buck Institute for Research on Aging. Dr. Lithgow's lab is committed to discovering genes that can be targeted and molecular interventions that can be implemented to slow the onset of age. This contributes to answering one of the major questions that has helped morph the emerging field of geroscience: how can we capture physiological youth to limit the time an individual is at risk and suffering from age-related disease? The goal is not to prolong life but to optimize health for as long as possible. I'd be remiss if I didn't pose the question like the Buck does… how can we "live better longer?"

Dr. Lithgow's lab specifically addresses this question by serving as one of the three labs to host the *Caenorhabditis* Intervention Testing Program (CITP). The CITP is ultimately a drug screen designed to find compounds that promote healthy aging. Compound efficacy is measured by the ability of compounds to extend lifespan and delay physiological decline across genetically diverse *Caenorhabditis* species. You might be thinking, "why use worms to discover compounds that limit age-related disease in humans?" This question, is in part, addressed by the hypothesis of the CITP: if a compound is robust enough to affect genetically diverse *Caenorhabditis* species, then the compound is likely exerting an effect through pathways that are evolutionarily conserved and therefore present in mammalian species as well. By using *Caenorhabditis,* the CITP can "weed out" compounds likely to be ineffective and provide evidence for compounds likely to be effective in future mammalian pre-clinical studies.

Furthermore, the project addresses the importance of providing reproducible data. Replicate studies are built into the CITP paradigm to observe if compounds are robust enough to exert an

effect when differences are organically introduced into assays. These differences include variance in lab technician and location of the lab itself. Besides the Buck Institute, the University of Oregon and Rutgers University also host the CITP project. Each lab provides studies indicating if compound efficacy can be replicated when differences in location, time and lab technician are introduced into assays. In effort to limit lab induced variation across the differing host labs, protocols, reagents, techniques, and conditions for maintaining the *Caenorhabditis* strains have been standardized for each CITP host lab to follow.

So, what does testing these compounds actually look like? Compound efficacy is usually measured via a lifespan assay. The worms are plated on petri dishes which contain the compound of interest. Overtime we count the number of alive vs dead animals to observe if the compound is extending lifespan. If a 10 % lifespan extension is observed, an automated lifespan assay is run to confirm the results. In the automated lifespan assay, a machine keeps track of survival as opposed to manual tracking by a lab assistant. To further observe compound effects a "healthspan" assay is run where we observe the effect of compounds on physiological movement of the animal over time. This is done with a software that records the swimming motion of the animal. If the compound better preserves the physiological swimming movement over time, then the intervention is said to "extend healthspan."

This summer, I mostly worked on a lifespan assay with the compound Urolithin A. Urolithin A is a compound that derives from common nutrient sources such as walnuts, pomegranate seeds, aged wines, and other berries. This compound is believed to delay physiological decline via a restoration in mitophagy, or a process that rids cells of poorly functioning mitochondria (organelle that provides cells with energy). With age, individuals tend to experience the buildup of dysfunctional mitochondria frailty. If Urolithin A can restore mitophagy, it is expected that it might be able to extend lifespan and healthspan. We are currently still working on the assay. I am excited to see if Urolithin A will progress through CITP, so we can observe its healthspan effects!