2022 Buck Summer Scholar: Caroline Voorhis

My name is Caroline Voorhis, and I am a rising senior at Marist College in Poughkeepsie, New York, studying Biomedical Sciences and Spanish. At school, my research focused on DNA damage repair in *Caenorhabditis elegans*, a tiny worm frequently used to study analogous processes in humans. Under the direction of Dr. Paula Checchi, our lab aimed to understand how deficits in *C. elegans* DNA repair mechanisms may help explain pathologies in humans, including ovarian aging and cancer. Though aging is related to my college research, what most drew me to research at the Buck Institute for Research on Aging was a book I read last fall, entitled *Why We Get Sick,* by Dr. George Williams and Dr. Randolph Nesse. *Why We Get Sick* takes an evolutionary approach to medicine; it examines why diseases we experience in the present day may be trade-offs to advantageous traits in the Stone Age: the environment to which humans are evolved. My favorite chapter explored genes related to senescence (which is believed to cause deterioration in bodily or cognitive function in advanced age). The authors suggested that many genes advantageous in youth in the Stone Age have a senescent effect in old age, and since almost no one in the Stone Age survived long enough to experience the negative side effects of these genes, they were passed on, causing many age-related ailments of today.

At the Buck Institute, I continue to work in *C. elegans* in Dr. Gordon Lithgow's Lab, mentored by Dr. Dipa Bhaumik. The Lithgow Lab focuses on restoring the mechanisms that keep young organisms in a balanced state of well-being (homeostasis) as they age. In my research, I examine the homeostasis of proteins in mutant *C. elegans*.

Think of proteins like string bracelets: they start out one dimensionally, like a single thread, and they are manipulated into their functional shape. Like string bracelets require a person to weave or braid them, a type of molecule called a chaperone assists in the folding of proteins into their final conformation. Over time, proteins may become damaged by stresses to the organism, like excessive heat. These stresses cause proteins to unfold, requiring the assistance of chaperones to repair them. This protein upkeep and maintenance is known as proteostasis (protein homeostasis).

As we age, a greater number of proteins unfold. At the same time, chaperones that maintain them become less efficient, resulting in masses of damaged proteins, called aggregates, that can have a damaging effect in the organism. In humans, protein aggregation is a known contributor to many neurodegenerative diseases, including Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS).

To help us understand the complexities of human neurodegenerative diseases, we can study protein aggregation in the worm. *C. elegans* live for about three weeks, making them a helpful tool to watch aging processes, conserved in humans, play out in a short period of time. It was observed that otherwise healthy worms had a marked increase in protein aggregates as they aged; in as little as a third of their lifespan, aggregated protein increased dramatically.

Since we know that proteins aggregate in aging worms and that chaperones play a role in proteostasis, my research focuses on protein aggregation in a mutant *C. elegans* strain with a nonfunctional *hsf-1* gene. *Hsf-1* (heat shock factor 1) regulates the production of many chaperones in the worm and is also present in humans. In my experiment, I plan to harvest both mutant and healthy worms to compare their aggregated protein at different points in their lifespan. Since *hsf-1* is such an important gene, we anticipate seeing an accelerated aging phenomenon play out in the mutant. We expect that *hsf-1* mutant worms will have more protein aggregates than nonmutant worms of the same age, since the mutants do not have the chaperone system, overseen by *hsf-1,* necessary to repair proteins as they become damaged.

After the worms are collected and the insoluble protein fraction extracted, the sample will be sent away for analysis in order to determine exactly what types of proteins are present. Once identified, the proteins can act as new targets for experimentation, providing insight into the way that other genes contribute to the complexities of declining proteostasis.

This research is exciting because it may help us better understand the role that chaperones play in neurodegenerative disease. Elucidating even a small portion of the cause of neurodegenerative disease can give us a starting point to begin new research that will further our comprehension and eventually lead to new ideas for treatment.

I am incredibly grateful to be part of this research and will wait eagerly for updates as this project continues beyond the summer. Aging research becomes ever-more important, as our population grows older and diseases of aging, like Alzheimer's, become more prevalent. I am excited to have experienced working in aging biology and will take forward what I've learned from this experience into a career in medicine.