

2022 Buck Summer Scholar: Alexa Schlotter



My name is Alexa Schlotter, and I am a rising junior at Columbia University studying biomedical engineering and computer science. I am interested in a career at the intersection of the life sciences and technology, especially in relation to the biological aging process. This past year, I worked in the Miller Lab at the Columbia Irving Medical Center Mailman School of Public Health. At the Miller Lab, I focused on researching the transgenerational effects of environmental toxicants like pesticides on the development of neurodegenerative diseases. This summer at the Buck Institute, I have joined the Newman Lab. The Newman Lab focuses on investigating the role that ketone bodies play in promoting health and preventing Alzheimer's disease

and decline in age-related memory. The long-term goal of the Newman Lab is to develop therapies that harness ketone bodies to increase the resilience of aging adults against age-related stresses and diseases. Ketone bodies are small metabolites that are synthesized primarily in the liver from fatty acids and are then exported for use as an energy source when the glucose level present is lower than what is energetically needed by the body.

My project this summer focuses on the NLRP3 inflammasome. The NLRP3 inflammasome is an immune receptor that is part of the innate immune system, the first line of defense against bacterial, viral, and fungal infections. The inflammasome is activated by a signal, which could include toxins from bacterial infections or double-stranded RNA from a viral infection.

When the NLRP3 inflammasome is activated, it secretes an inflammatory molecule called interleukin 1B (IL-1B). IL-1B can increase expression of genes for fever, pain, and hypotension, allowing for immune cells to infiltrate damaged tissue. This makes NLRP3 a key part of the immune system, protecting against a host of different infections. However, when the NLRP3 inflammasome is not properly regulated, it can lead to the development of a variety of inflammatory conditions, including Alzheimer's, diabetes, and various cancers. Therefore, the development of therapies combating these conditions has focused on inhibiting the NLRP3 inflammasome in different cell types.

Of interest in my project are microglia, a population of immune cells that are present in the central nervous system (CNS). Microglia are co-localized with amyloid- β plaques, deposits of amyloid- β protein in the brain that are a common hallmark of Alzheimer's disease (AD). This suggests that microglia may play a role in the early stages of the development of AD. In recent years, interest has risen in harnessing the effects of ketone bodies, particularly β -hydroxybutyrate (BHB), to develop therapies to combat Alzheimer's disease in the early stages. BHB levels are significantly lower in the blood of AD patients, indicating it is correlated with AD development.

Because of this possible connection, it is hypothesized that BHB may play a role in inhibiting the NLRP3 inflammasome in microglia, meaning it may be able to play a preventative role in Alzheimer's development. To test this hypothesis, I treated cells with varying concentrations of BHB and other ketone bodies and observed the secretion levels of IL-1B. Lowered concentrations of IL-1B would indicate that BHB is able to inhibit NLRP3-mediated secretion of IL-1B.

2022 Buck Summer Scholar: Brennen Keuchel



Hello, my name is Brennen Keuchel, and I am a rising senior at Vanderbilt University in Nashville, Tennessee, studying Human Development and Molecular and Cellular Biology. At Vanderbilt, I was introduced to the world of aging research in the lab of Dr. Kris Burkewitz, where I am currently conducting research into age-related changes in neurons. Specifically, I am studying changes in a sub-cellular structure called the endoplasmic reticulum, which is essential for communication and protein folding in a cell. Dysregulation of these functions has been associated with neurodegenerative disease. My experiences in the Burkewitz lab have inspired me to pursue a career in research in the biology of aging. Leading up to this past summer, I wanted an experience where I could be exposed to the diversity of aging research and make

meaningful contributions to a scientific project. Luckily, I was given an opportunity at the Buck Institute this summer in the lab of Dr. Malene Hansen to study the interrelation between age and the cellular recycling process known as autophagy.

Although most cellular entities (proteins, organelles, etc.) function properly during youth, many will slowly lose their ability to function over time. When a dysfunctional entity interacts with the rest of the cellular environment, it can cause a multitude of detrimental effects, potentially leading to disease. To alleviate the accumulating dysfunction that might ensue, cells have evolved to undergo autophagy. In this process, the dysfunctional entities are isolated from the rest of the cell in a structure called the autophagosome, broken down to their molecular components, and even reused to create new and fully functional entities.

My project is focused on deciphering how a protein (p62/SQSTM-1 in humans) that helps recruit cellular components for autophagy can promote healthy aging. In the model organism *Caenorhabditis elegans*, a transparent roundworm around 1mm in length, a genetically manipulated *C. elegans* strain was created with extra copies of the gene coding for our p62 protein (called SQST-1 in *C. elegans*). This strain, which is able to generate more copies of the SQST-1 protein, shows an increased lifespan as well as increases in both the number and size of autophagosomes in neurons.

However, we do not know how the specific proteins involved in autophagy are affected by SQST-1 overexpression. If we can understand the specific autophagic activities that SQST-1 modifies when it is overexpressed, we may be able to design more specific and effective therapeutics in the future that can target those specific mechanisms.

To establish this understanding, I employed genetic crosses between the SQST-1 overexpression strain and other *C. elegans* strains with fluorescent tags on autophagy proteins that SQST-1 interacts with. I then compared how the localization and intensity of the fluorescent autophagy proteins change in response to SQST-1 overexpression. I am excited to generate new data that informs our understanding of longevity and contributes to the research at the Buck!

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.

2022 Buck Summer Scholar: Grace Qi



Hi! My name is Grace Qi, and I'm a neuroscience major at Duke University, but I'm originally from Virginia. I have been fascinated with the brain and age-related neurological diseases since starting college and am excited to be working at the Buck Institute this summer! At Duke, I study the role of circadian rhythms in Alzheimer's Disease (AD) in the lab of Dr. Carol Colton. My project has been focused on investigating disruptions in circadian rhythms that occur in various regions of the brain in mouse models of Alzheimer's Disease, with the goal of determining whether such changes contribute to cognitive decline and memory loss. At the Buck Institute, I have been working in Dr. Pankaj Kapahi's lab studying protein trafficking mechanisms in Alzheimer's Disease with fruit flies. Using fruit flies gives me the ability to test a variety of genetic manipulations for their efficacy against age-related diseases like AD. Dr. Kapahi's lab has historically been focused on elucidating how dietary restriction promotes longevity and slows aging. My project was born out of a study that identified a protein called Oxidation Resistance 1 (OXR1) that mediates the effect of dietary restriction on lifespan. Further work determined that this protein plays important roles in protein trafficking mechanisms that could impact neurodegeneration in major diseases like Alzheimer's Disease.

Protein sorting and trafficking within cells is a crucial process that is known to be disrupted in neurodegeneration. Diseases like Alzheimer's Disease and Parkinson's Disease are primarily characterized by proteins that aggregate together due to improper modification or degradation. A major hypothesis in the field is that these protein aggregates (amyloid and tau for Alzheimer's, alpha-synuclein for Parkinson's) disrupt normal neuronal functioning and cause neuronal degeneration that eventually lead to cognitive decline, loss of motor function, or memory loss. Studying the pathways that are responsible for the proper sorting of proteins throughout the cell will give insight into the causes of protein aggregates and neurodegenerative diseases. My project has been focused on a complex called the retromer that is responsible for sorting amyloid precursor protein, the precursor to amyloid aggregates, to its appropriate cellular destination. This pathway is of particular importance since OXR1, the mediator of dietary restriction-induced longevity, has been shown to play roles in regulating the retromer complex and declines with age. Thus, age-related disruptions in OXR1 and retromer sorting could lead to improper trafficking of amyloid precursor protein and neurodegeneration. My results indicate that overexpression of OXR1 in fly models of Alzheimer's Disease protect neurological function with age. These findings indicate that OXR1 and the retromer complex may be valuable targets for therapeutics that could revolutionize the way diseases that involve protein aggregates are diagnosed and treated. I look forward to seeing how this work will continue to expand our view of neurodegeneration towards a treatment for some of the most devastating diseases facing humankind.

2022 Buck Summer Scholar: Kaitlyn Hung



My name is Kaitlyn Hung, and I am a rising 3rd-year undergraduate at Northwestern University, majoring in biology and minoring in data science and global health. I plan to attend graduate school, achieve a Ph.D. in biology, and pursue a career in research. At Northwestern, I work in Dr. Clara Peek's lab in the Department of Biochemistry and Molecular Genetics. There, I study circadian rhythms in muscle. Circadian rhythms are centered in the brain and influence when we sleep and wake, but they are also found throughout the body and influence many other processes. I study the role of circadian rhythms on glucose metabolism, working to understand how disrupted circadian rhythms (from jet lag, shift work, etc.) affect metabolic diseases like obesity and type 2 diabetes.

More broadly, I am interested in studying how key aspects of lifestyle such as exercise, diet, and sleep influence health and disease. I stumbled upon the aging field and realized it connected many of my interests. This summer, I joined Dr. Eric Verdin's lab, which studies the interconnection between the immune system and metabolism during aging. Inflammation is characteristic of aging, with baseline inflammation increasing as we age due to improper function of the immune system. The Verdin Lab studies how natural metabolites produced by our bodies, like NAD⁺, influence the immune system during aging to try to better understand the causes and mechanisms of inflammation.

My project focuses specifically on understanding the processes behind female reproductive aging. The female reproductive system is the first to age, with women undergoing a gradual loss in fertility that ultimately ends in menopause. An earlier age of menopause is correlated with the development of age-related diseases and shorter lifespans, making it imperative to develop therapies to improve fertility and delay female reproductive aging. Additionally, the average age at which women give birth has increased globally in the past few decades. Childbearing at an older reproductive age increases the risk of miscarriage, birth defects, and pregnancy complications. Given that no clinically proven therapies exist, it is important to find ways to slow reproductive aging and improve fertility at an older age.

The metabolite NAD⁺ has a broad physiological function, involved in pathways from energy metabolism to the immune system and DNA repair. NAD⁺ levels have been shown to decrease with age leading to the development of age-related diseases such as neurodegenerative diseases, metabolic diseases, and cancer. The decline in NAD⁺ also occurs in the ovary during female reproductive aging, contributing to loss of fertility. Furthermore, increasing NAD⁺ levels improves many aspects of female reproductive aging. Despite this important role for NAD⁺ in female reproductive aging, the cause of the decrease in NAD⁺ is unknown.

My project studies the enzyme CD38, one of the primary consumers of NAD⁺. CD38 is becoming a key actor in the aging field as it increases with age in several tissues, driving the decline in NAD⁺ levels. However, the role of CD38 in female reproductive aging and the decline in NAD⁺ is unknown. To understand the role of CD38, we must first understand where CD38 is found in the ovary and how its expression changes with age. Knowing when and where CD38 is expressed in the ovary will allow us to perform research using drugs and more specific models to target CD38, bringing us one step closer to developing therapies to address reproductive aging.

2022 Buck Summer Scholar: Seth Talyansky



Hello! My name is Seth. I am twenty-one years old. I am a senior at Stanford University majoring in biology with a concentration in neurobiology. I am interested in understanding why brain health declines with age in the hope of learning how to mitigate debilitating and fatal neurological diseases. I also expect that a better knowledge of brain dysfunction will provide insights into the causes of the whole-body aging process, which increases risk of disease in all organ systems, as well as lead us to discover interventions that minimize these harmful effects.

At Stanford, I do research in the Greicius Lab in the School of Medicine, working with Professor of Neurology Michael Greicius and Quantitative Science Unit Assistant Director of Computational Biology Dr. Yann Le Guen on studying the genetic risk factors for Alzheimer's disease and other dementias. This summer at the Buck Institute, I am glad to be working with Professor Pejmun Haghighi and postdoctoral fellow Jill Farnsworth.

Human nerve cells connect to each other and muscle cells at synapses. The properties of these junctions are plastic, that is, adaptable. One kind of plasticity is homeostatic. This is the tendency of a synapse to preserve its overall function in the nervous system in response to changes in the presynaptic cell, such as an increased tendency of the neuron to fire, or in the postsynaptic cell, such as a loss of receptors for the signaling molecule on the muscle cell. Homeostatic plasticity is critical to normal nervous function, and impairment of this mechanism causes dysregulation of synaptic connections and has been widely observed under disease conditions. In the Haghighi Lab, we are studying precisely how homeostatic plasticity operates with an aim to uncover how its breakdown may in fact be a driver of age-related neurological disease.

We are working with the neuromuscular junction (NMJ) in the fruit fly *Drosophila*, a well-established model for human synapses. In flies, two main types of receptors at the muscle detect signals from the neuron: glutamate receptors (GluR) containing or lacking subunit IIA (GluRIIA). Eliminating GluRIIA-containing receptors induces homeostatic plasticity at the NMJ. This adaptation, which takes the form of reduced release of the signaling molecule from the neuron, is known to be triggered by a signal sent in reverse, from the muscle cell back to the neuron (termed the retrograde signal). One of the features of the GluRIIA-containing receptors is a robust ability to transmit calcium ions into the cell. Calcium is a prominent signaling molecule known to interact with many proteins and initiate many biological pathways inside cells.

We hypothesized that the decrease in calcium influx into the muscle, associated with loss of GluRIIA-containing receptors, induces the retrograde signaling from the muscle to the neuron. We tested this hypothesis by increasing calcium influx through GluRIIA-lacking receptors and investigating whether this would diminish the retrograde signal and homeostatic compensation. Our results so far have shown that this is indeed the case. Our work therefore suggests a key role for calcium signaling in the induction of homeostatic plasticity at synapses. As loss of synaptic homeostasis has been associated with many neurodegenerative diseases, our findings point to new therapeutic avenues.

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. elegans* 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, 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!

2022 Buck Summer Scholar: Varun Sridhar



Varun Sridhar is an undergraduate Biology major at Hofstra University in the 8-year BS-BA/MD program in association with the Zucker School of Medicine at Hofstra/Northwell. At Hofstra, Varun works in Dr. Michael Does's lab to investigate the cellular mechanism that the SARS-CoV-2 spike protein implicated in COVID-19 utilizes to cause lung tissue to become susceptible to inflammation. Varun also works in the Neurocognition of Speech Lab at Hofstra with Dr. Susan DeMetropolis to examine language and cognition links in stroke survivors dealing with aphasia, which encompasses a variety of language disorders. Varun's interactions with elderly dementia patients while volunteering at a nursing home and his prior neuroscience research experiences, most notably a summer internship at the Buck Institute as a high school junior, sparked his interest in studying neurodegenerative diseases and inspired him to pursue a career in medicine. As a Summer Scholar at the Buck Institute, Varun is working with Dr. Grant Kauwe in Dr. Tara Tracy's lab. The Tracy Lab focuses on studying the events that cause dysfunction to occur in the synapses, or points of connection between neurons in the brain, which lead to cognitive decline and memory loss present in Alzheimer's disease and frontotemporal dementia.

Under normal circumstances, a crucial aspect of synaptic function that allows the brain to form and retrieve memories is the ability of synapses to strengthen their signal transmissions between neurons based on stimulation of brain cells from new experiences. After being stimulated from the outside environment, neurons communicate with other neurons through the release of neurotransmitters, which are signaling molecules that bind to receptor proteins on the surface of other neurons to stimulate them. To transmit a stronger signal between neurons, synapses that are stimulated require a greater number of receptors to bind to the neurotransmitters and receive the signal. To produce these receptor proteins, a process known as protein synthesis occurs that involves many other supporting proteins to carry out the initial steps of synthesis. Varun is investigating the cellular mechanisms by which tau, a key protein that drastically increases in the brain in Alzheimer's disease and other tauopathies, disrupts protein synthesis, leading to synaptic dysfunction, cognitive decline, and memory loss. Dr. Kauwe and Varun are utilizing human neurons and mice with genetic mutations found in frontotemporal dementia patients as models to study tau's effects on synapse function. With decades of research and clinical trials not yielding any effective treatments or cures for tauopathies, the long-term goal of this project is to provide a basis for developing novel therapeutics to restore proper synapse function and prevent memory loss.

2022 Buck Summer Scholar: Zhixin Zhang



My name is Zhixin Zhang, and I recently graduated from the University of California, Berkeley where I majored in Bioengineering. At my home institute, I'm a member of Dr. Irina Conboy's laboratory that studies aging and rejuvenation. In the Conboy Lab, I worked with Dr. Etsuko Watanabe, Dr. Alexandra Benoni, and Dr. Chao Liu on elucidating the mechanism with which cancer affects muscle protein synthesis to understand cachexia, a muscle wasting syndrome that accompanies many cancers. I'm motivated by my research to continue studying the pathology of age-related diseases and hope to pursue a career developing aging interventions. I was fortunate to

join Dr. Judy Campisi's laboratory through the Buck Summer Scholars Program, where I was mentored by Dr. Kohsaku Numa and Dr. Koji Kitazawa. The Campisi Lab studies cellular senescence, a state of permanent cell cycle arrest induced by stress and seeks to understand the drivers of senescence and their relationship to age-related pathologies.

Cellular senescence is maintained by major tumor suppressor pathways as a restraint on uncontrolled cell proliferation in cancer. Even though senescent cells stop dividing, they remain metabolically active and are characterized by altered gene expression and gain of senescence-associated secretory phenotype (SASP), a set of secreted factors that can exert effects on neighboring cells. As senescent cells accumulate in aging tissues, their SASP can promote inflammation locally and even systemically. Chronic inflammation is linked to the pathology of most age-related diseases, including diabetes, Alzheimer's disease, atherosclerosis, and more.

My project in the Campisi Lab looked at how senescent cells in the aging ocular surface at the front of the eye can drive the pathology of dry eye disease (DED). DED is a common age-related disease affecting over 16 million people in the US, causing a decreased quality of life for patients and a substantial economic burden on society. DED is characterized by instability of the tear film and chronic inflammation at the ocular surface. Notably, the prominent pro-inflammatory factors present in dry eye overlaps with SASP, suggesting that senescent ocular surface cells may mediate the chronic inflammation of DED.

Specifically, I studied whether dipeptidyl peptidase-4 (DPP4) can mediate the pro-inflammatory SASP in DED. DPP4 is a transmembrane protein abundantly expressed on senescent cells and not proliferating cells, and it is a multifunctional protein that can cleave other molecules, has immune costimulatory function, and binds other molecules. Importantly, DPP4 can activate key pathways that are master regulators of SASP, which means that DPP4 may have a role in mediating the chronic inflammation in DED. We hope to clarify the role of DPP4 in the pathology of DED and propose a novel intervention for DED through its inhibition. Currently, the treatment of DED through artificial tear fluid, and immunosuppressive drugs in moderate to severe cases, can only alleviate the symptoms of DED but fail to address the source of the chronic inflammation. If DPP4 proves to be a key mediator of senescent cell secreted factors involved in DED, inhibition of DPP4 could be a powerful therapeutic that addresses the crux of the pathology of the disease.