2023 Buck Summer Scholar: Anna Girtle

My name is Anna Girtle, and I am entering my final year at University College London where I am studying cell biology. I am interested in pursuing a career focused on improving our understanding of human diseases so that we can better treat them. Last year I worked in the Gems Lab at University College London's Institute of Healthy Ageing. The Gems Lab works with the model system *C. elegans* to understand the underlying processes that cause age-related pathologies, and how these pathologies lead to death. During my time there, I explored liposomes as a delivery system for potential life-extending drugs and researched the role of autophagy genes in lifespan. This summer at the Buck Institute, I had the opportunity to join the Ellerby Lab, which focuses on understanding the processes underlying neurodegenerative disorders with hopes of identifying novel therapeutic targets.

During my 12 weeks at the Buck Institute for Research on Aging, I worked on two projects involving the role of the retromer complex in disease. The retromer is a sort of "machine" in our cells composed of discrete components which come together to mediate protein sorting. A functional retromer complex ensures toxic proteins are degraded and essential proteins are returned to their appropriate cellular compartments. When the retromer components fail to come together correctly, protein sorting is disrupted and can contribute to disease.

Of particular interest to my research is the gene *OXR1*, which encodes a protein that stabilizes the retromer components. I worked with fibroblasts derived from patients with a loss-of-function *OXR1* mutation. We are interested in examining how age-associated molecular changes are altered with the loss of *OXR1*, and whether the phenotypes can be rescued by the compound R55, which pharmacologically stabilizes the retromer.

The second project I worked on involved human iPSC-derived neurons expressing a form a mutant tau, a protein involved in many neurological disorders. Mutant tau has been shown to interfere with retromer function, which is thought to be involved in synaptic transmission. We therefore monitored electrophysiology metrics in diseased and healthy neurons, with and without R55 treatment, to determine whether retromer stabilization improves disease phenotypes.

Ultimately, the goal of these projects was to better understand the role of the retromer complex in aging and disease, with the hopes that it may be an important therapeutic target to pursue in the clinic.

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2023 Buck Summer Scholar: Debra Buggs

Hi! My name is Debra Buggs. I am a recent graduate from Oglethorpe University, a private college in Brookhaven, Atlanta. I received my B.S. in Biology with a minor in chemistry. During my last semester at Oglethorpe, I had the chance to participate in two in-class research projects which inspired me to pursue an MD-PhD instead of just an MD. Under the guidance of Dr. Allison Roessler, I studied the spiropyran mechanophore, a force responsive molecule that undergoes a color change when enough force is applied. I wanted to understand how the steric size and electronic properties of substituents affects the mechanochemical activation of spiropyran so that we can control its color change for mechanical purposes. I also did a project under the guidance of Dr. David Katz where I investigated how modulating open and closed chromatin affects health-related phenotypes in the model organism *Caenorhabditis elegans*, a transparent roundworm 1mm in length. I used the *eap-1* gene (H3K9me3 reader) as a tool to open and close sections of chromatin. Because *eap-1* is a K9 antagonist, it modulates the opening of closed (K9) chromatin. Without *eap-1*, closed chromatin that would normally get opened and transcribed stays closed. From this, I could gain a better understanding of the functions those H3K9me3 chromatin sections in a variety of phenotypes such as fertility (brood size assay), sensory ability (chemotaxis), and learning and memory (t-maze assay).

This summer, I got the exciting opportunity to continue to work with *C. elegans* at the Buck Institute for Aging Research in the lab of CSO and Professor Malene Hansen under the guidance of Dr. Hiroshi Ebata, a postdoc in the lab. The research goal of the Hansen lab is to understand the roles of autophagy, our body's cellular recycling system, in aging.

As humans age, we are exposed to many stressors that cause damage to our cellular components. Autophagy acts as a homeostatic mechanism to clear these damaged components from our cells, thereby keeping us healthy. However, over time, waste products can accumulate and eventually render our cells non-functional. In this way, we can think of cellular aging as the balance between the damages we accrue and the rate our bodies are able to clear this damage or waste. Aging has been associated with a decline in the efficiency of autophagy, which can lead to the buildup of cellular debris (e.g., protein aggregates) and eventually lead to age-related diseases such as cancer and Alzheimer's. Thus, it is important to understand the process of autophagy and the mechanisms that underly it.

My project was focused on investigating the role of the autophagy-related (ATG) protein ATG-16 and its WD40 domain. More specifically, I was interested in using this protein as a tool to better understand canonical vs non-canonical autophagy roles through the ATG-16 WD40 domain. Canonical autophagy uses ATG proteins to remove damaged cellular components via lysosomal degradation. However, in non-canonical autophagy, some ATG proteins including ATG-16 and its WD40 domain, can "moonlight" in alternate pathways. To this end, genetically manipulated *C. elegans* with either a deletion of the protein, a deletion of its WD40 domain, or a point mutation within the WD40 domain were characterized in various health and autophagy assays to learn more about the role of ATG-16 and its WD40 domain. Hopefully this research will inform the less well-studied non-canonical roles of ATG proteins and thus better inform interventions for age-related diseases linked to autophagy.

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2023 Buck Summer Scholar: Kaya Ceyhan

My name is Kaya Ceyhan, and I recently graduated from Ohio State University, where I minored in Molecular Genetics and minored in History. I am interested in combating neurodegeneration through a career in medicine and research. I worked in Dr. Nicolas Wein's lab at Nationwide Children's Hospital in Columbus, Ohio, during my undergraduate. In the Wein lab, I focused on assessing the efficacy of AAV gene therapy vectors for rare neurodegenerative disorders such as Duchenne Muscular Dystrophy.This summer at the Buck Institute, I worked in the Newman lab. The Newman lab seeks to leverage small molecule metabolites for therapeutic development in age-related diseases. Cells utilize ketone bodies as an alternative energy source when glucose levels are low, however, ketone bodies have numerous non-energetic functions that have not been fully explored. The long-term mission of the lab is to develop therapeutics which leverage endogenous metabolism to increase functionality and independence in older adults.

During the summer, I had the opportunity to work on two separate projects. The first project focused on establishing a detailed timeline of changes in the insoluble protein compartment (insolublome) in the mouse brain following administration of a ketogenic therapeutic. In neurodegenerative diseases, loss of protein homeostasis (proteostasis) is a key hallmark. Previous research in the lab has discovered that the ketone body beta-hydroxybutyrate (BHB) can regulate protein solubility in the brain, targeting proteins related to neurodegenerative diseases. However, while evidence of the change is robust, further investigation is needed to clarify a timeline of what happens in the brain insolublome. To deliver BHB, we orally administer a ketone ester that is cleaved to produce ketone bodies, including BHB, without any change to dietary composition. Looking across the treatment timeline in the insolublome, we investigated overall changes in protein concentration as well as proteins associated with neurodegenerative diseases like Alzheimer's disease. By analyzing the effects on the overall insolublome and specific proteins over a more detailed timeline following ketone administration, further steps can be made toward developing ketogenic therapies for neurodegenerative diseases.

Furthermore, I also looked at the role immune response plays in contributing to Delirium. Delirium is a sudden and severe change in brain function that leads to confusion, altered consciousness, and cognitive impairment. The immune system, particularly its inflammatory response, has been identified as a significant player in the onset and progression of Delirium. Elevated levels of certain cytokines, which are proteins that mediate and regulate immune and inflammatory responses, have been linked to the development of delirium in both clinical and pre-clinical settings. Through my project at the Newman lab, I have sought to characterize the effects of cytokines on delirium-like symptoms in mice. By focusing on the intricate relationship between the immune system and brain function, we aim to pinpoint specific inflammatory markers associated with Delirium. Better characterizing specific factors in immune response is vital to better understanding the causes and potential treatments for Delirium.

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2023 Buck Summer Scholar: Lea Baskin Monk

My name is Lea Baskin Monk. I am a 4th-year biochemistry major at UCLA, where I work as an undergraduate researcher in the Thomas Rando Lab. In the Rando Lab, I study muscular aging. A significant manifestation of skeletal muscle aging is a decline in regeneration upon injury, which results from diminishing muscle stem cell activity and an altered muscle niche environment. I study the mechanisms behind these changes in the skeletal muscle with the goal of better understanding skeletal muscle aging and informing therapeutic interventions.

As a Buck Summer Scholar, I worked in Judith Campisi's lab. The Campisi Lab studies cellular senescence, a fascinating cell state that is likely evolutionarily selected for to prevent early-life cancer and promote tissue repair. However, as an individual ages, senescent cells accumulate and are associated with chronic inflammation and age-related diseases such as Alzheimer's, osteoarthritis, and (paradoxically) late-life cancer. In response to a stressor, such as DNA damage, senescent cells halt cell division by upregulating tumor suppression pathways and secreting inflammatory factors. These factors are collectively referred to as the senescence-associated secretory phenotype (SASP) and magnify the influence of senescent cells on their environment by interacting with nearby cells. While senescent cells have been identified in many tissues, they have different senescence profiles, driven by their tissue context and the type of senescence-inducing stressor. This heterogeneity prevents a single definition from describing all senescent cells, but opens a rich and yet-to-be-studied diversity of cellular senescence in disease.

This summer, I worked with PhD student Jun-Wei Brendan Hughes to study cellular senescence in idiopathic pulmonary fibrosis (IPF). IPF is a highly degenerative and age-associated disease in which scar tissue accumulates in the lung, causing progressive pulmonary failure. The average individual survives only three to five years post-diagnosis. While IPF is the most common type of pulmonary fibrosis, its underlying causes are unknown, and few treatments exist. Recently, the accumulation of senescent cells in the lung was implicated in the progression of IPF. This summer, I studied the relationship between cellular senescence in the lung and IPF using RNA sequencing techniques. We are particularly interested in the heterogeneity of senescence profiles in IPF and healthy lung cells. Elucidating the effects of senescence in IPF is essential to better understand IPF progression and develop more effective therapeutics.

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2023 Buck Summer Scholar: Olivia Wilson

My name is Olivia Wilson, and I am a rising senior majoring in Cell and Molecular Neuroscience at Scripps College, in Claremont, California. At Scripps, I work in Dr. Melissa Coleman's lab investigating the neural circuitry underlying female zebra finch song preference formation and maintenance, with an emphasis on the role of dopamine in these mechanisms. The lab performs song preference behavioral assays on zebra finches treated with dopamine agonists and uses immunohistochemistry to examine the brains of paired versus unpaired finches. At the Buck Institute for Research on Aging this past summer, I worked with Sudipta Bar, a postdoctoral fellow in Dr. Pankaj Kapahi's lab. The lab is focused on investigating the potential of dietary restriction to slow age-related diseases and extend lifespan, as well as the nutrient-signaling pathways that underlie these benefits. Specifically, my project aimed to characterize the role of several gene candidates in a *Drosophila melanogaster* model of tauopathy, with applications to the study of Alzheimer's Disease (AD), one well-known tauopathy disease.

Tauopathies are a diverse class of diseases that involve the abnormal changes to tau proteins, resulting in toxic aggregations and cellular dysfunction. Tau proteins are critical for the structural integrity and proper functioning of neurons, the cells in the brain responsible for complex information processing, communication, and behavior generation. Neurons, like other cell types, can maintain their structural integrity because of the function of a cytoskeleton, a network of protein filaments and fibers within the cell acting like a vertebrate's skeleton. One type of protein filament composing this dynamic cytoskeletal network consist of microtubules, which are long tubular structures made up of neatly arranged subunits critical for neuron shape, structure, and the movement of substances around the cell. These microtubules are stabilized by tau proteins, which are subject to dysfunction in the context of neurodegenerative disease producing aberrant neuronal communication and eventually neuron death. In the Kapahi Lab, I studied a transgenic model of tauopathy in fruit flies, wherein mutant human tau proteins are expressed, causing neurodegenerative phenotypes that largely recapitulate characteristics of Alzheimer's disease. Specifically, my project sought to identify promising gene candidates with a role in the pathogenesis of complex and poorly understood tauopathies.

I first examined the effect of silencing these gene candidates on the lifespan and healthspan of normal flies, then characterized whether the silencing of these individual genes influenced neurodegenerative disease phenotypes in transgenic tau fly populations. My work revealed that silencing a gene central to a highly conserved inflammatory response can increase lifespan in flies, indicating that reducing this inflammatory pathway may be neuroprotective.

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2023 Buck Summer Scholar: Owen Donayre

My name is Owen Donayre and I attend the University of California, Berkeley. I am majoring in Molecular and Cell Biology with an emphasis in Genetics, Genomics, Evolution, and Development with a minor in Marine Science. During the school year, I work in the Harland Lab under Dr. Michael Abrams conducting research to characterize sleep in the jellyfish species *Cassiopeia xamachana.* We have shown that these jellyfish do exhibit sleep-like states upon which a period of cellular growth ensues, just like humans! Because we know that during sleep, humans enter a state of heightened cellular repair and growth, this could be interesting to show how this is an evolutionarily conserved mechanism. At the Buck Institute, I work in the Kapahi Lab with Dr. Kenneth Wilson exploring the effects and mechanisms driving dietary restriction-induced extension of lifespan.

Mustard (mtd), the fly homolog to human *Oxidation Resistance 1 (OXR1)*, plays a crucial role in preserving cellular recycling processes and proper trafficking of proteins and fats. *OXR1* was initially found to be highly involved in protecting neurons from cellular stress but a recent study has shown that its involvement with the retromer complex may better illustrate its involvement in several neurodegenerative diseases such as Parkinson's and Alzheimer's disease. The retromer complex signals proteins for trafficking to either be reused throughout the cell or degraded in the lysosome and the balance of these two processes is important for maintaining proper neuronal health. When we inhibited flies' ability to make this OXR1 protein, we saw there was also a decrease in another protein named *ALDH*, or aldehyde dehydrogenase. *ALDH* plays a crucial role in the metabolization of alcohols both naturally occurring and ingested and is also involved in cellular growth, differentiation, and survival. Dysregulation of *ALDH* leads to harmful effects, such as elevated cellular stress and cell death. Furthermore, decreased *ALDH* levels were seen in the brains of patients with Parkinson's disease. While there is currently no established mechanism connecting *mtd* and *ALDH,* the Kapahi Lab is currently seeking to find the relationship between these two genes. This is an important question to answer as it will help us further understand how our ability to respond to alcohol changes not only with age but with the infliction of neurodegeneration as well.

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2023 Buck Summer Scholar: Ronak Jaisalmeria

Hello! I am a rising sophomore at Rice University in Houston, TX, majoring in cellular and molecular neuroscience. At Rice, I work in Dr. Robert Krencik's lab, which is part of the Houston Methodist Research Institute. Our research focuses on understanding the connection between neurons, the cells that communicate in the nervous system, and the supportive cells called astrocytes. Under the guidance of MD-PhD candidate Megh Patel, my project investigates specific astrocyte-secreted factors and their impact on creating new connections between neurons.

My broader interest lies in comprehending the mechanisms behind learning and memory, especially in neurological diseases like Alzheimer’s disease. I'm curious about targeting these mechanisms and molecules to develop treatments for such conditions. This led me to discover Dr. Tara Tracy's lab at the Buck Institute. There, under Dr. Grant Kauwe's mentorship, I worked on a research project studying how disruptions in neuron connections, known as synapses, contribute to cognitive and memory decline in Alzheimer’s disease.

Neurons communicate across synapses using neurotransmitters that bind to specific receptors on the next neuron, triggering a response. When a particular synapse is frequently activated, the receiving neuron increases the number of receptor proteins. This process, known as synaptic strengthening, is crucial for memory formation and learning.

My work with Dr. Kauwe investigates the role of tau, a protein linked to Alzheimer's disease, in the disruption of synaptic strengthening, leading to memory and cognitive decline. To explore this, we use human patient-derived neurons and transgenic mice to study tau's effects on synaptic function.

Ultimately, our goal is to develop effective and potent therapies for tau-related diseases, particularly Alzheimer's disease.

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2023 Buck Summer Scholar: Sydney Becker

My name is Sydney Becker, and I am an incoming third year undergraduate student at the University of California, Davis, majoring in biochemistry and molecular biology. I intend to pursue a PhD in biochemistry and conduct research focused on the development of novel therapeutics that will address age-related diseases. At Davis, I work in Dr. Justin Siegel's lab where my experience largely includes *de novo* enzyme design and SNP analysis focused on designing, testing, and implementing *de novo* enzymes. The lab's overarching goals include using computational and wet lab approaches to improve human health, food industries, and combat climate change. Moreover, I have also worked under the supervision of Dr. Angela Gelli, whose lab is focused on resolving the mechanisms of neuroinfections in the brain. In the Gelli Lab, I elucidated a possible cooperative action between two proteins during *Cryptococcus neoformans* penetration that may play a mechanistic role in blood-brain barrier penetration and infection. This summer, I joined Dr. Eric Verdin's laboratory under Postdoctoral Fellow Dr. Génesis Vega Hormazabal and PhD candidate Christina Alexandru. The Verdin Lab studies the intersection between the immune system and metabolism to try to better understand the causes and mechanisms of inflammation during aging.

My project focused specifically on understanding the processes behind brain aging and neurodegeneration via the blood-brain barrier. The blood-brain barrier is a thin layer of cells that repairs the central nervous system of the brain from the vascular system, maintaining critical brain homeostasis. While essential molecules, ions, and cells are allowed to pass between the CNS and vascular system, the brain is protected against daily fluctuations in body metabolism, pathogens, and disease. Changes in the blood-brain barrier have been characterized during pathogenesis and aging, including a "leaky" blood-brain barrier, which is a state where the blood-brain barrier can no longer prevent molecules, ions, and cells from going between the body and brain. This has been correlated with the presence of senescent cells, but limited studies have elucidated potential mechanisms responsible for this physiological phenomenon. Also of importance to BBB health is the coenzyme NAD+, involved in a number of metabolic processes. While NAD+ levels have been shown to decline with age, contributing to neurodegenerative diseases and cancer, the cause of this decrease is unknown.

My project studied the multifaceted enzyme CD38, one of the primary consumers of NAD+ in mammalian cells. CD38 is likely responsible for driving the decline in NAD+ levels and has been shown to increase with age - but the mechanistic explanation for this remains unclear. To understand the role of CD38 on NAD+ decline in the brain, we must first understand how CD38 levels are changing in the brain during aging. We must also understand if the decline of NAD+ within the BBB can be associated with other aging-related phenomena such as the infiltration of cytokines and chemokines into the brain. Knowing the mechanism behind NAD+ changes and the associated "leaky" blood-brain barrier will bring us one step closer to developing therapies to address neurodegenerative diseases and other age-associated changes in the brain.

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2023 Buck Summer Scholar: Will Nickols

Will Nickols is a rising fourth-year at Harvard College where he studies chemical and physical biology and statistics. At Harvard, he works in the Curtis Huttenhower lab building biostatistical and computational biology tools for working with ‘omics data. In particular, his work currently focuses on developing software to better understand the links between particular microbial species and metagenome-associated diseases, such as inflammatory bowel disease and colorectal cancer. After seeing the impact age can have on many of these diseases, Will became interested in studying the fundamental mechanisms of aging and elucidating how underlying processes can simultaneously increase someone’s risk for many age-related diseases. At the Buck Institute, Will was part of the Chuankai Zhou lab, which studies mitochondrial aging and proteostatis in budding yeast. In particular, Will supported computational work on a variety of projects, including computational modeling of proton movement in mitochondria and mitochondrial ribosome structure analysis.

Mitochondria are primarily known as the energy producers of eukaryotic cells, where they cycle protons between the mitochondrial matrix and the intermembrane space to generate ATP. Mitochondrial dysfunction is a hallmark of aging, and it has been implicated in a variety of age-associated diseases including non-alcoholic fatty liver disease, type II diabetes, and Alzheimer’s disease. As cells age, the proton gradient between the mitochondrial matrix and intermembrane space tends to decrease, and protons might leak from mitochondria into the cytoplasm. To better understand this phenomenon, one of Will’s projects involved quantifying the proportion of protons that leave their normal cycling in mitochondria and are shed to the cytoplasm.

To this end, Will developed a 3D modeling system in Python to quantify the fates of protons exported to the mitochondrial intermembrane space. When a proton is pumped through the electron transport chain to the mitochondrial intermembrane space, it travels pseudo-randomly before returning to the mitochondrial matrix through ATP synthase or exiting the intermembrane space through membrane pores. This model incorporated previously published biological parameters in yeast and estimated that approximately 1% of protons leak from mitochondria into the cytoplasm. Since this proportion is quite dependent on a few key modeling parameters, obtaining more accurate estimates for those parameters will be an important next step.

In a separate project, Will also worked on analyzing the structure of mitochondrial ribosomes, complexes of rRNA and proteins that translate mRNA from mitochondrial genes into proteins. Ribosomes are made of two subunits held together by bridges that consist of proteins and rRNA. These bridges differ in composition and location across different ribosomes and ribosome conformations, but the degree to which each bridge contributes to ribosome stability is not understood quantitatively. To understand these contributions, another of Will’s projects involved modeling the free energy of association for individual bridges under a variety of physical assumptions. By determining the relative strength of these bridges, this project helped elucidate the interplay between ribosome structure and function and will help identify future drug targets.

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