BSAS 2025

9th Annual Buck Student Aging Symposium

April 10th, 2025

BSAS 2025

Buck Graduate Student Society

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8:00 - 9:00 AM	Breakfast & Registration
9:00 - 9:10 AM	Opening Remarks
9:10 -10:10 AM	Arnold J. Kahn Memorial Lecture: Dr. Cornelia Weyand
10:10 - 10:55 AM	Session 1 Talks: Worthy Gutierrez (Masters student, Kapahi Lab) Zachery Mayeri (Masters student, Andersen Lab) William Chandler (Masters student, Schilling Lab)
10:55 - 11:15 AM	Break
11:15 AM - 12:00 PM	Career Panel
12:00 - 1:10 PM	Lunch + Reserved Tables
1:10 - 1:15 PM	Sponsor Talk: Novogene
1:15 - 2:30 PM	Session 2 Talks: Jewel Mangalathil (Masters student, Zhou Lab) Varunya Kattunga (Research associate, Andersen Lab) Myla Gupta (Masters student, Kapahi Lab) Lindsay Gann (Masters student, Kapahi Lab) Alex Chebykin (Masters student, Winer Lab)
2:30 - 3:45 PM	Poster Session
3:45 - 4:00 PM	Break
4:00 - 5:00 PM	Session 3 Talks: Adele Finch (PhD student, Webb Lab) Doyle Lokitiyakul (PhD student, Tracy Lab) Josef Byrne (PhD student, Melov Lab) Andrew Rodriguez (PhD student, Garrison Lab)
5:00 - 5:20 PM	Awards and Closing Remarks
5:20 PM	Reception

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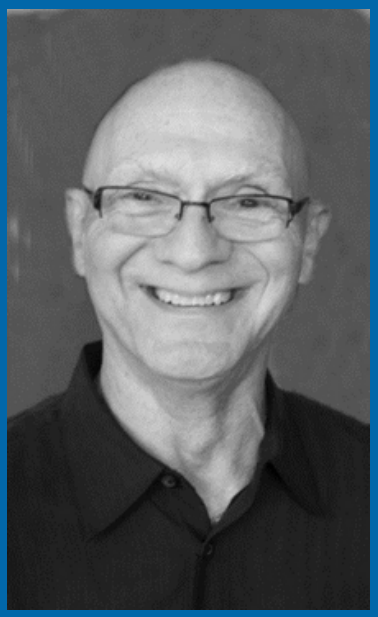
Arnold J. Kahn



Starting in 2022, the BSAS keynote has been renamed the Arnold J. Kahn Memorial Lecture. We are deeply grateful to Arnie's relatives: Dr. and Mrs. C. Ronald Kahn and Jane Carey Kahn who have committed to support the BSAS keynote this year and in future years. With their sponsorship we are able to reach preeminent scientists from around the world and this year we welcome Cornelia Weyand for the 4th Arnold J. Kahn Memorial Lecture. Arnie graduated from the University of Louisville receiving a BS and MS in biology and then received his PhD in developmental biology from Columbia University. After a post-doc at the University of Wisconsin, he took his first faculty position at Syracuse University. This was followed by subsequent positions at Washington University in St. Louis, where he was initially Professor of Biomedical Science and ultimately Assistant Dean for Biomedical Sciences at the School of Dental Medicine.

He then served as Director of the Pediatric Research Institute and Professor of Pediatrics and Orthopedic Surgery at St. Louis University. In 1990 he moved to California to become Professor and Chairman of the Department of Growth and Development at the University of California, San Francisco School of Dentistry. In 1996 and 2002, he was Visiting Professor at Hebrew University in Jerusalem. Since 2006, he has been a Professor Emeritus at UCSF, but remained active as a Visiting Scientist at the Buck Institute in Novato, CA.

Dr. Kahn published more than 200 papers, abstracts, and book chapters on a wide range of topics, and mentored dozens of fellows and students. Earlier in his career, he served as Chairman of the Gordon Conference on Bones and Teeth and as Secretary/Treasurer of the American Society for Bone and Mineral Research. His most recent research interests were on aging and longevity, serving as a member of the Longevity Consortium at California Pacific Medical Center, Visiting Scientist at the Buck Institute for Age Research and serving on the editorial board of the Journal of Gerontology.

Arnold J. Kahn Memorial Lecture by Cornelia M. Weyand, MD, PhD

Chair, Atherosclerosis and Vascular Inflammation Study Section National Institutes of Health
Professor of Medicine and Immunology, Mayo Clinic
Professor Emeritus, Stanford University

Metabolic checkpoints in autoimmune tissue inflammation

Autoimmune disease is traditionally understood as aberrant immunity against self-antigens, but recent insights have redirected attention to the immune aging process as a critical risk factor of autoimmunity. Older individuals lose the ability to generate lasting, highly specific adaptive immune responses and gain a state of low-grade smoldering inflammatory activity, reflective of dwindling adaptive immunity and poorly controlled innate immunity. In predispose individuals, the immune aging process promotes frank autoimmune disease. A hallmark of immune aging is the restructuring of metabolic networks as regulators of immune effector functions. We have identified critical metabolic checkpoints in patients with the autoimmune disease rheumatoid arthritis (RA). In T cells from RA patients, insufficient mitochondrial DNA repair causes mitochondrial impairment that redirects multiple T cell effector functions. mtDNA leakage leads to inflammasome assembly, the T cells die a lytic death. RA T cells have low levels of ATP due to low efficiency of the electron transport chain. The TCA cycle reverses, and acetyl-CoA is released into the cytosol. Excessive lipogenesis promotes lipid droplet deposition and stimulates formation of invasive membrane structures. Overall, accumulation of acetyl-CoA results in cytoskeletal acetylation, cellular polarization, and high cellular motility.

A downstream consequence of mitochondrial failure in RA T cells is the expansion of the rough endoplasmic reticulum. This leads to the accumulation of mRNAs that encode for membrane-integrated molecules, most importantly, the cytokine tumor necrosis factor (TNF). We have identified the underlying defect: insufficient mitochondrial release of the amino acid aspartate depletes the cytosolic pool of NAD, signaling chronic ER stress. This metabolic defect translates into excessive TNF production and enables the RA T cell to drive TNF-dependent tissue inflammation.

Together, metabolic deviations caused by the failure of mitochondrial DNA repair transform RA T cells into proinflammatory effector cells.

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Student Talks

Worthy Gutierrez

Master of Science Program
Dominican University

Faculty Mentor
Pankaj Kapahi, PhD

Investigating the Molecular Basis of Metabolites that Confer Protection Agaisnt Sleep and Neurological Disorders in Drosophila Neurodegenerative Models

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by tau protein aggregation, leading to neuronal loss and cognitive decline. Affecting over 24 million people worldwide, AD currently has no cure, and existing treatments provide only temporary relief. Sleep disturbances are closely linked to AD progression, impairing the brain's ability to clear toxic proteins and exacerbating neuroinflammation. Moreover, sleep deficits negatively impact caregivers, creating a vicious cycle. Metabolic changes may offer novel therapeutic targets and biomarkers for AD. This study utilizes Drosophila melanogaster to investigate metabolites and genes associated with AD and sleep disturbances. Mendelian randomization (MR) will be employed to identify metabolites causally linked to both conditions. Metabolites identified through MR will be supplemented in fly models of AD to assess their potential to improve sleep and mitigate neurodegeneration. The focus metabolite, L-alanine, was supplemented in an ad libitum (AL) diet. Assays including sleep analysis, lifespan and healthspan measurements (such as climbing ability for neuromuscular function), and brain histology (cell death and reactive oxygen species), were conducted to evaluate its therapeutic potential. Our findings demonstrate that L-alanine supplementation improves sleep and ameliorates neurodegenerative phenotypes. Furthermore, knockdown of alanine aminotransferase (ALAT), the enzyme converting alanine to pyruvate, induced a sleep deficit that was rescued by alanine supplementation. These results suggest a potential neuroprotective role for L-alanine in AD, warranting further investigation.

William Chandler

Dominican University Masters Program

Faculty Mentor

Birgit Schilling, PhD

The Degenerative Decline of the Musculoskeletal System with Aging: Bone Fracture Remodeling and Chondrocyte Senescence

Cellular and molecular mechanisms underlying musculoskeletal aging by integrating investigations into chondrocyte senescence to gain insights of degenerative effects of aging. In parallel with the analysis of collagen dynamics during bone fracture healing to provide insights in the biological changes from age in bone fracture healing. In primary human chondrocytes, senescence is induced and characterized by hallmark features including increased expression of cell cycle regulators, nuclear flattening, and cell hypertrophy. Mitochondrial dysfunction is proposed as a driver for mitochondrial-induced dysfunction-associated senescence (MiDAS), contributing to the deterioration of articular cartilage. To address this, the natural metabolite Urolithin A (UA) is evaluated for its potential as a senolytic agent, with its efficacy measured using a Fully Automated Senescence Test (FAST) that provides an unbiased quantification of senescence signatures. In a complementary investigation, the study examines the remodeling process during bone fracture healing, which involves sequential phases of bone remodeling. Spatial proteomics through MALDI is employed to compare young and aged mouse groups, focusing on the differential identification fibril organization of key collagen proteins, notably collagen type 1 alpha 1 and alpha 2. These proteins are implicated in age-related delays in fracture healing, as result of alterations in their assembly and function. Cellular senescence observed in human chondrocytes with the changes in collagen dynamics that impair fracture healing, this integrated approach provides a comprehensive view of musculoskeletal degeneration with aging. The insights gained pave the way for developing targeted therapeutic strategies aimed at mitigating the degenerative effects of aging in cartilage.

Zachary Mayeri

Master of Science Program
Dominican University
Faculty Mentor
Julie Andersen, PhD

Inducing mitophagy to suppress neuropathology in Alzheimer's Disease

Despite FDA-approved amyloid-beta (Aβ) therapies in Alzheimer's disease (AD), tau pathology remains untreated and is closely linked to cognitive decline. Mitophagy, the process of mitochondrial degradation, is vital for maintaining neuronal health, and its dysregulation is implicated in AD. Recently, the Andersen and Lithgow labs identified a natural compound (MIC) that induces mitophagy and extends the lifespan of C. elegans. We hypothesized that MIC would significantly mitigate neuropathology in AD by targeting tau pathology. In this study, aged 3x-Tg AD mice were fed an MIC-containing diet, and immunohistochemistry was performed on hippocampal tissue to visualize Aβ and phospho-Tau (pTau) lesions. While MIC had little effect on Aβ, it significantly reduced pTau, including its nuclear and perinuclear localization. These results highlight MIC as a promising candidate for treating tau pathology, addressing an unmet need in AD.

Jewel Mangalathil

Master of Science Program
Dominican University

Faculty Mentor
Chuankai (Kai) Zhou, PhD

Mechanisms of Rapid Lysosomal Acidification

Lysosomal pH regulation is essential for proper cellular function, influencing degradation, recycling, and signaling pathways that maintain homeostasis. In this study, we investigated a rapid lysosomal acidification process induced by nutrient starvation. Using the pH Lysosomal Activity Reporter (pHLARE) biosensor, we observed an immediate decrease in sfGFP fluorescence, indicating a sharp increase in lysosomal acidity within 5 seconds induced by nutrient starvation. To determine whether nutrient deprivation was responsible for this acidification, we added amino acids, vitamins, glucose, and salts back to the medium. While amino acid supplementation partially restored sfGFP fluorescence within 30 minutes to 1 hour, it failed to suppress the rapid lysosome acidification, suggesting that additional factor(s) are responsible for the induced rapid lysosomal acidification. Understanding these rapid lysosomal acidification may provide new insights into cellular adaptation mechanisms and potential therapeutic targets for lysosome-associated diseases.

Lindsay Gann

Master of Science Program
Dominican University

Faculty Mentor
Pankaj Kapahi, PhD

DOR/TP53INP regulates organismal aging through ovarian senescence in Drosophila melanogaster

Reproductive decline due to ovary aging occurs relatively early in the female lifespan. Menopause, characterized by the cessation of menses, is associated with increased risk for systemic diseases such as cardiovascular disease, obesity and diabetes, and osteoporosis. Furthermore, research shows a link between age at natural menopause and lifespan, but the mechanism behind this association is not clear. Our lab has identified TP53INP (DOR) in Drosophila melanogaster through research into late-life mortality. Inhibition of DOR in the whole body of the fly leads to decreased lifespan and decreased healthspan markers, as well as markers of ovarian senescence. This study aimed to find the mechanism driving the systemic effects of DOR by inhibiting its expression in specific tissues of the ovary. We tested this hypothesis by inhibiting the expression of DOR in the germline stem cell as well as the follicle and escort cells of the fly ovary. Assays included lifespan, starvation, gut permeability, climbing, fecundity, senescence marker staining, and RNA-seq. We found that DOR inhibition in the germline stem cells did not lead to a decrease in lifespan or healthspan markers. DOR inhibition in the follicle and escort cells was associated with a significant decrease in lifespan, with inconsistent results on healthspan markers. These findings highlight the importance of ovarian tissue function to the systemic health of the organism and highlight the need for more research into ovarian health and lifespan.

Alex Chebykin

Master of Science Program
Dominican University

Faculty Mentor
Dan Winer, MD
David Furman, PhD

Leveraging microgravity to model metabolic aging in the immune system

Existing models for aging do not recapitulate human biology well. Here we used short-term (24 hours) simulated microgravity exposure and evaluated the effects on energy metabolism and gene expression profiles in human peripheral blood mononuclear cells (PBMCs) from young (20-30 y.o) and old (65+ y.o.) human donors through the use of a recently developed flow cytometry-based single-cell energetic metabolism by profiling translation inhibition (SCENITH) method and RNA sequencing. We observed significant overlaps in aging and simulated microgravity on metabolic function, particularly in innate immune system cells. These results will advance our understanding of dysregulation of immunometabolism in both aging and the microgravity environment and we can test potential interventions to rescue these phenotypes.

Varunya Kattunga, MS

Research Associate

Faculty Mentor

Julie Andersen, PhD

Uncovering Novel Mitophagy Pathways and Drugs Through Deep Cellular Phenotypic Profiling

Mitochondrial dysfunction is a hallmark of aging and a key driver of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. A major contributor to mitochondrial dysfunction is impaired mitochondrial quality control (QC), including the failure to selectively eliminate damaged mitochondria via mitophagy. Multiple mitophagy pathways are known, yet few of them have been specifically targeted pharmacologically. We present here a live-cell, high-throughput / high-content imaging platform for deep phenotypic profiling of mitochondria in cell cultures, designed to uncover novel modulators and mechanisms of mitophagy. Using a cell line expressing a genetically encoded mitochondrial ATP biosensor combined with time-course confocal imaging we monitored the responses of microscopically observable mitochondrial phenotypes to a compounds in a small molecule library. This approach revealed dynamic mitochondrial phenotypes, including morphology changes, ATP heterogeneity, and mitophagy. To interpret this rich dataset, we employed two complementary analysis strategies: (1) a feature-based analysis to directly quantify mitophagy, and (2) a deep learning approach to cluster images based on visual similarity, revealing latent phenotypic patterns not captured by traditional metrics. This platform provides an unprecedented view into mitochondrial QC dynamics and offers a powerful approach for identifying new mitophagy pathways. Ultimately, our goal is to use this system not only to discover compounds that support mitochondrial turnover, but also to dissect their mechanisms in a way that informs therapeutic strategies for age-related decline.

Myla Gupta

Master of Science Program
Dominican University

Faculty Mentor
Pankaj Kapahi, PhD

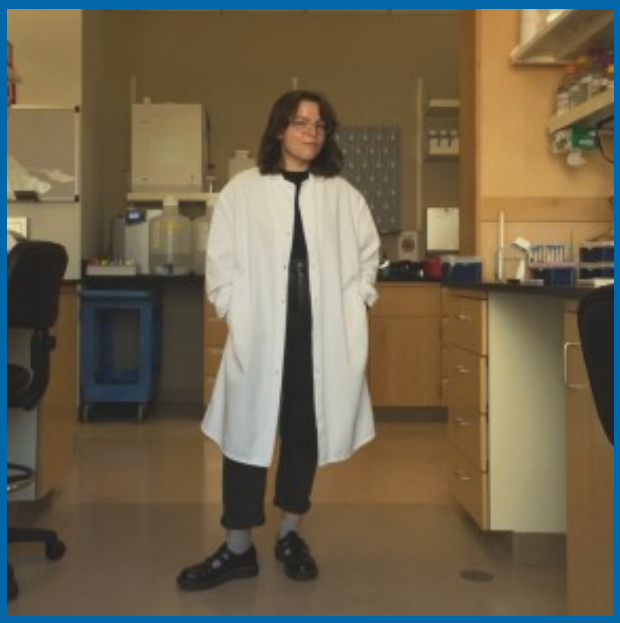
Neural expression of Abd-B in adulthood modulates aging variance in Drosophila melanogaster through the mTOR pathway

In this study, we used the model Drosophila melanogaster to investigate mechanisms of aging variance by modulating neural expression of the developmental HOX gene Abdominal-B (Abd-B). Because Abd-B has known mammalian homologs, Abd-B's aging mechanism in flies may be conserved in humans, offering targets for human treatment from this and following studies. We hypothesized that neural expression of Abd-B is sufficient to drive aging, and that Abd-B shortens lifespan through its role as a transcription factor modulating expression of other interactor genes.

Our lab conducted a Drosophila Genome-Wide Association Study (GWAS) targeting aging regulators, which indicated Abd-B to be a candidate for regulating aging variance. We tested this association using a dietary restriction (DR) diet to model Abd-B expression, as DR has been established as a robust method of lifespan extension. The lifespan effects we observed from Abd-B manipulation on flies placed on DR indicated Abd-B's role in aging variance; the interaction between a proven lifespan-extension method and a lifespan-shortening gene illustrated the role and scope of Abd-B's regulation. Our lab has seen changes in gene transcription with age in neurons particularly, so this study assessed the tissue specificity of Abd-B expression and determined that neural expression was sufficient to modulate aging variance. Modulating Abd-B expression in the brain influenced Drosophila lifespan variance and health, and was determined to enact these effects through upregulation of the mTOR pathway.

Addie Finch

Neuroscience graduate student
Brown University
Faculty Mentor
Ashley Webb, PhD



Investigating the mechanisms of mitophagy in supporting hippocampal neurogenesis during aging

The formation of new neurons in the hippocampus (neurogenesis) starkly decreases throughout lifespan, contributing to age-associated cognitive decline. The endogenous source of new neurons in the adult brain is neural stem cells (NSCs), and most NSCs exist in a reversible, cell-cycle arrested state of quiescence. Quiescent NSCs may become activated and proliferate, thereby integrating into hippocampal circuitry. Decline in neurogenesis is partly attributed to a deepening of quiescence that occurs with age, meaning that aged NSCs have a reduced capacity to become activated. Additionally, NSCs exhibit a significant decline in mitochondrial function throughout aging that correlates with a loss of proliferative potential and neurogenesis. This may be due to age-associated dysfunction in mitophagy, the process by which damaged and excess mitochondria are degraded within the lysosome. We have observed that quiescent NSCs are enriched for damage-associated mitophagy genes and, through live cell imaging, have shown an increased targeting of mitochondria for degradation in quiescent NSCs. We have also uncovered evidence of a significant shift in mitophagy in aged quiescent NSCs compared to young NSCs. Additionally, we have identified a mitophagy receptor, Optineurin (Optn), that may play a critical role in regulating mitophagy in quiescent NSCs. The evidence provided here suggests that mitophagy may be a key metabolic quality control mechanism that maintains the functional quiescent NSC pool to support the formation of new neurons and cognitive function throughout aging.

Josef Byrne

Buck-USC Biology of Aging PhD Program
University of Southern California
Faculty Mentor
Simon Melov, PhD

Lower for Longer: Assessing Early Statin Use for Atherosclerosis and Aging

Atherosclerosis remains the leading cause of mortality in older adults, commonly manifesting as heart attacks or strokes. Yet large-scale imaging studies reveal that subclinical plaque is already common among presumed "low-risk" individuals in midlife, suggesting current short-term risk assessments may vastly underestimate true lifetime vulnerability. These findings align with a cumulative exposure model in which even moderate LDL cholesterol levels, if sustained over decades, can lead to notable arterial damage. This presentation examines the rationale for a "lower for longer" approach to LDL management centered on earlier and more widespread use of statins. While statins are widely recognized for reducing cardiovascular events, guidelines often recommend their initiation based on short-term risk thresholds, potentially missing an opportunity to prevent plaque formation in people seemingly at low risk today. Furthermore, systemic consequences of atherosclerosis and how these may intersect with the aging human are considered. While taking into account potential side effects and adherence challenges in managing LDL levels with statins over a lifetime, this presentation aims to assess how the vast majority of individuals may benefit from curbing atherosclerosis well before it becomes symptomatic. Although more concrete and targeted evidence is needed, the "lower for longer" hypothesis calls for a reexamination of current atherosclerosis prevention paradigms and the assessment of the role atherosclerosis may play more broadly in human aging biology.

Doyle Lokitiyakul

Buck-USC Biology of Aging PhD Program
University of Southern California
Faculty Mentor
Tara Tracey, PhD

Role of EIF4B in local activity-dependent translation and synaptic plasticity

Long-term potentiation (LTP), a form of synaptic plasticity linked to the formation of new memories, is defined as the persistent strengthening of synaptic connections in response to neuronal activity. Protein synthesis is required for the expression of LTP at synapses, and neuronal activity regulates the translation of specific mRNAs in dendrites. The activity-dependent mechanisms that regulate translation initiation in dendrites could impact the expression of LTP. Eukaryotic translation initiation factor 4B (eIF4B) is an RNA binding protein that facilitates the recruitment of the preinitiation complex to mRNA, promoting the initiation of translation. The function of eIF4B has been primarily characterized in non-neuronal cells, but the role of eIF4B in translation initiation in neurons in not well understood. To study the role of eIF4B in neurons, we generated a lentivirus for expression of a short hairpin (shRNA) to knockdown eIF4B in human iPSC-derived neurons. Control human iPSC-derived neurons exhibited increased puromycin labeling in dendrites after cLTP induction compared to unstimulated neurons, indicating enhanced protein synthesis in dendrites during LTP expression. This enhancement of protein synthesis during LTP was blocked in human iPSC-derived neurons with eIF4B knockdown, suggesting that eIF4B is required for activity-dependent translation in dendrites. The knockdown of eIF4B also blocked the recruitment of postsynaptic AMPA receptors during LTP expression in human iPSC-derived neurons, supporting that eIF4B is required for the expression of LTP. Overall, our findings suggest that eIF4B could be an activity-dependent molecular switch that turns on protein synthesis in dendrites for the expression of LTP at synapses.

Andrew Rodriguez

Buck-USC Biology of Aging PhD Program
University of Southern California
Faculty Mentor
Jennifer Garrison, PhD

Neuropeptide Regulation of the Heat Shock Response

Heat stress and aging are both well-studied causes of molecular damage, which animals can overcome via an evolutionarily conserved, hormetic heat shock response that has been well characterized in the model organism Caenorhabditis elegans (C. elegans), where its activation has been repeatedly shown to extend lifespan. Activating the pair of primary thermosensory neurons in the worm's head is both necessary and sufficient for driving the heat shock response across the body, however the relevant signaling molecules released by the primary thermosensory neurons has never been identified, and these sensory neurons do not have any synapses with the serotonergic neurons that mediate the response in peripheral tissues. Whether the original signals are released outside of synapses or instead require interneurons to relay the transmission, a leading candidate is the neuropeptide nematocin – after all, neuropeptides can not only be released outside of synapses, they even drive excitatory synaptic transmission for these thermosensory neurons, where nematocin is most highly expressed. Indeed, current findings suggest a key role for nematocin in regulating the animal's physiological response to heat stress. Identifying drivers of the heat shock signaling pathway may elucidate the phenomenon of age-associated dysregulation of inter-tissue communication, thereby pointing to therapeutic targets for age-related diseases.

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Posters

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#1 Steven Wrobel

Master of Science Program
Dominican University

Faculty Mentor
Akos Gerencser, MD, PhD

Deep bioenergetic phenotyping to reveal long-term effects of exercise on mitochondria in muscle biopsies from elderly individuals

Mitochondrial dysfunction is one of the hallmarks of aging. A cornerstone of this dysfunction is a loss in the bioenergetic function of mitochondria, which encompasses oxidative phosphorylation and other functions linked to respiration. Skeletal muscle is of particular interest for our research as a key property of aging is frailty and the loss of skeletal muscle mass. Skeletal muscle can respond to stressors such as vigorous exercise, and exercise is one of the most effective anti-aging interventions. Here we study the effects of exercise on aging in mitochondria from human skeletal muscle biopsies using Seahorse XF respirometry, assisted by a novel automated method using liquid handling robotics for enabling a deep bioenergetic phenotyping assay. The MOVE (Molecular Optimization via Exercise) study aims to enroll 80 elderly (>65 yo) participants comparing former elite athletes to healthy sedentary individuals. As one of the multiple outcomes of this study, we are testing if exercise provides long-lasting quantitative or qualitative differences in skeletal muscle mitochondria, in respect of substrate utilization, uncoupling, capacities to make ATP, to work against resistance, and metabolic flexibility.

#2 Ariel Floro

Buck-USC Biology of Aging PhD Program
University of Southern California

Faculty Mentor
Eric Verdin, MD

Immunophenotyping of peripheral blood mononuclear cells from healthy older adults after daily ketone ester injestion

Aging leads to dysfunction in the immune system, resulting in increased susceptibility to infections and decreased responsiveness to vaccines. This was highlighted during the COVID-19 pandemic as old age was the highest risk factor for hospitalization and death due to SARS-CoV-2 infection. Ketogenic diets and fasting have been researched as interventions against aging and they work in part by increasing circulating levels of ketone bodies. Exogenous ketones, such as ketone ester drinks, have been studied as alternatives to improve adherence by directly supplementing ketone bodies. As ketone bodies circulate throughout the blood, they interact with many immune cell types that are also present. For example, beta-hydroxybutyrate, the most abundant ketone body produced, has anti-inflammatory properties, such as inhibiting the NLRP3 inflammasome, and recent studies suggest that it may augment T cell responses. In this placebo-controlled, double-blinded study, healthy older adults (>65 years old) ingested a ketone ester drink or placebo daily for 12 weeks. Peripheral blood mononuclear cells were isolated from participants' blood and analyzed using high-dimensional flow cytometry. The results of this study will help to clarify the effects of ketone bodies on immune function in older adults, potentially informing therapeutic strategies against immune aging.

#3 Ling-Hsuan Sun

Buck-USC Biology of Aging PhD Program
University of Southern California

Faculty Mentor
Malene Hansen, PhD

Non-canonical roles for autophagy protein ATG16 in neuronal exopher biogenesis and longevity

During autophagy, cellular components are recycled through sequestration into autophagosomes, which fuse with lysosomes for degradation. A key early step is the conjugation of ATG8 proteins to membranes via a complex including ATG16. Beyond canonical autophagy, recent findings suggest non-canonical autophagy (NCA) functions, where ATG8 is lipidated onto alternative vesicles, potentially contributing to degradation or secretion. In mammalian cells, ATG16 facilitates some forms of NCA, with its WD40 domain playing a key role. However, the mechanisms underlying NCA vesicle formation remain unclear, as does its potential role in aging.
Our lab found that neuronal inhibition of early autophagy genes suppresses polyQ aggregation, extends lifespan, and enhances exopher biogenesis in C. elegans (Yang et al., Nature Aging, 2024). Exophers are large vesicles that expel neurotoxic contents, and these phenotypes require ATG-16.2, a C. elegans ATG16 ortholog, and its WD40 domain. To determine whether exopher formation represents an NCA event, I examined ATG8 proteins in exophers originating from touch neurons. My preliminary data show that ATG8 localizes within exophers, forming puncta-like structures in a lipidation-dependent manner. I am currently characterizing these ATG8-positive structures and their regulation by ATG-16.2.
These findings suggest that exophers may represent a novel class of NCA vesicles regulated by ATG-16.2. Understanding non-canonical roles of autophagy genes in cellular quality control, aging, and neurodegeneration may provide new insights into therapeutic strategies for age-related diseases.

#4 Josef Byrne

Buck-USC Biology of Aging PhD Program
University of Southern California

Faculty Mentor
Simon Melov, PhD

The Aging Human Postmenopausal Ovary: A Multi-Omic Atlas

Menopause marks not only the end of female fertility but also the onset of a broader health decline associated with aging. While reproductive longevity has historically been understudied, recent advances have begun to illuminate the biological factors influencing female health before menopause. However, the molecular and cellular changes that occur in the ovary after menopause remain poorly understood. In this study, we used a multi-omic approach with patient-matched samples to characterize the aging postmenopausal ovary (ages 50–84) from 40 human donors. Utilizing recently developed technologies in dispersed snucRNA-seq (10X Flex Kit, multiplexed fixed RNA profiling) and spatial whole-transcriptome single-molecule FISH at subcellular resolution (Nanostring/Bruker CosMx), we identified and validated diverse cell types in the aging ovary. We also discovered transcriptionally distinct Activated Stromal cell populations that are enriched or depleted with age and bear DNA damage and cell-cycle arrest markers. Extending beyond the transcriptome, we have profiled the proteome using mass spectrometry and identified pathways associated with fibrosis and inflammation enriched with age. Leveraging this multi-omic dataset with patient-matched samples across diverse technologies, our team continues to uncover the molecular underpinnings that define the aging postmenopausal human ovary, enabling potential interventions to address the systemic health decline following menopause.

#5 Jun-Wei Brendan Hughes

Buck-USC Biology of Aging PhD Program
University of Southern California

Faculty Mentor
Judith Campisi, PhD

DNA damage drives neuronal Alzheimer's disease phenotypes

Cells face tens of thousands of DNA lesions every day, and if the cell cannot faithfully repair those lesions, DNA damage response (DDR) signaling persists which drives critical cell fate decisions like apoptosis or senescence. Increases in DNA damage and oxidative lesions, and decreases in DNA repair, all coincide with the onset of neurodegenerative disorders, such as Alzheimer's (AD) and Parkinson's disease, as well as general cognitive decline with age, and are thought to be early drivers of these diseases. Human models highlight these relationships as patient-derived directly induced neurons (iNs) from fibroblasts of AD patients display abnormal gene expression and chromatin states and higher levels of oxidative stress and DNA damage. Transdifferentiation models are advantageous in aging research due to the retention of age-specific transcriptomic and epigenetic signatures, relative to induced pluripotent stem cell models. Using this system, we show significant gene expression concordance between iNs after DNA damage and AD iNs. Weighted gene correlation network analysis identified seven genes regulating whole pathway responses in the DNA damaged iNs. Investigating the protein response in iNs after DNA damage showed increases in senescence-associated protein p21, but no increase in p16 and nuclear size, as well as no decrease in HMGB1 and LMNB1. When compared to fibroblasts of the same donor after DNA damage, p16 increased and LMNB1 decreased, as canonically expected. Ultimately, DNA damage may be a driver of neuronal AD phenotypes and uncovering targets that stabilize the genome could lead to novel AD therapeutics.

#6 Misaki Belser

Buck-USC Biology of Aging PhD Program
University of Southern California

Faculty Mentor
Ashley Webb, PhD

A new method for generating young and aged hypothalamic neurons via direct reprogramming

The hypothalamus is the central regulator of homeostatic processes such as circadian rhythms, body composition, and hormonal states. These processes are well-known to change with age, yet how specific neuronal cell types in the hypothalamus alter during aging remains poorly understood. This is in part due to sparsity of hypothalamic cell types and technical challenges in isolating neurons from the brain. We thus are developing a system to directly reprogram fibroblasts into POMC hypothalamic neurons, first starting with reprogramming mouse embryonic fibroblasts (MEFs). POMC neurons are hypothalamic regulators of energy homeostasis and are altered with age. We found that the reprogramming factors SIX3, LHX1, ASCL1, and MYT1L (SLAM factors) successfully convert MEFs into induced POMC neurons (iPOMCs). Reprogramming was confirmed using POMC-eGFP reporter fibroblasts and immunocytochemistry for neuronal markers. Using RT-qPCR to detect POMC-specific gene expression, we further validated cell fate conversion and detected specific POMC subtypes. To understand the contribution of the different SLAM factors, we examined how removal of individual factors impacted reprogramming efficiency. Removal of LHX1 caused the greatest loss in efficiency both in terms of the percentage of GFP positive cells and gene expression levels through qPCR. Thus, LHX1 is a crucial element in the reprogramming, while combined SLAM factors result in the greatest reprogramming efficiency. In summary, we have developed a novel system of direct reprogramming to generate iPOMC cells in a dish. Future work will leverage iPOMCs to determine mechanisms of POMC aging, providing key insight into how energy homeostasis is altered with age.

#7 Pascale Foreman

SPARC Post-baccalaureate
Buck Institute

Faculty Mentor
Tara Tracy, PhD

Developing translational methods of delivery of KIBRA peptide for synapse repair in Alzheimer's Disease

Loss of memory due to synaptic dysfunction is a key mechanism that underlines Alzheimer's disease (AD) and related tauopathies. Long-term potentiation (LTP) is a function essential for learning and memory formation and occurs at synapses between neurons. Targeting synapse repair and rescuing LTP may be a viable option for reversing neurodegeneration and restoring memory in AD and related tauopathies. KIdney/BRAin (KIBRA) protein is a postsynaptic protein that is critical for plasticity and memory, and is decreased in the brains of AD and tauopathy patients. To address this, we developed a modified KIBRA peptide (KBpep) that can permeate the cell membrane and mimic the functions of endogenous KIBRA. To study the effects of KBpep in vivo, we utilized tauKQ mice, which exhibit impaired LTP and impaired hippocampal-dependent memory. Intracerebroventricular (ICV) delivery of KBpep through osmotic pump successfully restored LTP and improved memory.

To advance toward clinical application, we are exploring intranasal administration due to its minimally invasive nature and ability to circumvent the blood brain barrier. When delivering KBpep intranasally, KBpep successfully reaches the hippocampus within 6 hours and interacts with its downstream target, protein kinase M ζ (PKMζ). To investigate potential downstream mechanisms, we performed immunostaining for various protein kinase C (PKC) isoforms, revealing striking and specific distributions of different PKC isoforms across distinct hippocampal regions. These findings support the therapeutic potential of KBpep in reversing tauopathy-related synaptic plasticity impairment and reversing memory loss and highlight its potential translation through intranasal administration.

#8 Allison Linkous

SPARC Post-baccalaureate
Buck Institute

Faculty Mentor
Malene Hansen, PhD

Investigating how autophagy regulates intestinal barrier function in aging and age-related diseases

Autophagy is a conserved catabolic process that plays an essential role in cellular homeostasis by recycling organelles and protein aggregates via lysosomal degradation. Autophagy is also important for the health and function of different tissues, including the barrier function of aging intestines, though the mechanism is unknown. Intestinal barrier function is critical for nutrient absorption, metabolism, and defense against pathogens. Both autophagy and intestinal barrier function are known to decrease with age and in age-related diseases,' so understanding how the intestinal barrier is regulated and how function can be prolonged during aging is of the utmost importance. Our lab previously found that C. elegans intestines become leaky with age. However, this leakiness can be delayed in long-lived mutants in an autophagy-dependent manner. The connection that remains to be explored is how autophagy is specifically regulating intestinal barrier function with age. Currently I have identified promising markers of epithelial morphology that show age-related changes. Using these markers, I have uncovered a correlation between mis-localization of epithelial morphology and disruption in the intestinal barrier. Preliminary results also suggest that neuronally expressed amyloid beta, but not muscle expressed amyloid beta causes intestinal barrier defects. As my project develops, the results of this study will help reveal how autophagy promotes intestinal integrity, and how intestinal health can affect the health and function of other tissues in the body, and vice versa.

#9 Anja Sandholm

SPARC Post-baccalaureate
Buck Institute

Faculty Mentors
Judith Campisi, PhD
Lisa Ellerby, PhD

Modeling Oligodendrocyte Dysfunction in Alzheimer's Disease Using Age-Preserved Directly Converted Human Cells

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder predominantly affecting the elderly, characterized by the progressive loss of neuronal function and cell death. Emerging evidence suggests that dysfunction of oligodendrocytes — the glial cells responsible for myelin production and neuronal metabolic support — may contribute significantly to neuronal impairment in AD. Given the critical role of myelin in maintaining neuronal integrity, its disruption may exacerbate neuronal dysfunction and cell loss. To investigate the contribution of oligodendrocyte dysfunction in AD within an aging context, we directly converted human fibroblasts from AD patients directly into human-induced oligodendrocyte-like cells (dc-hiOLs) via overexpression of transcription factors SOX10, OLIG2, and Nkx6.2. Direct differentiation preserves the age-related epigenetic marks of the donor which are essential for modeling the aging signature underlying AD pathology. Comprehensive analyses, including bulk RNA sequencing and immunocytochemistry, were employed to assess cellular processes vital for the functions of mature dc-hiOLs. Elucidating mechanisms of AD-related oligodendrocyte dysfunction will facilitate future screens for disease-targeting drugs.

#10 Alberto Herrera Rodarte

SPARC Post-baccalaureate
Buck Institute

Faculty Mentor
Jennifer Garrison, PhD

Evaluating the Impact of Reproductive Histories on Alzheimer's Disease Outcomes

Female reproductive aging has been associated with Alzheimer's Disease (AD) risk; observational studies in humans have looked at how factors like reproductive span or reproductive onset influence AD risk, though research findings have been contradictory. To clarify the connection between reproductive history and AD outcomes, we need to thoroughly document individual reproductive histories and look at this data in the context of AD severity. From this, we can then clearly identify patterns of reproductive history that correlate with increased or decreased AD severity. These patterns can then be tested by manipulating reproductive history to see if these reproductive trajectories cause changes in AD severity. Comprehensive analysis of reproductive histories and control isn't feasible in mammalian models. This prompted the use of C. elegans, in which an individual's reproductive history can be tracked throughout life using tools including microscopy, fluorescent reporters, and counting laid events. C. elegans also has AD models with quantifiable phenotypes that facilitate our analysis of reproductive biology and AD. We are testing several genetic backgrounds that provide unique reproductive histories to investigate AD phenotype severity. Our models act through gametogenesis and ovulatory signaling to alter reproductive history. Our first model expresses excess ovulatory signal, the second reduces ovulatory inhibition signaling, and the third provides an expanded germline stem cell pool for gametogenesis. By looking at these reproductive backgrounds and monitoring for AD phenotypes, our findings can inform how reproductive histories can cause changes in AD severity and could inform how reproductive aging in humans influences AD outcomes.

#11 Sahiba Dogra

SPARC Post-baccalaureate
Buck Institute

Faculty Mentor
Julie Andersen, PhD

Investigating the mitochondrial targets of two autophagy-inducing compounds and their role in neurodegeneration

Accumulation of protein aggregates is a key hallmark of neurodegenerative disease that affects millions of people nationwide. Despite autophagy's essential role in clearing protein aggregates, there are no FDA-approved treatments for neurodegeneration that target autophagy. We aim to identify druggable targets within the autophagy pathways critical to alleviating neurodegenerative plaques by investigating the Mitophagy-Inducing Compound (MIC) and Urolithin A (UA). Both compounds induce autophagy and alleviate key neurodegenerative phenotypes such as tau and amyloid beta accumulation, in preclinical models. However, MIC's short half-life and the untested clinical efficacy of UA in neurodegeneration are obstacles in translating these compounds into therapeutics. To address these issues, we leverage the biological targets of these two compounds to identify novel therapeutic pathways and screen for more pharmacologically viable compounds. In this study, we validate the mitochondrial pyruvate carrier (MPC1) as a target of UA and investigate the biological relevance of heat shock protein 10 (HSP10) as a direct binding partner of MIC. MPC1 and HSP10 are key players in mitochondrial homeostasis and bioenergetics. Using cellular thermal shift assay (CETSA) westerns, we show that UA causes thermal destabilization of the target protein, confirming drug-target interaction. To validate the biological relevance of HSP10, we will knock down HSP10 before MIC treatment to assess whether HSP10 is required for MIC's protective effects against neurodegenerative phenotypes. These findings will yield novel protein targets to screen for autophagy-targeted therapeutics that alleviate neurodegeneration.

#12 Varunya Kattunga

Research Associate
Buck Institute

Faculty Mentor
Julie Andersen, PhD

Scripted Programming of Acoustic Liquid Handling

Precise and flexible liquid handling is essential for designing complex, high-throughput biological assays, including drug screening, dose-response studies, and time-course experiments. Acoustic dispensing, which allows contactless transfer of very small volumes, supports these designs but requires complex, often manual programming to translate assay layouts into executable instructions. To streamline this process, we developed user-friendly, script-based tools in Wolfram Mathematica that automate picklist generation for the Beckman Coulter Echo 650 acoustic liquid handler, integrated within Revvity's Plate:Works scheduling software. These tools convert simple Excel-based inputs—defining plate maps and compound inventories—into all necessary files for automated execution, including picklists, inventory, and process instructions. The Assay Picklist Generator supports multi-compound dosing at defined concentrations and is ideal for assays such as mitochondrial membrane potential time courses. The Screening Picklist Generator is tailored for library screening, enabling redistribution of compounds from 320-compound source plates into 384-well assay plates with 240 active wells, across multiple concentrations with built-in controls. Both tools include error-checking features and are optimized to reduce unnecessary plate movements, increasing efficiency and reproducibility. In our hands, these tools significantly improved the scalability and reliability of high-throughput assay setup within an automated robotic workcell. Future iterations will extend compatibility to conventional pipette-based platforms to broaden accessibility across labs.

#13 Duncan Croll

Research Associate
Buck Institute

Faculty Mentor
Judith Campisi, PhD

Isolating DNA Damage as a Contributor to AD-Like Transcriptomic Traits in Induced Neurons

Alzheimer's disease (AD), the most common cause of dementia, can be divided into two major categories. The first is familial AD, which occurs around middle age, follows a hereditary pattern, and results from a distinct set of mutations. The second and more common form is sporadic AD, which occurs later in life, follows no hereditary pattern, and for which the underlying mechanisms remain poorly understood. The accumulation of DNA damage in neurons with age is thought to be a possible contributor. Our group is studying this potential mechanism of AD disease initiation in vitro using induced neurons (iNs) as a model system. iNs are generated by reprogramming human patient-derived fibroblasts. AD patient-derived iNs show a transcriptomic concordance with post mortem AD patient brain tissues and unlike iPSC based models of AD, they retain transcriptomic, epigenetic, and mitochondrial signatures of human aging. Data from our group indicate that inducing DNA damage in non-AD patient-derived iNs via irradiation produces a phenotype that is transcriptomically similar to that of AD patient-derived iNs. However, it is unclear whether this can be attributed to DNA damage or other forms of stress caused by the irradiation. To determine whether irradiated non-AD iN's similarity to AD iNs is attributable to DNA damage or a more general stress state, we conducted a time-course bulk RNA-Seq study on non-AD patient derived iNs subjected to DNA damage via an alternative means, Doxorubicin treatment, in addition to a non-DNA damage related stressor, Antimycin A, which causes mitochondrial dysfunction.

#14 Rachel Butterfield

Research Associate
Buck Institute

Faculty Mentor
Judith Campisi, PhD

Temporal Dynamics of DNA Damage Repair in Irradiated Neurons and Fibroblasts

DNA damage is a significant biomarker of aging, with broad implications in neurodegeneration and other age-related diseases. Double-strand breaks (DSBs) are particularly problematic and are associated with cognitive decline in Alzheimer's Disease (AD). Cellular responses to insults such as DNA damage determine cell fate, and instances of DNA damage response (DDR) can lead to an accumulation of senescent cells characterized by resistance to apoptosis, senescence-associated secretory phenotype (SASP), and cell cycle arrest. As post-mitotic cells, neurons may rely on unique DDR pathways compared to other cell types to persist and preserve their phenotype. Though increasing resilience, this preservation technique is also mutagenic, increasing their vulnerability to genomic instability. This study aims to reveal the protein-level functional consequences of DDR pathways in induced neurons (iNs) compared to human dermal fibroblasts (HDFs) by identifying early and late response genes, pathway activation differences, and cell cycle-dependent vs. independent repair mechanisms. This experiment used bulk RNA-sequencing (RNA-seq) time-course at 8 hours, 24 hours, 48 hours, and 14 days post irradiation (IR) to provide time points for a diverse gene expression profile during distinct phases of DDR for both iNs and HDFs. Investigating the overlapping and distinct mechanisms between iNs and HDFs aims to clarify the pathways that neurons occupy to persist while providing a better understanding of the mechanisms of neuronal DDR that may serve as therapeutic targets for neurodegenerative diseases such as AD.

#15 Saam Doroodian

Associate Scientist
Buck Institute

Faculty Mentor
Malene Hansen, PhD

Autophagy Activator AA-20 improves proteostasis and extends C. elegans lifespan

Autophagy, the process by which cells break down and recycle cytosolic waste, is vital for health and longevity, but it naturally declines with age, contributing to age-related diseases. The degradation of cellular components through autophagy is essential for longevity and healthy aging. In this study, we characterized a new small-molecule activator of autophagy called AA-20 that enhances autophagy and lipid droplet clearance in the nematode C. elegans. AA-20 reduces polyglutamine aggregation and lipid droplet levels in C. elegans in an autophagy-dependent manner, where it also promotes fitness. Consistently, we found that AA-20 extends lifespan in C. elegans in an autophagy-dependent manner. Interestingly, our findings suggest that AA-20 acts, at least in part, through a mechanism involving the transcription factor EB (TFEB), but without inhibiting the protein kinase mTORC1. Collectively, our results identify a new autophagy activator AA-20, which may have potential therapeutic implications for aging-related proteinopathies and lipid storage disorders.

#16 Desi Stoyanova

Research Associate
Buck Institute

Faculty Mentor
Chris Benz, PhD

Epigenetic Vulnerability of ERBB2+ Breast Cancers: Targeting CBP/EP300-mediated ERBB2 Transcript Stability

We explored the hypothesis that a new epigenetic approach for treating ERBB2-amplified and overexpressing human breast cancers might be to use small molecule inhibitors of two nuclear coactivators needed for nuclear ERBB2 mRNA synthesis and its stabilization for cytoplasmic export: CREB-binding protein (CREBBP, or CBP) and the highly homologous E1A-binding protein, p300 (EP300). Within 2-6 h of treatment, these recently developed CBP/EP300 inhibitors significantly reduce total cellular ERBB2 mRNA (relative to GAPDH mRNA) by routing nuclear ERBB2 transcripts away from their nuclear speckle sequestration and into the nucleoplasm's RNA exosome system for 3'-5' decay by the exonuclease DIS3. RNA fluorescence in situ hybridization (RNA-FISH) imaging of untreated/control SKBR3 and BT-474 cells show that steady-state ERBB2 transcripts are stabilized within nuclear speckles and co-localized with the riboproteins ALYREF, HuR, and CBP (but not with nucleoplasm-localized EP300). Nuclear ERBB2 mRNA specifically binds to CBP (but not EP300), ALYREF, and HuR; and this specific binding to ERBB2 mRNA is lost within 2-6 h of CBP/EP300 inhibition. Our findings support the mechanistic model that CBP/EP300 inhibitors selectively destabilize nuclear ERBB2 transcripts by selectively diverting them away from ALYREF-, HuR-, and CBP- mediated speckle sequestration, stabilization and nuclear export, and toward rapid decay by the RNA exosome system. Thus, small molecule CBP/EP300 inhibitors represent a promising new treatment approach to epigenetically silence the ERBB2 oncogene, offering a new treatment option for patients with treatment-refractory ERBB2+ breast cancers.

#17 Ester Hernandez

Clinical Research Associate
Buck Institute

Faculty Mentor
John Newman, MD, PhD

Age-Related Differences in Ketone Metabolism: A Study of Ketone Ester Responses Across Lifespan

Ketone supplements, such as ketone esters, induce ketosis without other dietary changes and have demonstrated many potential applications in younger adults. However, their metabolism by older adults is unknown. This study investigated the metabolic responses to ketone ester consumption across the lifespan, to understand how aging influences blood ketone responses.

This study was an open-label, single-arm, observational study of n=82 adults (37=Male, age=20-70y). After an overnight fast, subjects consumed 360 mg/kg/lean body mass of ketone ester (bis-octanoyl-(R)-1,3-butanediol) in a beverage. Then, capillary blood samples were collected at regular intervals for 4h and beta-hydroxybutyrate (BHB) was assayed using a handheld device. Endpoints were peak BHB concentration (Cmax), area under the curve (AUC).

The analysis of BHB Cmax across five decades showed no overall effect, with the highest Cmax being observed in the 41-50y group, while the lowest was in the 51-60y group (p=0.5, age 20-30y =1.42, 31-40y =1.37, 41-50y =1.68, 51-60y =1.32, 61-70y =1.50 mM). In contrast, although there was no overall difference in BHB AUC between age groups (p=0.24) there was a notable difference between the 21-30y and 61-70y groups (p=0.03). Linear regression analysis revealed a relationship for BHB AUC and age (R^2=0.08, p=0.01), but not for BHB Cmax and age (R^2=0.01, p=0.37).

We cautiously interpret our data to suggest a relationship between increasing age and changes to ketone metabolism that increases AUC but not Cmax. We plan to expand the sample size to 400 subjects to improve our ability to detect-age related differences in exogenous ketone metabolism

#18 Connor Hatfield

Research Associate
Buck Institute

Faculty Mentor
Julie Andersen, PhD

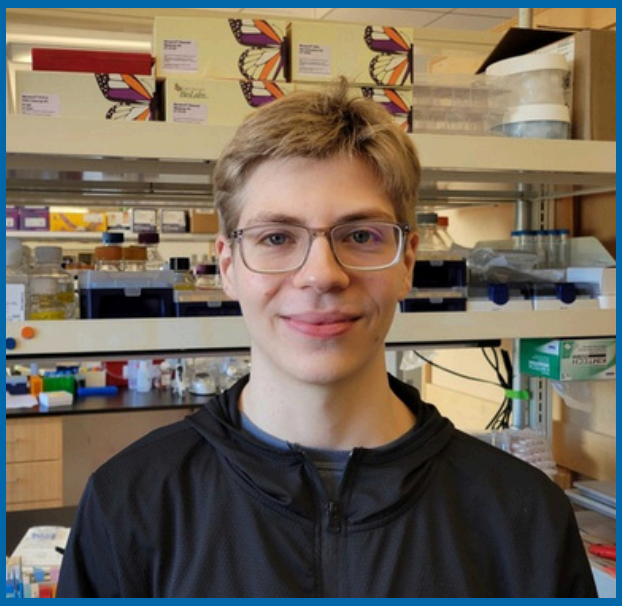
Fluorescence Monitoring of ATP/ADP Stimulated by E2 in Estrogen-Responsive Breast Cancer Cells

Estrogen-receptor positive (ER+) breast cancer is responsible for significant morbidity and mortality, with "ER-positive, HER2-negative breast cancer... account[ing] for about 70% of all breast cancers" (Burstein, 2020). This study aims to quantitatively assess the impact of estrogen on the bioenergetics of ER+ breast cancer cells. The primary hypothesis of this work is that estrogen promotes a metabolic shift toward a high cytosolic ATP/ADP ratio by kinetic alteration of bioenergetic fluxes (Mookerjee, 2024). This elevated ATP/ADP ratio then drives ATP utilization toward the synthesis of macromolecules (e.g., proteins, lipids) that support cancer cell proliferation (Ainscow & Brand, 1999). To test this, we will measure the impact of estrogen on bioenergetic fluxes within ER+, MCF7 cells using extracellular flux analysis, and will monitor the intracellular ATP/ADP ratios of MCF7 cells in the presence and absence of estrogen using fluorescence microscopy. Based on previous work by Pacheco-Velázquez et al. (2022), we expect to see increases in both glycolytic and oxidative ATP production pathways when estrogen is present, with a possible preferential increase in the glycolytic pathway (Mookerjee, 2024). We also expect to observe an increase in the cytosolic ATP/ADP ratio in the presence of estrogen, which will shunt ATP utilization towards macromolecule biosynthesis and thus cell proliferation (Ainscow & Brand, 1999). If our hypothesis is confirmed, these findings could facilitate the identification of therapeutic targets and lead to the development of new metabolic therapies for ER+ breast cancer.

#19 Ilya Osipov

Post-baccalaureate
Buck Institute

Faculty Mentor
Ashley Webb, PhD



Single nucleus analysis reveals sex differences in X chromosome aging in hypothalamic neurons

A major feature of aging across many species is the presence of sex differences, including differences in mean and maximum lifespan, response to longevity interventions (e.g., calorie restriction), and susceptibility to various age-related diseases. The mechanisms underlying these differences are not well understood. An intriguing possibility is that sex differences in mice and humans may have partially arisen due to sex-specific changes to the X chromosome during aging. Females have two copies of the X chromosome, one of which - called the inactive X (Xi) - is silenced during development and kept silenced throughout life to achieve parity in X chromosome gene expression with males, who are XY. This inactive X is rich in heterochromatin, and specifically repressive epigenetic marks including DNA methylation and histone H3K27me3. It is well known that aging is associated with alterations to heterochromatin and epigenetic marks; therefore, it is possible that the inactive X chromosome may respond differently than autosomes to these and other age-related changes. Our lab previously found by snRNAseq that female mice undergo a change in hypothalamus gene expression in several genes involved in X-inactivation with age, a notable example being Xist, which is the master of X chromosome inactivation and a female-specific transcript. Here, we have expanded this inquiry using single nucleus multi-omics (RNA- and ATAC-seq) data to test the hypothesis that X chromosome gene expression in females is more prone to age-related increases than the autosomes, and that this is specific to females. We observed that female hypothalamic neurons had an enrichment in genes whose expression increased significantly with age on the X chromosome compared to the autosomes, whereas male hypothalamic neurons did not display this, indicating that female X chromosome gene expression may be more prone to age-related de-repression.

#20 Ryan Smith

Azenta

Harnessing the Power of Multiomics from Fresh and Fixed Patient Sample Characterization

The omics era has greatly expanded the repertoire of approaches available for researchers and clinicians to unravel the complexity underpinning human health: Next Generation Sequencing (NGS) approaches can characterize genomes, epigenomes, transcriptomes, and proteomes. The analyses are critical to assess in individuals both pre- and post-treatment during therapeutic development and early-stage clinical trials. Peripheral blood mononuclear cells (PBMCs) offer a non-invasive approach that, when combined with omics tools, can provide a near holistic view of immune processes across patient cohorts. Meanwhile, Formalin Fixed Paraffin Embedded (FFPE) tissues are a staple in clinical diagnostics and an ideal means to store archival tissue but can be difficult to work with in traditional NGS assays. Here we detail workflows using both fresh and fixed patient samples to rapidly produce a diverse set of multiomics results including genomics, epigenomics, transcriptomics, and proteomics.

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Career Panel

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Cornelia Weyand, MD-PhD
Rheumatologist, Mayo Clinic
Faculty, Mayo Clinic

John Newman, MD-PhD
Assistant Professor, Buck Institute
Associate Professor, UCSF Geriatrics

Manish Chamoli, PhD
CSO partner, LongGame Ventures
Visiting Scientist, Buck Institute

Shona Mookerjee, PhD
Associate Professor, Touro University

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Reserve tables

Malene Hansen, PhD

Chief Scientific Officer and Professor

Investigating the role and regulation of autophagy in aging and age-related diseases

Dr. Hansen was born and raised in Denmark and received her M.Sc. and Ph.D. from Copenhagen University. Starting in 2001, Dr. Hansen carried out postdoctoral studies in the laboratory of Professor Cynthia Kenyon, Ph.D., at the University of California, San Francisco. She established her laboratory in 2007 at Sanford Burnham Prebys Medical Discovery Institute in La Jolla, CA, studying molecular mechanisms of aging, and joined the Buck Institute in 2021 as Chief Scientific Officer and faculty member.

Dr. Hansen has been recognized for her research throughout her career, including an Ellison Medical Foundation New Scholar in Aging Award, a Glenn Award for Research in Biological Mechanisms of Aging, a Julie Martin Mid-Career Award in Aging Research and a Breakthrough in Gerontology Award supported by the Ellison Medical Foundation and American Association for Aging Research (AFAR). In 2021, she received the Irving Wright Award of Distinction from AFAR. Moreover, her lab has been funded by federal grants from the National Institute on Aging and the National Institute for General Medical Sciences. Dr. Hansen serves as an ad hoc reviewer for multiple scientific journals and is a past chair of the National Institute of Health's Cellular and Molecular Mechanisms of Aging study section.

Dr. Hansen has organized a number of international scientific conferences, including the Cold Spring Harbor Laboratory's meeting on Mechanisms of Aging from 2014-2018 and the 2020 Keystone meeting on Aging. She also co-organized the 2020/2022 Gordon Research Conference on Autophagy. She is currently the co-organizer of the Cold Spring Harbor laboratory's meeting on Proteostasis.

Nathan Price, PhD
Professor

AI-driven advancements and models for pioneering scientific wellness and enhancing human healthspan.

Dr. Nathan Price is Professor and Co-Director of the Center for Human Healthspan at the Buck Institute for Research on Aging. His academic career includes previous positions as Professor and Associate Director of the Institute for Systems Biology, and Assistant Professor at the University of Illinois, Urbana-Champaign. Dr. Price holds affiliate faculty status at the University of Washington in Bioengineering and Computer Science & Engineering. Dr. Price has authored over 210 peer-reviewed publications and delivered more than 250 talks and keynotes.

His work has garnered numerous accolades. In 2019, he was named one of 10 Emerging Leaders in Health and Medicine by the National Academy of Medicine, and in 2021 he was appointed to the Board on Life Sciences of the National Academies of Sciences, Engineering, and Medicine (NASEM). Additional recognition includes an NSF CAREER award, being named a Camille Dreyfus Teacher-Scholar, and receiving the 2016 Grace A. Goldsmith Award for his work in pioneering "scientific wellness." He is also a fellow of the American Institute for Medical and Biological Engineering and was Chair of the NIH Study Section on Modeling and Analysis of Biological Systems (MABS). He was the 2023 recipient of the Alexander & Mildred Seelig Award for science from the American Nutrition Association.

Dr. Price's expertise extends beyond academia into the business world. He is also the Chief Scientific Officer of Thorne, a science-driven wellness company that serves approximately 5 million customers and 50,000 health-care practitioners. Previously he was Co-CEO of Onegevity, an AI health intelligence startup company that merged with Thorne, and he was part of the presenting team who took the resulting Thorne HealthTech through its NASDQA IPO in 2021. He was co-founder and served on the Board of Directors of Arivale. He was also a finalist for the EY Entrepreneur of the Year for NY in 2021 and selected as one of the 86 "Notables in Healthcare" by Crain's New York in 2022 and 2023. He has also co-authored a bestselling book, The Age of Scientific Wellness, with Lee Hood, and written for popular outlets such as The Wall Street Journal, Los Angeles Times, and Scientific American.

Dr. Price has served on the Board of Trustees of the Health and Environmental Sciences Institute (HESI), the Pacific Northwest Board of Advisors for the American Cancer Society, and the Oversight Board for the University of Virginia's Wallace H. Coulter Center for Translational Research. He has served on numerous advisory boards for both academic institutions and industry leaders, including Roche, Providence St. Joseph Health, Sera Prognostics, Navican, Basepaws, Trelys, Rue Four Health, ProPetDx, and the Novo Nordisk Foundation Center for Biosustainability. He has also contributed his expertise to national committees, including the NAM committee reviewing omics-based tests for clinical trials, and a series of workshops in 2023 on AI and biodata in the US and Southeast Asia, co-sponsored by NASEM and the U.S. State Department.

Eric Verdin, MD

President and Chief Executive Officer, Professor

Understanding epigenetic regulators of the aging process.

Dr. Verdin is the president and chief executive officer of the Buck Institute for Research on Aging. A native of Belgium, Dr. Verdin received his Doctorate of Medicine (MD) from the University of Liege and completed additional clinical and research training at Harvard Medical School. He has held faculty positions at the University of Brussels, the National Institutes of Health (NIH), and the Picower Institute for Medical Research. Dr. Verdin is also a professor of medicine at University of California, San Francisco.

Dr. Verdin studies how metabolism, diet, and small molecules regulate the activity of HDACs and sirtuins, and thereby the aging process and its associated diseases, including Alzheimer's. He has published more than 270 scientific papers and holds more than 18 patents. He is a highly cited scientist (top 1 percent) and has been recognized for his research with a Glenn Award for Research in Biological Mechanisms of Aging and a senior scholarship from the Ellison Medical Foundation. He is an elected member of several scientific organizations, including the American Association for the Advancement of Science, the American Society for Clinical Investigation, and the Association of American Physicians. He also serves on the advisory council of National Institute on Drug Abuse at the National Institutes of Health.

Dr. Verdin has extensive experience working with biotech companies. He is a founder of Acylin (purchased by Abbvie). He served on the scientific advisory boards of Elixir, Sirtris (purchased by GSK), Calico (Google), and Nokia, and he also served as advisor to Sofinnova Ventures. Dr. Verdin has also worked for several years as a consultant to Novartis, GSK, J&J, Altana, Roche, Pfizer, and other biotech companies.

Ashley Webb, PhD
Associate Professor

Investigating the molecular mechanisms of brain aging and neurodegeneration

Dr. Webb received her PhD from the University of Washington and did her postdoctoral work with Dr. Anne Brunet at Stanford University. She started her laboratory at Brown University, where she was promoted to Associate Professor with tenure and became the Associate Director of the Center on the Biology of Aging. Dr. Webb joined the Buck Faculty as an Associate Professor in 2023.

Dr. Webb has received awards for her work in the aging field, including a Glenn Award for Research on Mechanisms of Aging, and a junior faculty award from the American Federation for Aging Research. Her lab is funded by the NIH National Institute on Aging and the National Science Foundation. Dr. Webb is a member of the AFAR National Advisory Council and the Board of Directors for the American Aging Association. She serves as reviewer for the Glenn Foundation and is a member of the NIH's Cellular Mechanisms of Aging and Development study section.

Dan Winer, MD
Associate Professor

Understanding the role of the immune system in aging and chronic metabolic disease.

Dr. Dan Winer received an Honor's BSc in immunology from the University of Toronto, followed by an MD from the University of Ottawa in 2002. He then completed residency training in Anatomical Pathology at the University of Toronto in 2007. Subsequently, Dr. Winer did a three-year post doc in immunology at Stanford University in the laboratory of Stanford Blood Center director, Dr. Edgar Engleman. During this time, Dr. Winer, collaborating with his twin brother Dr. S. Winer at the University of Toronto, spearheaded a new initiative which identified the adaptive immune system as an important player in the control of metabolic diseases such as obesity related insulin resistance and type 2 diabetes. Dr. D. Winer returned to Canada in 2010 and became an Assistant Professor at the University of Toronto in 2011, where he ran an obesity and inflammation research lab associated with the Toronto General Research Institute (TGHRI), before joining the Buck Institute.

Dr. D. Winer is the recipient of several awards including the Hubert Wolfe Award in Endocrine Pathology, the Benjamin Castleman Award for human pathology research (sponsored by the United States and Canadian Academy of Pathology and the Massachusetts General Hospital), the Amgen early investigator award (Endocrine Society), and the Canada Research Chair in Immunometabolism.

Robin Snyder, PhD

Vice President, Communications

Career summary and path in science

Award-winning healthcare communications professional with proven expertise in creating strategic initiatives to support and enhance corporate and brand reputation. Former journalist with broad experience in storytelling and excellent verbal and written communications skills. Comfortable and skilled at managing through influence. Results-driven and passionate about working in an innovative healthcare environment

Previous experiences

- **Director, Science Communications**
  - Genentech, 2005-2017
- **Senior Vice President**
  - Ketchum, 1999-2005
- **TV News Producer**
  - KPIX CBS5, 1992-1999
- **Education**
  - Penn State University
    - BA, Political Science
  - Rutgers University
    - PhD, Political Science

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