# 2026 AGING RESEARCH SYMPOSIUM

**UAB Alumni House and the Alys Stephens Center**

**March 3, 2026**

**2026 UAB Aging Research Symposium**

*Co-Organizers*

UAB MEDICINE
Integrative Center for Aging Research

UAB
Nathan Shock Center
of Excellence in the
Basic Biology of Aging

UAB MEDICINE
Alzheimer's Disease Center

The UAB Integrative Center for Aging Research is supported as a University-Wide Interdisciplinary Research Centers (UWIRC) Program by the UAB Office of Research. The UAB Nathan Shock Center (P30AG050886) and Alzheimer's Disease Research Center (P30AG086401) are supported by the NIH National Institute on Aging.

The organizers of the 2026 UAB Aging Research Symposium would like to thank the UAB Evelyn F. McKnight Brain Institute for their generous support of this year's event:

THE EVELYN F. McKNIGHT BRAIN INSTITUTE
UNIVERSITY OF ALABAMA AT BIRMINGHAM
*Preserving memory, enhancing life*

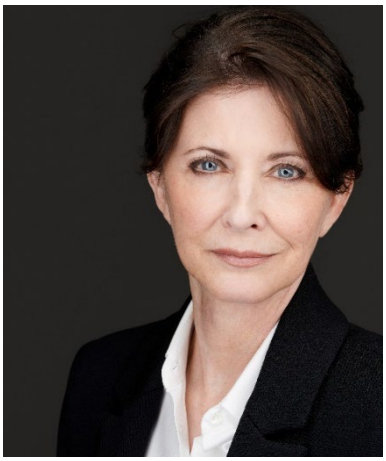
# AGENDA

| | | |
|---|---|---|
| 7:30 AM | **Breakfast & Registration** | UAB Alumni House<br>1301 10th Avenue S, Birmingham, AL 35294 |
| 8:30 AM | **Welcome**<br>Ken Boockvar, MD, MS | *Dr. Boockvar is the Gwen McWhorter Endowed Professor in Geriatric Medicine, Division Director of UAB Gerontology, Geriatrics, and Palliative Care, and Director of the UAB Integrative Center for Aging Research.* |
| **SESSION I** | ***New Approach Methodologies***<br>Chair: Erik Roberson, MD, PhD | *Dr. Roberson is the Rebecca Gale-Heersink Endowed Chair and Vice Chair for Basic & Translational Research in the Department of Neurology at UAB where he directs the UAB Alzheimer's Disease Research Center (ADRC) in addition to the Killion Center for Neurodegeneration and Experimental Therapeutics (KCNET).* |
| 8:35 AM | ***KEYNOTE: Cosmic Brain Organoids: Investigating the effects of microgravity on iPSC-derived neural organoids on the International Space Station***<br>Paula Grisanti, DMD, MBA<br>Scott Noggle, PhD | *Dr. Grisanti is Chief Executive Officer and a founding member of the National Stem Cell Foundation (NSCF), headquartered in Louisville, KY.*<br>*Dr. Noggle is currently a Senior Scientific Advisor to the National Stem Cell Foundation (NSCF), with expertise in stem cell biology and developmental neurobiology, working at the intersection of microgravity research and neurodegeneration.* |
| 9:35 AM | ***Modeling Aging in Organoid-based Models: Challenges and Opportunities***<br>Ian Berg, PhD | *Dr. Berg is an Instructor in the UAB School of Engineering where he teaches engineering design and biomedical engineering programs. He joined the Sethu Lab in the Cardiovascular Diseases Division of UAB in 2021 where he has been developing 3D, iPSC-based models of cardiac tissue to investigate bacterial infection.* |
| 10:05 AM | BREAK | |
| 10:20 AM | ***KEYNOTE: Diet, Metabolism, Genetic Risk, and the Path to Cognitive Resilience***<br>Sara Burke, PhD | *Dr. Burke is a Professor and Head of the University of Arizona Department of Neuroscience. Her research programs aim to identify changes in the coordination between different brain regions over the lifespan and how this contributes to impairment in advanced age, as well as to develop therapeutic strategies for alleviating cognitive dysfunction in older adults.* |
| 11:25 AM | ***New Approach Methodologies at Southern Research***<br>Doug Bartels, PhD | *Dr. Bartels is the Director of Strategic Initiatives at Southern Research, where he helps partners build the evidence base and define clear next steps for translation. He has 25 years of experience using biomarkers and patient genetics to translate therapeutic concepts and reduce development risk.* |
| 12:00 PM | **Lunch & Networking** | |
| 1:00 PM | **Welcome**<br>Chris Brown, PhD | *Dr. Brown is the Vice President for Research at UAB. He is also a tenured professor in the Department of Biology. He serves as vice chair of the Research Strategic Initiative Executive Steering Committee, an initiative to empower research excellence, impact, scholarship, and innovation to drive knowledge and job creation focused on increasing our positive impact and improving society.* |

**SESSION II** ***Advancing Longevity***
Chair: Ken Boockvar, MD, MS

| | | |
|---|---|---|
| 1:05 PM | ***KEYNOTE: Yes, Virginia, there really are Blue Zones and we have a lot to learn from them***<br><br>Steve Austad, PhD | *Dr. Austad holds the inaugural Protective Life Endowed Chair in Healthy Aging Research at UAB, where he is also a Distinguished Professor and former Chair of the Department of Biology. In addition, he is the founding Director and current co-director of the UAB Nathan Shock Center of Excellence in the Basic Biology of Aging. He is also a co-Director of the Nathan Shock Centers Coordinating Center.* |
| 2:00 PM | ***Keeping the power on for healthy aging and longevity***<br><br>Keshav K. Singh, PhD | *Dr. Singh is the Joy and Bill Harbert Endowed Chair and Professor of Genetics, Dermatology, and Pathology at UAB. He is the Founding Editor-in-Chief of the Mitochondrion journal and the Scientific Founder and Chief Scientific Officer of Yuva Biosciences. His research investigates how mitochondrial dysfunction—an integrative hallmark that connects and intersects with every other hallmark of aging—drives aging and limits healthy longevity.* |
| 2:30 PM | **Elevator Pitch Presentations**<br><br>*Concise, 2- to 3-minute presentations of selected abstracts* | **Gloria Benavides, PhD, Research Scientist, UAB**<br>*Mitochondrial Evaluation of Fresh 3D Brain Tissues and Organoids*<br>**Ene Enogela, PhD, Postdoctoral Fellow, UAB**<br>*Racial segregation across the life-course and life-space Mobility: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study*<br>**Jonathan Flowers, MS, Graduate Student, UAB**<br>*The Impact of Vitamin B12 Supplementation on the Gut Epithelia of Aged Female Mice*<br>**Konstantinos Papanikolaou, PhD, Postdoctoral Fellow, UAB**<br>*Bacterial Infection Induces Hallmarks of Cellular Senescence in Skeletal Muscle of Old Mice*<br>**Pheven Yohannes, Undergraduate Student, UAB**<br>*Amygdalar Dysfunction in Aging and Chronic Fear Contributes to PTSD and ADRD Neuropathological Changes* |
| 3:00 PM | BREAK | |
| 3:15 PM | ***The Southern Population Aging Research Center: Providing New Opportunities for Aging Research***<br><br>Mieke Thomeer, PhD | *Dr. Thomeer is a Professor in the Department of Sociology at the University of Alabama at Birmingham. She is also co-director of the Southern Population Aging Research Center, a Demography & Economics of Aging Center funded by the National Institute on Aging, and the co-lead of the Program Development Core and the Communication and Dissemination Core.* |
| 3:40 PM | **EXPERT PANEL DISCUSSION**<br>Moderator: Steve Austad, PhD | ***The Future of Aging Research***<br>Panelists:<br>Doug Bartels, PhD<br>Sara Burke, PhD<br>Scott Noggle, PhD<br>Mieke Thomeer, PhD |
| 4:20 PM | **Closing Remarks**<br>Ken Boockvar, MD, MS | |
| 4:30 PM | **Poster Session and Reception** | Alys Robinson Stephens Performing Arts Center<br>Lower Lobby<br>1200 10th Avenue S, Birmingham, AL 35205 |

# SESSION I: KEYNOTE SPEAKERS

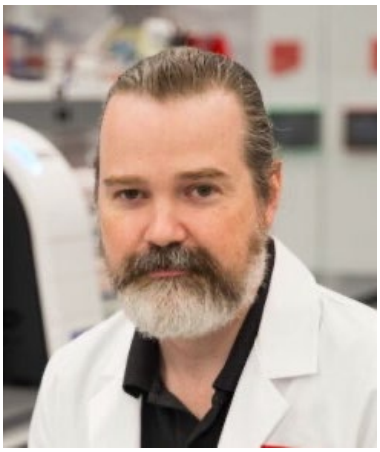


**Paula Grisanti, DMD, MBA**
*Chief Executive Officer*
*National Stem Cell Foundation*

**Dr. Grisanti** is the CEO and a founding member of the National Stem Cell Foundation (NSCF), headquartered in Louisville, KY. Since 2018, NSCF has been funding a collaborative research study of neurodegeneration on the International Space Station with brain organoids derived from the iPSC's of people with Parkinson's disease and primary progressive MS. Six missions have been completed to date, with additional ground research and another three flights between now and 2027 covered by grant from NASA. Future flights will include organoids derived from the cells of people with Alzheimer's, including those with mutations linked to early onset forms of the disease. This research team developed a patent-pending cryovial technology enabling long-duration preservation of cells in space, now widely adopted by the space community, and was the first to publish on the accelerated maturation of cells in microgravity.

As part of its education and workforce development platform, NSCF underwrites the National STEM Scholar Program, a collaboration with the Gatton Academy of Mathematics and Science at Western Kentucky University. The program provides advanced STEM training, national network building, and "big idea" project funding for middle school science teachers nationwide. There are currently 100 teachers in 37 states who have been through the program and will have collectively reached more than 190,000 middle school students in the U.S. by June 2026. Nearly 43% teach in mid-to-high poverty schools and 39% teach in towns with a population under 15,000.

She is a longstanding member of the International Women's Forum Kentucky chapter and currently serves on the Delta Dental of Kentucky Board of Directors and the Executive Women's Alumni Advisory Board to the University of Louisville School of Business.



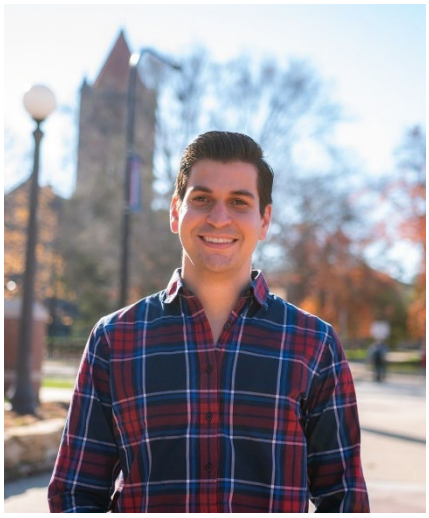
**Scott A. Noggle, PhD**
*Senior Scientific Advisor*
*National Stem Cell Foundation*

**Dr. Noggle** is currently a Senior Scientific Advisor to the National Stem Cell Foundation (NSCF), with expertise in stem cell biology and developmental neurobiology, working at the intersection of microgravity research and neurodegeneration. He has been a scientific leader at the New York Stem Cell Foundation Research Institute (NYSCF), where he led the development and implementation of automated systems for deriving and differentiating thousands of human pluripotent stem cell lines into novel disease-relevant cell types and tissue-like organoid models, including those for diabetes, Alzheimer's disease, and Parkinson's disease. His recent research with the National Stem Cell Foundation focuses on modeling human neurodegenerative disease in advanced neural and glial systems in microgravity, with an emphasis on how microgravity influences cellular and developmental neurobiology and neuroinflammation, with applications to neurodegeneration.

## Cosmic Brain Organoids: Investigating the effects of microgravity on iPSC-derived neural organoids on the International Space Station

Research conducted on the International Space Station (ISS) in low-Earth orbit (LEO) has shown that microgravity alters white and gray matter of the brain demonstrated in post-flight brain imaging in astronauts and mouse models. To investigate the effects of microgravity on the nervous system, we generated three-dimensional human neural organoids from induced pluripotent stem cells (iPSCs) derived from people affected by Primary Progressive Multiple Sclerosis (PPMS), Parkinson's disease (PD), and non-symptomatic controls by differentiating them toward cortical and dopaminergic fates and integrating isogenic microglia. Over several missions these organoids were cultured for month-long experiments using static and dynamic culture methods and live samples were returned to Earth. Our findings demonstrated human neural organoids derived from iPSCs show increased neural maturity in microgravity and undergo consistent changes in neurodegeneration-related pathways. Exploring the effects of microgravity on the nervous system may aid in the discovery of novel countermeasures for the consequences of space exploration while providing insights into neurodegenerative diseases on Earth.

# SESSION I: PLENARY SPEAKER



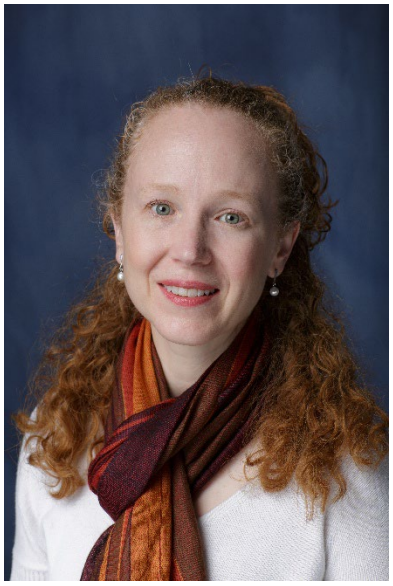
**Ian Berg, Ph.D.**
*Instructor*
*School of Engineering*
*UAB*

**Dr. Berg** is an Instructor in the School of Engineering where he teaches fin engineering design and biomedical engineering programs. Dr. Berg earned his undergraduate in Mechanical Engineering from the University of Illinois at Urbana Champaign. After graduating, he spent 3 years working in the medical device industry before returning to UIUC to complete his PhD in Biomedical Engineering where his thesis focused on the biomechanics of liver progenitor cell differentiation. He joined the Sethu Lab in the Cardiovascular Diseases Division of UAB in 2021 where he has been developing 3D, iPSC-based models of cardiac tissue to investigate bacterial infection. Ian continues to support the tissue engineering projects in the Sethu Lab. His teaching involves project-based courses where students must use design thinking and their engineering skills to invent and build solutions to real world problems.

## Modeling Aging in Organoid-based Models: Challenges and Opportunities

New Approach Methodologies (NAMs) have emerged as an alternative that can overcome shortcomings associated with animal models by combining novel in-vitro human organoids and tissue chips with computational models to more accurately predict patient specific responses that have greater translational relevance. Aging is the primary risk factor for major chronic illnesses, including cancer, cardiovascular disease, progressive neurodegenerative diseases, and type 2 diabetes. Progressive loss of physiological function in organs and tissues results as a consequence of accumulated molecular damage, cellular senescence, and inflammation resulting in increased vulnerability to disease. A major concern with organoids and tissue chip models is the challenges associated with replicating long-term human physiological aging in a short-term, in-vitro setting. This talk will focus on our lab's efforts to create organoid and tissue chip models of various organs and tissue, highlight efforts by us and others to model aspects of aging and disease, detail methods to quantitatively and qualitatively assess aging in organoids and finally, discuss the possibility of exploiting the space environment that is known to promote accelerated aging for disease modeling.

# SESSION I: KEYNOTE SPEAKER



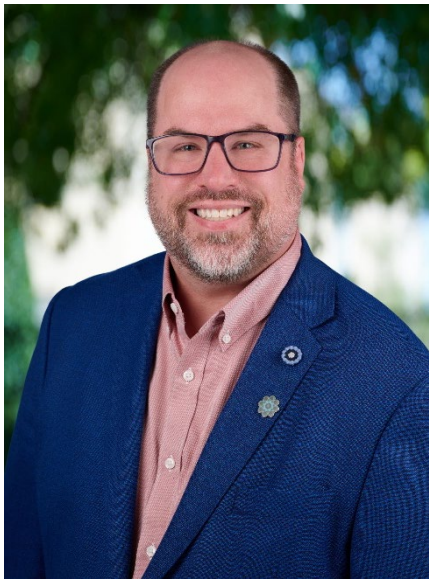
**Sara N. Burke, Ph.D.**
*Professor and Head*
*Department of Neuroscience*
*University of Arizona*

**Dr. Burke** is a Professor and Head of the Neuroscience Department at the University of Arizona, moving recently from the University of Florida where she served as Director of the Center for Cognitive Aging and Memory. Her research program is dedicated to understanding the biological mechanisms that underlie cognitive aging and vulnerability to Alzheimer's disease and related dementias (ADRD). Trained at the University of Oregon (M.S., Psychology) and the University of Arizona (Ph.D., Neuroscience, minor in Pharmacology), Dr. Burke integrates systems neuroscience, metabolism, and behavior to determine how age and genetic risk factors alter brain network function and memory. Her research focuses on how changes in neural circuit dynamics, synaptic communication, and brain energy metabolism contribute to cognitive decline across the lifespan. A central theme of her work is that cognitive impairment emerges not from isolated molecular changes, but from disruptions in coordinated neural systems supporting higher cognitive functions. Using rodent models that parallel human cognitive aging, her laboratory combines in vivo neurophysiology, functional connectivity mapping, behavioral testing, spatial metabolomics, and dietary interventions to study brain function from molecules to networks to behavior. Over the past two decades, Dr. Burke has made significant contributions to understanding how aging affects medial temporal lobe circuits, including the hippocampus and perirhinal cortex, and how these changes impair recognition memory and mnemonic discrimination. More recently, her laboratory has expanded to examine how metabolic flexibility, dietary interventions, and genetic risk factors such as APOE4 influence neural oscillations, connectivity, and cognitive performance. Through NIH- and foundation-funded research, her team is developing mechanistic models linking metabolism to synaptic dynamics and identifying therapeutic targets to enhance cognitive resilience. Her overarching goal is to identify actionable pathways that promote healthy brain aging and extend cognitive healthspan.

## Diet, Metabolism, Genetic Risk, and the Path to Cognitive Resilience

Cognitive aging is not driven by widespread neuron loss, but by dynamic alterations in synaptic function, network organization, and metabolic dysregulation. This talk will integrate findings from systems neuroscience and geroscience to argue that cognitive aging is fundamentally a problem of metabolic–synaptic coupling. Drawing from mechanistic studies in rat models, including an APOE4 knock-in rat model of Alzheimer's disease genetic risk, data will be presented that examine how aging alters hippocampal and prefrontal network dynamics and disrupts oscillatory coordination. Importantly, these neural changes may be overcome by enhancing metabolic flexibility. Nutritional ketosis and other metabolic interventions reveal that ketone body utilization remains viable in aging, and enhancing metabolic flexibility can improve insulin sensitivity, network organization, and cognitive performance. However, APOE4 genotype modifies these metabolic responses, suggesting that distinct therapeutic strategies may be required for late-onset Alzheimer's disease. By bridging electrophysiology, behavior, and spatial metabolomics, this work reframes cognitive aging as a systems-level challenge rooted in energy regulation and highlights metabolism as a tractable and translational therapeutic axis for promoting cognitive resilience.

# SESSION I: PLENARY SPEAKER



**Dr. Bartels** has 25 years of experience using biomarkers and patient genetics to translate therapeutic concepts and reduce development risk. He spent two decades at Vertex Pharmaceuticals, shaping translational strategy across rare and infectious diseases, nephrology, and neurology in programs that resulted in eight approved therapies. He is now Director of Strategic Initiatives at Southern Research, where he helps partners build the evidence base and define clear next steps for translation.

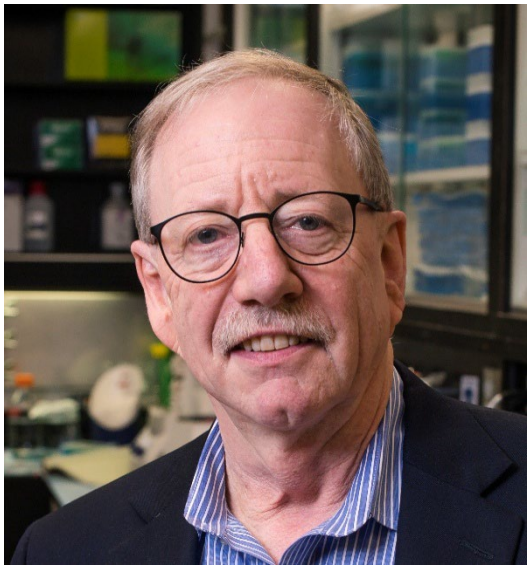
**Doug Bartels, Ph.D.**
*Director, Strategic Initiatives*
*Southern Research*

## New Approach Methodologies at Southern Research

The passage of the FDA Modernization Act 3.0 and 2025 FDA Roadmap to Reduced Animal Testing has established the regulatory latitude to utilize non-animal data in formal submissions. However, the transition toward New Approach Methodologies (NAMs) remains an incremental, future-facing objective. This transition is particularly critical for Medical Countermeasures (MCMs) against known, unknown, and AI-generated biological threats, where narrowing the gap between pathogen discovery and therapeutic intervention is a matter of both national security and public health preparedness. In these high-stakes scenarios, traditional animal models frequently lack human relevance, making human-centric NAMs an essential tool for rapid response - especially in those instances where human clinical study is neither practical nor ethical, necessitating MCM approval under the FDA Animal Rule.

This presentation outlines SR's entry into the NAMs landscape with a focus on infectious disease, prioritizing the generation of actionable data in human-relevant systems to drive MCM discovery and development. Our strategic framework focuses on evaluating safety, effectiveness, and Mechanism of Action (MoA) through high-fidelity platforms to accelerate timelines and reduce reliance on animal models. Rather than positioning NAMs as immediate substitutes for animal studies, we examine how defining specific Contexts of Use (CoU) and embedding results within a formal Weight of Evidence (WoE) framework enables regulators to judge these technologies as fit-for-purpose for specific regulatory decisions. SR's approach toward the evaluation, validation, and standardization of NAMs may not only assist UAB faculty as they integrate these methodologies into their own research but provide opportunities to collaborate.

## SESSION II: KEYNOTE SPEAKER



**Steve Austad, Ph.D.**

*Protective Life Endowed Chair in Healthy Aging Research*
*Distinguished Professor, Dept of Biology*
*UAB*

**Dr. Austad** holds the inaugural Protective Life Endowed Chair in Healthy Aging Research at the University of Alabama at Birmingham (UAB), where he is also a Distinguished Professor and former Chair of the Department of Biology. In addition, he is the founding Director and current co-director of the UAB Nathan Shock Center of Excellence in the Basic Biology of Aging, one of 8 such NIH-funded Centers in the US. He is also a co-Director of the Nathan Shock Centers Coordinating Center. Outside of UAB, he is Scientific Director of the New York-based American Federation for Aging Research. Originally trained in evolutionary ecology, Dr. Austad became interested in aging during South American field studies on opossums. He has been studying the biology of aging at levels from molecules to populations for more than three decades. He has particular expertise in the development of novel animal models for aging research. His current research focuses on sex differences in aging biology and how aging interacts with disease vulnerability with the long-term goal of developing interventions that slow the age-related decay in human health. He has published seven books and more than 220 scientific papers covering nearly every aspect of the biological aging process. His academic awards include Caroline P. and Charles W. Ireland Prize for Scholarly Distinction, the George C. Williams Prize, the Robert W. Kleemeier Award for outstanding research, the Geron Corporation-Samuel Goldstein Distinguished Publication Award, the Nathan A. Shock Award from the National Institute on Aging, the Irving S. Wright Award of Distinction in Aging Research, and the French IPSEN Foundation Longevity Prize. He is an elected fellow the American Association for the Advancement of Science, the Gerontological Society of America, and the New York Academy of Medicine.

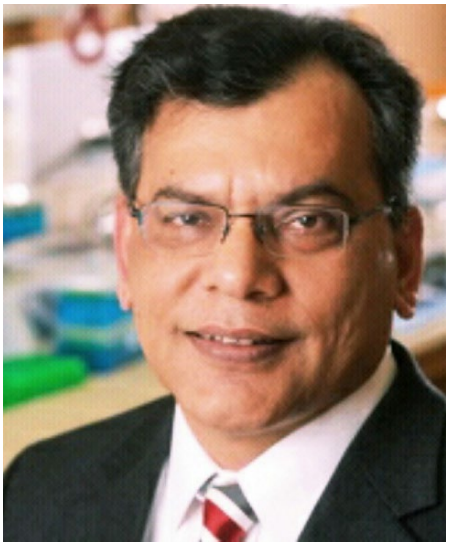
Dr. Austad maintains a keen interest in communicating science to the general public, and in that capacity has served on the Science Advisory Board of National Public Radio and has been an exhibition consultant to the Oregon Museum of Science and Industry, the Perot Museum of Nature and Science in Dallas, Texas, and the American Museum of Natural History in New York City. He has written more than 150 popular science articles and essays for print and electronic media. His trade book, Why We Age (1997), has been translated into eight languages. His latest books include To Err is Human, To Admit It is Not (Resource Publications, 2022), a collection of short essays on diverse topics and Methuselah's Zoo: what nature can teach us about living longer, healthier lives (MIT press, 2022).

Prior to entering aging research, Dr. Austad with a degree in English literature was a newspaper reporter, drove a taxicab in New York City, trained large cats for the Hollywood film industry, and hustled pool nation-wide. With his PhD in evolutionary ecology, he has done field research in multiple parts of the United States, Venezuela, England, Kenya, Micronesia, Melanesia, and Papua New Guinea.

### Yes, Virginia, there really are Blue Zones and we have a lot to learn from them Defenses

So-called Blue Zones, geographic and temporal regions of exceptional human longevity, have been identified in four regions of the globe, Sardinia, Italy; Ikaria, Greece, Okinawa, Japan, and Nicoya, Costa Rica. Recently the validity of the exceptional ages of people living in Blue Zones has been questioned. My talk will present research validating the exceptional longevity of people in each of the four Blue Zones, describe which ones seem to be disappearing or remaining stable, and also identify several newly discovered Blue Zones. Finally, I will discuss what we have learned, and will learn, about living longer, healthier lives from understanding the biological and environmental factors that lead to Blue Zones.

# SESSION II: PLENARY SPEAKER



**Keshav K. Singh, Ph.D.**
*Joy and Bill Harbert Endowed Chair Professor*
*Departments of Genetics, Dermatology, and Pathology*
*UAB*

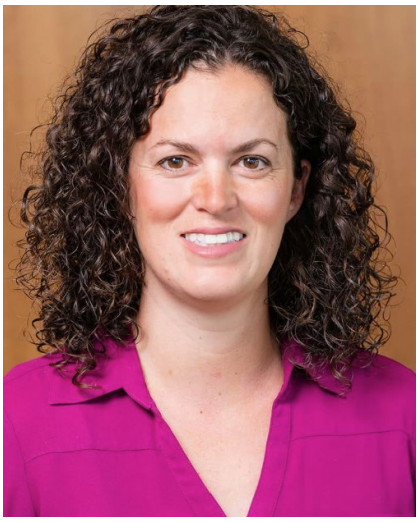
**Dr. Singh** is the Joy and Bill Harbert Endowed Chair and Professor of Genetics, Dermatology, and Pathology at UAB. He is the Founding Editor-in-Chief of the *Mitochondrion* journal and the Scientific Founder and Chief Scientific Officer of Yuva Biosciences. His research investigates how mitochondrial dysfunction—an integrative hallmark that connects and intersects with every other hallmark of aging—drives aging and limits healthy longevity. He developed a one-of-a-kind mouse model in which aging can be manipulated on demand, accelerated, and then reversed, enabling precise tissue- and organ-specific dissection of aging mechanisms. Using this platform, his laboratory is designing interventions to prevent, slow, and reverse aging phenotypes, including skin wrinkles and hair loss, as well as aging-associated diseases, with clear strategies for translation to humans.

## Keeping the power on for healthy aging and longevity

Presentation objectives:

i) Understand the role of mitochondria in healthy aging.
ii) Demonstrate Mitochondrial dysfunction is driver of aging.
iii) How restoring mitochondrial function undo skin aging and hair loss.

# SESSION II: PLENARY SPEAKER



**Dr. Thomeer** is a Professor in the Department of Sociology at the University of Alabama at Birmingham. She is also co-director of the Southern Population Aging Research Center, a Demography & Economics of Aging Center funded by the National Institute on Aging, and the co-lead of the Program Development Core and the Communication and Dissemination Core. Dr. Thomeer's research on how childbearing and parenthood is linked to mid- and later-life health has been funded by the National Institute of Health, and she is a previous Deputy Editor of the Journal of Marriage and Family.

**Mieke Beth Thomeer, Ph.D.**
*Professor*
*Department of Sociology*
*UAB*

## The Southern Population Aging Research Center: Providing New Opportunities for Aging Research

The Southern Population Aging Research Center (SPARC) is a new P30 Demography & Economics of Aging Center funded by the National Institute on Aging. Although NIA has funded P30 Centers for more than 30 years, the South has had limited infrastructure to support population aging research. SPARC fills this gap by expanding opportunities for research and training in a region facing significant aging-related challenges. In this talk, Mieke Thomeer will outline the key goals of SPARC, including unique opportunities for population aging researchers at UAB to develop innovative research. She will also discuss some of the current research by SPARC affiliates at the three hub institutions: UAB, the University of Maryland College Park, and the University of Maryland Baltimore County.

# POSTER ABSTRACTS

1. **A Pilot Investigation of Exercise-Induced Cytokine Changes and Psychosocial Correlates in Older Adults with HIV**

**Tyler Bagley,** Lilly Fritz, Michael Hankes, Silvienne Sint Jago, Thomas Buford, Taylor Taylor, Raymond Jones

Affiliations: UAB Center for Exercise Medicine, UAB School of Health Professions, UAB Heersink School of Medicine, UAB School of Public Health, Washington University St. Louis, Birmingham/Atlanta Geriatric Research, Education, and Clinical Center

**Objective:** With anti-retroviral therapy (ART), PWH are living longer and experiencing comorbidities driven by inflammation. Exercise is a well-known method for reducing inflammation; however, in PWH, there are several barriers that may limit exercise participation. The primary objective of this study was to assess the efficacy, safety, and feasibility of a 6-week high intensity interval training (HIIT) intervention among older people living with HIV (PWH) and co-occurring hypertension. The secondary objective was to evaluate the cytokine levels and feelings towards exercise of the participants, and how that changed from baseline to post-intervention.

**Methods:** A research nurse collected blood at specified intervals (baseline and post-intervention) for cytokine analysis. Inflammatory cytokines included in analysis were: IL-10, IL-6, TNF-α, and hsCRP. An Exercise Benefits/Barriers scale was conducted at the same timepoints to assess the participants' feelings towards exercise, and how that changed following the intervention.

**Results:** A total of 13 PWH participated in the study and 9 participants have complete cytokine measurements Participants were on average 61.5 years old, 44% Black, and 67% male. Inflammatory cytokines generally decreased from baseline to post-intervention with the exception of IL-10. Additionally, participants perceived exercise more positively following the intervention (133.7 vs. 135.8). Additionally, we found a negative correlation between perceived benefits of exercise and hsCRP post-intervention ($r= -0.84$; $p=0.008$).

**Conclusions/Broader Impacts:** Overall, this intervention was feasible for older PWH and co-occurring hypertension and may improve inflammatory levels and perceptions of exercise. The change in perceptions of exercise was related to the decrease observed in hsCRP levels. Follow-up studies are warranted to gain a better understanding of the relationship between cytokines and perceptions of exercise among older PWH and co-occurring hypertension.

**Acknowledgements:** Funding: This project was supported by the HIV and Aging Research Consortium (R33AG067069), UAB Center for Exercise Medicine, UAB Nathan Shock Center, and the Center for AIDS Research Network of Integrated Clinical Systems (CNICS).

## 2. Unraveling the Novel Genetic Connection Between Insomnia and Cognitive Impairment

**Morgan Barkley** [1], Carson Lambert [1], Girish Melkani[1, 2]

[1]Division of Molecular and Cellular Pathology, Department of Pathology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL [2]UAB Nathan Shock Center, Birmingham, AL 35294

Contact Email: motb@uab.edu crlamber@uab.edu gmelkani@uab.edu girishmelkani@uabmc.edu

### Introduction

Insomnia affects up to one-third of the global population and is strongly associated with cognitive impairment, including deficits in learning, memory consolidation, and executive function. Despite this clinical overlap, the genetic mechanisms linking insomnia to cognitive impairment remain poorly defined. Recent GWAS studies identified human candidate genes associated with insomnia, including candidate genes that show strong associations with cognitive impairment. However, the functional relevance of these genes and their mechanistic contribution to cognitive impairment have not been experimentally defined.

### Methods

To dissect the molecular pathways linking insomnia susceptibility to cognitive impairment, we an innovative utilized *Drosophila* models with conserved sleep regulation and memory/learning circuits. By using mushroom body specific driver (OK-107-Gal4), we knocked down *Drosophila* orthologs of human insomnia-linked genes.

### Results

Our initial results identified four candidate genes ***Mnt, Rapgap1, AtpSynC, and CG32264*** whose knockdown caused significant impairments in aversive olfactory memory. These findings were observed consistently in both 3-week-old flies and were exacerbated in 6-week-old flies, suggesting age-dependent vulnerability.

### Conclusion

Collectively, these findings suggest that insomnia-associated genes modulate sleep, cognitive behavior and disrupt neurobiological pathways including synaptic plasticity and inflammatory signaling which are essential for memory integrity.

### Future Directions

Defining the mechanistic links provides a foundation for identifying early biomarkers of cognitive impairment and developing targeted strategies to prevent insomnia-induced memory impairment.

### Acknowledgements

Fly lines were obtained from Bloomington and VDRC. This work was supported by National Institutes of Health (NIH) grants AG065992 and RF1NS133378 to G.C.M.

**3. Mitochondrial Evaluation of Fresh 3D Brain Tissues and Organoids**

**Gloria A. Benavides**[1], Xiaosen Ouyang[1], Cheng Jack Song[2], Jianhua Zhang[1] and Victor Darley-Usmar[1]

*[1]Mitochondrial Medicine Laboratory, Department of Pathology, [2]Department of Cell, Developmental, and Integrative Biology. University of Alabama at Birmingham*

The study of metabolism in 3D models such as live tissues and human organoids is fundamental to progress in both basic and translational research. Tissues and organoids provide physiological and pathological insight into multicellular function. In this pilot study, we optimized the conditions to measure mitochondrial function in fresh brain tissues and human stem cell derived kidney organoids with the use of improved technologies (Agilent XF Flex) that allow us to evaluate metabolic function. Freshly dissected mouse brain was sliced at 200 µM by a vibratome (Precisionary Instruments) then the slice was punched at 1 mm in different regions of the brain. Tissue (1 or 2 punched) was transferred to the XF Flex 3D capture microplate with XF-DMEM media and incubated for 1h in a non-$CO_2$ incubator. XF Flex analyzer (Agilent) was used to measure basal OCR and ECAR followed by injections of different concentrations of 5-30 µM oligomycin, 1-2 µM FCCP, 10 µM Antimycin A, and 50 mM 2-deoxy-glucose to evaluate respiration and glycolysis in the tissue. In summary we determined the best conditions for mouse brain preparation to study mitochondrial function as well as the differences between regions of the mouse brain. Also, we optimized the number of human kidney organoids needed for the assay.

This work was supported in part by UAB Nathan Shock Center P30 AG050886 (VDU, JZ).

**4. Late-Onset Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) Modeling in Drosophila Reveals Exercise-Driven Rescue of Age-influenced Muscle and Cardiac Dysfunction**

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**Introduction**
**MADD** is a rare lipid storage myopathy (**LSM**) caused by mutations in the electron transfer flavoprotein genes like **ETFDH**, leading to impaired mitochondrial fatty acid β-oxidation, lipid accumulation, and progressive skeletal and cardiac dysfunction. The lack of scalable *in vivo* models has hindered understanding of mutation-driven, age-dependent disease progression and longitudinal analysis of therapeutic response.

**Methods**
We engineered CRISPR knock-in Drosophila lines harboring patient-relevant **ETF-QO** mutations**,** fly ortholog of **ETFDH**. Age-dependent locomotor performance (flight index (**FI**), geotaxis), lipid burden and high-speed optical analysis of semi-intact hearts was performed. Whole-fly respirometry analysis, ATP production, ROS level and transcript analysis was conducted to probe bioenergetics, oxidative stress and signaling pathways. As a non-pharmacological intervention, moderate endurance activity (15 min/day for 2.5 weeks) was implemented.

**Results**
**ETF-QO** mutants recapitulated hallmark features of **MADD**, including progressive locomotor decline (**FI** reduced by ~65%) and ectopic lipid deposition in thoracic and abdominal tissues. Cardiac assessment revealed functional abnormalities, including reduced fractional shortening (**FS**), prolonged heart period, and increased arrhythmia index (**AI**), mirroring MADD-associated cardiomyopathy. *In vivo* respirometry showed reduced oxygen consumption in mutants, aligning with the locomotor and cardiac deficits. Mechanistically, **ETF-QO** dysfunction resulted in elevated oxidative stress, and diminished ATP production which improved under exercise along with **FS** and **AI**. RT-PCR suggested activation of the AMPK–PGC-1α–TFAM signaling axis, suggesting a compensatory mitochondrial biogenesis and energy stress response.

**Conclusions**
These findings establish a robust *Drosophila* model of MADD that captures age-dependent neuromuscular and cardiac pathology. This platform enables mechanistic studies of LSMs and provides a tractable system for testing therapeutic strategies.

**Future Directions**
Extension of these findings to human organoid models will enhance translation relevance and shed light on how LSM-dysfunction interacts with aging and shapes therapeutic response. Future study will test combinatorial interventions integrating exercise and nutraceutical approach with circadian modulation like time-restricted feeding.

**5. Sex Differences in Social Behavior and Fear Generalization in an Aging Rat Model**

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**Introduction**

Aging is associated with changes in social behavior and increased vulnerability to maladaptive fear responses. These behavioral alterations often differ by sex, and hormonal state may further contribute to variability in social and fear-related outcomes. However, the interaction between sex, estrous cycle stage, social behavior, and fear generalization in aging-relevant animal models remains incompletely understood. This study examines sex and hormone-related differences in social behavior and fear generalization using a comprehensive behavioral model in rats.

**Methods**

Male and female rats were studied using a multi-day behavioral paradigm. Baseline social behavior was assessed prior to fear conditioning using an open-field social interaction task with familiar and unfamiliar conspecifics, with behavior recorded and quantified using Ethovision tracking software. Female estrous cycle stage was determined via vaginal lavage following behavioral testing, and males underwent matched handling procedures. Post-conditioning sociability and fear generalization were assessed on a subsequent testing day in both social and non-social contexts. Behavioral outcomes were analyzed in relation to sex and estrous cycle stage.

**Results**

Preliminary data indicate that males exhibit less fearful social behavior compared to females, who show consistently higher levels of fearful social behavior following conditioning.

**Conclusion**

These findings support the utility of this behavioral framework for examining sex-dependent and hormone-related differences in social behavior and fear generalization in aging. Distinguishing baseline behavior from post-conditioning effects allows for clearer interpretation of how fear learning influences behavior across contexts.

**Future Directions**

Ongoing work will complete behavioral analyses and integrate neural measures to further characterize sex- and hormone-dependent patterns in fear-related behavior during aging.

## 6. The impact of dietary serine and glycine availability on aged skeletal muscle cell composition following injury

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### Introduction
~40% of older adults report a decline in mobility, caused in part by skeletal muscle (SkM) deterioration and remodeling with advancing age (i.e., sarcopenia). While the cause for these SkM changes is multifactorial, impairment in the regenerative process is one cause. Our lab determined that the endogenous availability of the nutritionally non-essential amino acids, serine and glycine (ser/gly), decline with age. Further, we found that when aged mice were fed a diet absent of ser/gly, SkM regeneration was impaired and adipocytes accumulated. The impact of dietary ser/gly on the SkM immune response after injury is unknown.

### Methods
Aged female C57BL/6N mice were randomized to one of two diets: ser/gly control ($SG_{CNT}$) or ser/gly depleted ($SG_{DEP}$). Mice were acclimated to the diet for four weeks prior to injury (i.e., intramuscular myotoxin injection in both tibialis anterior muscles). Muscles were collected 0, 3, 14, and 28 days post injury (dpi) and analyzed using qPCR to identify changes in cytokine abundance (pro-inflammatory: *Il6, Tnfα; and anti-inflammatory: Il4, Il10,* and *Gata3),* and with immunohistochemistry for macrophage abundance (pro-inflammatory: M1; and anti-inflammatory: M2).

### Results
We identified greater levels of cytokines (*Il6, Tnfα, Il4*, *Il10,* and *Gata3)* in the $SG_{DEP}$ (vs. $SG_{CNT}$) at 3 dpi. Intriguingly, there was ~200 fold increase of anti-inflammatory cytokines, when a pro-inflammatory response is expected, indicating altered immune response. Supporting this, we identified a significant increase in M2 macrophages in the $SG_{DEP}$ (vs. $SG_{CNT}$) at 3 dpi.

### Conclusions
These results support the hypothesis that reduction of endogenous ser/gly, via the diet, results in a robust anti-inflammatory phenotype and impaired SkM regeneration post-injury.

### Future Directions
Further directions are to identify how changes in the cytokine environment influence SkM stem cell activity following injury.

### Acknowledgments
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**7. Carboxy-terminal blockade of sortilin binding enhances progranulin gene therapy, a potential treatment for frontotemporal dementia**

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**Introduction**
Frontotemporal dementia is commonly caused by loss-of-function mutations in the progranulin gene. Potential therapies for this disorder have entered clinical trials, including progranulin gene therapy and drugs that reduce progranulin interactions with sortilin. Both approaches ameliorate functional and pathological abnormalities in mouse models of progranulin insufficiency. Here we investigated whether modifying the progranulin carboxy terminus to block sortilin interactions would improve the efficacy of progranulin gene therapy.

**Methods**
We compared the effects of treating progranulin-deficient mice with gene therapy vectors expressing progranulin with intact sortilin interactions, progranulin with the carboxy terminus blocked to reduce sortilin interactions, or GFP control.

**Results**
We found that expressing carboxy-terminally blocked progranulin generated higher levels of progranulin both at the injection site and in more distant regions. Carboxy-terminally blocked progranulin was also more effective at ameliorating microgliosis, microglial lipofuscinosis, microglial morphology changes, and lipid abnormalities including ganglioside accumulation and loss of bis(monoacylglycero)phosphate lipids. Behavioral abnormalities detected in progranulin-deficient mice using an unbiased machine learning analysis were absent after treatment with carboxy-terminally blocked progranulin but not corrected by unblocked progranulin. Finally, only carboxy-terminally blocked progranulin reduced plasma neurofilament light chain, a biomarker of axonal damage, in progranulin-deficient mice.

**Conclusions**
These results demonstrate that modifying the progranulin cargo to block sortilin interactions may be important for increasing the effectiveness of progranulin gene therapy.

**Future Directions**

Our findings suggest that the effectiveness of next-generation progranulin gene therapy approaches may be maximized by delivering a cargo with C-terminal modifications that prevent sortilin interactions.

**8. A Putative AMPK-dependent pathway underlying dopaminergic neurodegeneration in *C. elegans* following exposure to newly isolated bacteria-derived compounds**

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**Introduction**

We previously discovered that exposure to secondary metabolites from the common non-pathogenic soil bacterium, *Streptomyces venezuelae,* causes death of *C. elegans* dopaminergic (DA) neurons and human SH-SY5Y cultured cells. These previous experiments were performed with crude metabolite extract, yet the intricate toxicodynamic mechanisms remained elusive. Recently, we fractionated the major active components of the metabolite extract into two bioactive molecules using HPLC bio-guided fractionation. Since we are still awaiting the NMR data to confirm the chemical structure of the fractions, we refer to them as Peak 2 and Peak 3, with the latter identified as a pure compound.

**Methods**

We re-evaluated the effect of Peaks 2 and 3 using several phenotypic and biochemical assays previously reported for the crude extract. In addition, we examined whether these compounds affect health span or reduce stress resistance in N2 wild-type worms compared with mutants exhibiting impaired mitochondrial function (*mev-1*) or constitutive AMPK pathway activation (*flcn-1*). **Mobility indices were used as quantitative measures of health span.**

**Results**

DA neurodegeneration was exacerbated following exposure to *S. venezuelae* metabolic products. These compounds increased mitochondrial ROS levels and decreased ATP synthesis in ex vivo assays. The compounds reduced health span in N2 and *mev-1* mutants, indicated by a lower mobility index in the paraquat resistance assay. In *flcn-1* mutants, this reduction in mobility index was ameliorated, suggesting a potential involvement of the AMPK pathway.

**Conclusion**

This study elucidates novel gene by environment interactions that incites pathological cascades leading to neurodegeneration. We propose that chronic exposure to bacterial metabolite compounds triggers dopaminergic neurodegeneration, an effect possibly mediated by the mitochondrial-AMPK signaling axis.

**Future Directions**

We will co-treat animals with the metabolite compounds and AICAR. Afterwards, we will see if the pharmacological activation of AMPK by AICAR restores health span or is protective against dopaminergic neurodegeneration.

**9. Racial segregation across the life-course and life-space Mobility: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study**

**Authors:** Ene M. Enogela[1], Madeline R. Sterling[2], Lonnie Hannon III[3], Thomas W. Buford[4,5], Kathryn Foti[1], C. Barrett Bowling[6,7], Virginia Howard[1], Monika Safford[2], Shakia T. Hardy[8], Parag Goyal[2], Hugo G. Quezada-Pinedo[9], Natalie Colabianchi[10], Emily B. Levitan[1]

**Introduction**
Life-space mobility, an indicator of independence and social participation, reflects the distance, frequency, and assistance required to move beyond one's immediate environment. We examined the association of state-level racial segregation over the life course with life-space mobility assessed during mid-to-late adulthood.

**Methods**
Among Black and White participants in the REGARDS study born in 1940-1958 with residential information in childhood (age ≤ 19 years), young adulthood (age 20-39 years), and mid to late adulthood (age ≥ 40 years), state-level segregation measures (dissimilarity and isolation indices, per 1 SD) were constructed from census-tract data across U.S. decennial censuses (1940-2010). Least angle regression and multivariable linear regression models were used to identify relevant life-course hypotheses (accumulation, sensitive period, critical period, change, effect modification by present-day social conditions, and threshold effects) for associations of segregation measures with Life-Space Assessment (LSA) collected in 2013-2016.

**Results**
Among 2,885 participants (mean age 66 years [SD: 5.4]; 64% female; 33% Black race), Black individuals had lower LSA scores compared to White individuals [mean (SD): 74(30) versus 89(25), theoretical range 0-120]. In the overall cohort, higher childhood dissimilarity was positively associated (β = 1.40, 95% CI: 0.20, 2.59) with life-space mobility, but greater increases in dissimilarity over time (β range: -1.23 to -1.24) were linked to lower life-space mobility. For isolation, childhood exposures (β = -2.89, 95% CI: -4.21, -1.56) were associated with lower life-space mobility, while changes in isolation (childhood to young adulthood) were associated with higher life-space mobility (β = 1.75, 95% CI: 0.86, 2.63). Effect modification analyses showed stronger negative effects of dissimilarity among individuals reporting higher discrimination compared to lower discrimination, or low social support compared to high social support.

**Conclusion**
Lifetime exposure to segregation is associated with life-space mobility under sensitive period, change, and effect-modification hypotheses.

**Future directions**
Lifespace trajectories across aging phenotypes.

## 10. The Impact of Vitamin B12 Supplementation on the Gut Epithelia of Aged Female Mice

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### Introduction
Dysbiosis, the loss of beneficial symbionts and increase of pathobionts, is a recently-defined hallmark of aging that speaks to the major role of the gut on organismal health. Most research on gut epithelial health aims to understand how the microbiome influences the gut through metabolites but there is insufficient work showing how the host's metabolites and micronutrients (or lack thereof) deteriorate gut health over time. One essential micronutrient is vitamin B12, which generally decreases with advanced age but has not been investigated for its role in maintaining gut epithelial homeostasis during aging.

### Methods
Aged (20-22 months) C57BL/6N female mice received a defined, AIN93G diet. They were randomized to weekly (12 weeks) intramuscular injections of either (i) vehicle control (saline) or (ii) B12 supplementation. At 12 weeks, the colon, cecum, and fecal pellets were collected. The colon was embedded in paraffin using the swiss roll technique and stained with H&E, Alcian blue, and Sirius red. Cecum and fecal pellets were reserved for future analysis. MMA, a marker of B12 status, was quantified to determine if B12 supplementation improved B12 status in the aged mice.

### Results
Visualization of the colons through H&E suggests reduced inflammation and immune cell infiltration, increased goblet cells, and decreased epithelial renewal in the B12 supplemented (vs. control) mice. MMA levels were reduced in the supplemented (vs. control) mice suggesting that B12 supplementation improved B12 status.

### Conclusions
These results support the hypothesis that micronutrient status (i.e., B12 status) impacts host gut health, independent of dietary intake. Whether B12 supplementation improves microbial populations in aged individuals is yet to be determined.

### Future Directions
Future research will analyze spleen immune cell populations to better elucidate the effect of B12 supplementation on the immune system and to perform 16S sequencing to determine the effects on the microbiome.

### Acknowledgements
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**11. Behaviorally stimulated hippocampal metabolite fluctuations in TgF344-AD rats are sex-and age-specific**

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**Introduction**
Advanced age, which is associated with impaired systemic and cerebral metabolism, represents the greatest risk factor for Alzheimer's Disease (AD). These impairments, such as insulin resistance and cerebral glucose hypometabolism, increase the risk of developing AD, and significantly contribute to disease progression, highlighting the importance of glucose metabolism in cognitive function. Glucose utilization is essential for proper brain function, as it supports neurotransmission and cognitive processes. While cognitive loads typically cause modest depression of extracellular glucose, aged male rats exhibit pronounced and prolonged task-evoked depression in hippocampal extracellular glucose during spatial tasks.

Like humans with AD, the TgF344-AD rat model exhibits sex-dependent impairments in peripheral metabolism by middle age. However, cerebral glucose fluctuations in response to cognitive stimulation in this rat model, and the impact of sex and age on these processes, have not yet been investigated.

**Methods**
We cognitively stimulated young, middle aged, and aged (4, 14 & 24 months) male and female TgF344-AD rats and their wildtype (WT) controls using an object discrimination task. Brain microdialysis was used to collect interstitial fluid from CA3 of the hippocampus in 20-min bins and measure extracellular metabolites and neurotransmitters.

**Results**
While aged WT females exhibit increased hippocampal extracellular glucose after cognitive stimulation, aged WT males and aged TgF344-AD rats of both sexes do not. Middle aged females showed no differences in glucose dynamics following cognitive stimulation. We additionally quantified neurotransmitters, as metabolic perturbations can profoundly impact neuronal signaling. While aged male and female WT rats had significantly different glutamate response over time, there was only an effect of genotype in aged males.

**Conclusions**
These findings suggest that AD exacerbates age-related impaired glucose response in females, while impaired glutamate response is exacerbated by AD in aged males.

**Future Directions**
Future experiments will elucidate cell-type specific glucose dynamics in aging via fiber photometry during a cognitive task.

## 12. Sex-Specific Aging in Two *Drosophila* Species with Divergent Genome Sizes

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### Introduction

Sex-specific aging is common across many animals. However, the mechanism by which the sexes age differently is unclear. In *Drosophila melanogaster*, aging is associated with changes in gene expression and increased expression of repetitive elements in somatic tissue. Genome sizes and repeat content vary across the genus *Drosophila*, and how this variation affects aging is poorly understood. The *D. virilis* genome approximately twice the size of the *D. melanogaster* genome and contains a higher percentage of repeats. Accordingly, we will compare sex-specific aging in *Drosophila melanogaster* and *D. virilis*.

### Methods

We collected demographic data and created Kaplan-Meier survival curves to identify equivalent time points across sex and species. The animals were aged to these time points and dissected. To examine transcriptional changes across species, we sequenced RNA extracted from brain and thorax.

### Results

The Kaplan-Meier survival curves revealed decreased lifespan in males of both species as compared to females. The transcriptome analysis of *D. melanogaster* showed sex-specific changes in gene expression with age. Old males primarily showed decreased expression of genes involved in reproduction. Old females exhibited increased expression in many genes of diverse functions, potentially a sign of large-scale misregulation of transcription. The transcriptome analysis of *D. virilis* is currently ongoing and results will be reported.

### Conclusions

We find that observed sex differences in lifespan correspond to differences in age-related transcriptional changes. Additionally, the lifespan curves indicate that sex-specific aging occurs in multiple species of *Drosophila*, validating its use as a model genus for this study.

### Future Directions

Analyzing *D. virilis* transcription will allow for comparison of sex-specific aging phenotypes across species. Additionally, we are developing an analysis pipeline to compare repetitive element expression across species, which will allow us to compare misregulation of repeats across these species.

### Acknowledgments

We would like to thank the National Science Foundation for funding this project through grant #2213824.

13. **Establishing the freshwater crustacean, *Daphnia pulex*, as an alternative, short-lived animal model of healthspan and aging: impacts of diet and culture medium**

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**Introduction**
*Daphnia pulex* is commonly used in ecotoxicology and has potential as a model for aging biology. *D. pulex* reproduces by parthenogenesis, has a lifespan of less than 60 days, can be housed in small vials, and responds to dietary restriction with increased lifespan. Culture conditions vary across laboratories using *D. pulex* for longevity studies, thus generalizations of lifespan interventions are difficult. The objective of this study is to evaluate culture conditions that support health and longevity for *D. pulex*.

**Methods**
In Experiment 1, we fed daphnia live, unicellular green algae, *Raphidocelis subcapitata* (GA) and compared culture media, using either reconstituted moderately hard freshwater described by the Environmental Protection Agency (EPA) or COMBO medium formulated with trace elements. In Experiment 2, we used COMBO medium and fed daphnia either GA or a commercial, non-living algae concentrate, Shellfish Diet (SD). From four clonal lines, six neonates per treatment were housed individually in glass vials containing 50 mL of the respective medium (n=24 per treatment). Individuals were fed three days per week and inspected daily for survival and reproduction. Body length was measured weekly.

**Results**
The median lifespan (35.5±16 and 36.5±13 days) and average body length (3.10±0.16 and 3.09±0.12 mm) were similar for individuals held in either EPA or COMBO culture media; however, average total offspring produced was highest for those held in COMBO medium. The median lifespan was highest for individuals fed SD (74.5±22 and 38±13 days for SD and GA, respectively). Individuals fed GA reached maximum body length (3.12±0.10 mm) by week 6, whereas those fed SD reached maximum body length (2.95±0.07 mm) by week 10.

**Conclusions**
Culture medium did not impact lifespan but did influence reproduction. Diet had a strong effect on lifespan.

**Future Directions**
We will investigate diet to determine if dietary restriction or nutritional composition impact lifespan.

## 14. Circadian Restoration of Gamma Oscillation Power to Alleviate Hypersynchrony and Behavioral Deficits

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### Introduction

Current therapies for Alzheimer's disease (AD) offer limited benefit, and scalable preventive strategies remain out of reach. Cognitive dysfunction in AD is tightly linked to disrupted neuronal network synchrony, particularly gamma-frequency oscillations (30–80 Hz). Hyperexcitability in patients and mouse models shows strong diurnal patterning, suggesting interactions between circadian regulation, interneuron function, and circuit stability. Because inhibitory parvalbumin (PV) interneurons are key drivers of gamma oscillations, PV dysfunction across time-of-day may contribute to diurnal variability in network excitability.

### Methods

We assessed molecular clock rhythmicity and transcriptional profiles in PV interneurons and excitatory neurons from dentate gyrus and cortex, regions implicated in AD pathology. Using slice electrophysiology across circadian time, we evaluated whether PV intrinsic properties and circuit output are disrupted in AD mouse models. In parallel, we implemented a chemogenetic strategy to manipulate PV interneuron activity and measured network-level effects using a single cortical screw EEG lead. Ongoing optimization includes viral spread and ligand dosing to avoid excessive PV activation.

### Results

Pilot data show that chemogenetic activation of PV interneurons produces clear, robust changes in gross cortical activity and significantly increases gamma-band power in healthy PV-cre mice. Current experiments are titrating vector spread and drug concentration to modulate gamma activity without overactivating PV cells and clamping local network dynamics.

### Conclusions

PV interneurons provide a tractable entry point to manipulate gamma oscillations and overall circuit excitability, enabling direct tests of circadian-linked mechanisms relevant to AD-associated hyperexcitability.

### Future Directions

We will apply PV-targeted chemogenetic manipulation in the J20 AD mouse model to test whether restoring circadian-dependent gamma oscillatory patterns reduces hyperexcitability and improves cognitive outcomes, while refining dosing/spread for physiologic network modulation.

## 15. Caregiver Sex and Relationship with Stroke Survivors and Perceived levels of Emotional and Instrumental Support

**Greig, N.**, Uswatte, G., Grant, A., Biney, F., Bliss, H., Mark, V., Rathz, M., Bhaskar, B., Huddleston, S., Yarramsetty. M.

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### Introduction

Advanced age is a risk factor for stroke. Persons with Stroke (PWS) are commonly cognitively and physically impaired. Research exploring relationships among perceived-social support, caregiver relationship type and caregiver sex is limited.

We evaluated whether caregiver sex and relationship type (romantic/non-romantic) predict PWS' perception of social support. We hypothesized that PWS with female caregivers will perceive higher emotional and instrumental support, particularly if they have a female-romantic partner caregiver.

### Methods

DESIGN: Cross-sectional, correlational study
SETTING: University medical center.
SAMPLE: Adult PWS with mild-to-moderate cognitive impairment ($N$=48).
MEASURES: NIH Toolbox Perceived Emotional Support and Perceived Instrumental Support; Montreal Cognitive Assessment (MoCA). Separate hierarchical linear regression models predicted Perceived Emotional Support and Perceived Instrumental Support respectively: Block 1: [MoCA]; Block 2: [Caregiver Sex; Relationship Type]; Block 3: [Sex*Relationship].

### Results

The full model predicting Perceived Emotional Support from patient cognitive status, caregiver sex, relationship type and the interaction between caregiver sex and relationship type was not significant ($R^2$=.065, $F$(4,47) =0.75, $p$=.562). Caregiver sex and relationship type did not improve the model fit relative to cognitive status alone ($R^2_{\text{change}}$ = .003, $F_{change}$(2,44) =0.07, $p$=.932), nor did their interaction ($R^2_{\text{change}}$ = .058, $F_{change}$(1,43) =2.67, $p$=.110).

The full model predicting Perceived Instrumental Support from these same variables was not significant ($R^2$=.163, $F$(4,47) =2.1, p=.097). Caregiver sex and relationship type, however, improved the model fit relative to cognitive status alone ($R^2_{\text{change}}$ = .156, $F_{change}$(2,44) =4.09 $p$=.023). Caregiver sex did not predict Perceived Instrumental Support ($p$=.223). PWS with romantic partner caregivers showed a 7-point advantage in Perceived Instrumental Support ($p$=.013). The caregiver sex by relationship interaction was not significant ($R^2_{\text{change}}$ = .002, $F_{change}$(1,43) =.086, $p$=.771).

### Conclusion/Future Directions

PWS with romantic partner caregivers reported more instrumental support than those with non-romantic caregivers. Caregiver sex did not predict perceived support. The findings warrant further study in a larger sample.

## 16. Obesity-Linked Genes Sec16 and Rpt5 Drive Cardiac-Circadian Disruption Through Cross-Organ Communication

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**Introduction**
Obesity is a multifactorial disorder strongly associated with cardiovascular dysfunction and disruption of circadian rhythms. Disruption of coordination between the central circadian clock and peripheral oscillators such as the heart drives systemic physiological dysfunction yet underlying molecular mechanisms remain poorly understood. Genome-wide association studies have identified obesity-risk genes including *PSMC3* and *SEC16B*, which regulate proteostasis and endoplasmic reticulum (ER) function.

**Methods**
We are investigating gene functions using *Drosophila melanogaster* and AC16 human cardiomyocyte cell lines. In *Drosophila*, we performed tissue-specific knockdowns of conserved orthologs *Rpt5* and *Sec16*. Functional analyses assessed cardiac performance and sleep/ circadian architecture utilizing *3-weeks* (young) and *7-weeks* (old) flies. AC16 cells were used to find translational relevance in a mammalian cardiac model for our genes of interest.

**Results**
Cardiac suppression of *Rpt5* and *Sec16* in *3-weeks Drosophila* impaired heart performance and disrupted sleep/ circadian architecture, while neuronal knockdowns altered circadian behavior and compromised cardiac function. Cardiac-specific knockdown triggered inflammatory responses in the head, demonstrating systemic consequences of disrupted heart-brain signaling. AC16 validation studies confirmed conserved roles in cardiac function.

**Conclusions**
Obesity-linked genes act as genetic drivers coupling cardiac physiology with circadian control through both autonomous and non-autonomous mechanisms in age-dependent manner, establishing the first genetic *Drosophila* models of cardio-circadian disruption.

**Future Directions**
Future studies will employ transcriptomic profiling and interventions like TRF or small molecules to explore and restore stress and inflammation pathways mediating multi-organ desynchrony, providing a platform to uncover conserved pathways and accelerate strategies for mitigating obesity-associated cardiovascular risk.

## 17. CD36 Links Arteriolar Angiogenesis to Endothelial Cell Immunity in Development of Alzheimer's Disease

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**Background**
Alzheimer's disease (AD) displays profound cerebromicrovascular abnormalities, irregular arterioles, and potential abnormal immunity. CD36 is an antiangiogenic receptor in endothelial cells (ECs), which may regulate arteriolar angiogenesis. As an innate immunity receptor, CD36 may also be critical for the regulation of the immune property of vascular ECs. Ours and other studies suggest that abnormal CD36 expression may contribute to the development of AD.

**Hypothesis**
We hypothesize that CD36-associated abnormal arteriolar angiogenesis in the brain may be linked to dysregulated EC immunity, thus contributing to AD pathogenesis.

**Methods**
To test this hypothesis, we leveraged the Seattle Alzheimer's' disease brain cell atlas consortium. Using an available cohort of AD patients, we analyzed single nuclear RNA-seq data derived from the middle temporal gyrus (MTG) of brain tissues. Immunohistochemistry and immunofluorescence microscopy were utilized to evaluate blood vessels and ECs associated with angiogenesis in the brain tissues from the AD patients. Further, we evaluated CD36 expression by leveraging spatial transcriptomics data from the hippocampus of AD mice. To study underlying mechanisms, we established a diet-induced obesity model in *CD36* knockout mice, with specific deletion of CD36 in ECs and a genetically tagged enhanced GFP to the ribosome of the endothelia. RNA sequencing (RNA-seq) was performed by using isolated ribosome-bound mRNA directly from the brain vascular endothelia in knockout and control mice. RNA-seq data were utilized for the transcriptional profiling to identify gene signatures related to angiogenic signaling and EC immunity, and the expression of genes involved in lipid metabolism, endothelial functions, and AD.

**Results**
We identified three EC subpopulations including Endo 1, Endo 2 and Endo 3 in the MTG of AD patients. Endo 2, with moderately high expression of CD36, accounted for the majority of the EC population and correlated with a high level of APOE4 expression and a more advanced Braak stage in AD. There was significant global CD36 expression in the brain tissues of AD patients, along with high levels of CD36 in the endothelia of brain blood vessels. Spatial transcriptomics analysis demonstrated obvious CD36 expression in the brain ECs in the hippocampus of the AD mice. Mechanistically, CD36 could contribute to AD pathogenesis by affecting arteriolar angiogenesis and changing the gene signature in innate immune memory of brain ECs at transcriptional levels. Moreover, the genes related to CD36-mediated metabolic reprograming might play an important role in the regulation of EC immune memory.

**Conclusion**
Our study indicates that CD36-regulated arteriolar angiogenesis may be associated with the innate immunity in the brain ECs, which is essential in AD pathobiology. In particular, a specialized CD36-positive EC subset may contribute to AD pathogenesis due to mediating abnormal neurovascular immunity.

**18. HIV Testing Determinants Among Young and Middle-aged Adults Respondents to the 2024 Behavioral Risk Factor Surveillance System**

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**Introduction**
Routine HIV testing (HT) is recommended for adults aged 18–64 but remains underutilized. This study examines age-specific factors associated with recent HIV testing among
U.S. young (18–44 years) and middle-aged (45–64 years) adults, highlighting how differences in risk perception, healthcare utilization, and access to preventive services may shape testing behaviors.

**Methods**
This cross-sectional study used data from the 2024 Behavioral Risk Factor Surveillance System (BRFSS) to examine recent HT among young and middle-aged U.S. adults. HT prevalence was evaluated by age and sociodemographic factors, and Andersen's Behavioral Model guided multivariable logistic regression analyses to identify predisposing, enabling, and need-related factors associated with recent testing overall and by age group.

**Results**
Among 57,566 BRFSS respondents, 36% reported HT in the past 12 months. Among those recently tested, 69% were young adults. Recent testing was more common among non-White individuals, those reporting HIV risk behaviors (HRB), and adults with health insurance and a personal healthcare provider (PCP). In adjusted analyses, Black (OR 2.62; 95% CI: 2.48 – 2.77) and Hispanic adults (OR = 2.05; 95% CI: 1.94 – 2.16) had higher odds of testing than White adults, particularly among middle-aged Hispanic adults (OR 2.62; 95% CI: 2.38 – 2.88). Females, particularly those aged 45 – 64 years had lower odds of recent HT than males (OR 0.61; 95% CI: 0.57 – 0.65). Being unmarried, having a PCP and insurance were associated with increased testing. Reporting HRB was the strongest predictor of recent HT (OR 2.41; 95% CI: 2.28 – 2.55), consistent across age groups.

**Conclusions**
Recent HT among U.S. adults was influenced by predisposing, enabling, and need factors, with notable differences by race/ethnicity, sex, and age. Higher testing among individuals reporting HRB and those with healthcare access highlights the importance of perceived risk and access to care in promoting HT uptake.

**Acknowledgements:** Supported by the UAB Center for Exercise Medicine

**19. A forward genetic screen in *Caenorhabditis elegans* identifies *twk-14* as a modulator of α-synuclein-induced neurodegeneration**

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**Introduction**

α-synuclein (α-syn), a primary pathologic factor in Parkinson's disease (PD), chronically activates the mitochondrial unfolded protein response pathway ($UPR^{mt}$), resulting in the progressive neurodegeneration of *C. elegans* dopaminergic (DA) neurons. This was mediated through a conserved regulator of the $UPR^{mt}$, ATFS-1, which activates the transcription of hundreds of nuclear genes that are targeted to the mitochondria in response to mitochondrial stress. In an *atfs-1* loss-of-function (lf) background, the burden imposed by an unfettered ATFS-1-dependent transcriptional response is eliminated, resulting in robust neuroprotection from α-syn overexpression. However, the compensatory mechanisms that underlie α-syn neuroprotection are unknown.

**Methods**

A forward F3 genetic screen in *atfs-1(gk3094) (lf)* mutant background uncovered a nonsense allele of the *C. elegans twk-14* gene, *twk-14(ba20)*. This gene encodes KCNK12 in mammals; it is associated with regulating resting membrane potential and facilitating background leak $K^+$ currents. The mutation results in a stop codon instead of a tryptophan (Trp358*). We confirmed the *twk-14(ba20)* genetic lesion using CRISPR technology. A strain encoding a SNP was created in the endogenous gene product reflective of the Trp358* mutation [*twk-14(syb6863)*]. Worms expressing this allele were crossed to worms expressing either α-syn or GFP in the DA neurons. Similarly, the *twk-14(tm2522)* allele, which has a 342 bp exon deletion, was crossed to α-syn or GFP worm strains.

**Results**

The *twk-14(ba20)* allele from the forward genetic screen abolishes neuroprotection in the *atfs-1(gk3094*) *(lf)* mutant background. Consistently, the CRISPR-generated *twk-14(syb6863)* enhanced DA neurodegeneration. However, the *twk-14(tm2522)* mutants protected against DA neurodegeneration.

**Conclusion**

We hypothesize that the differential protection observed for the *twk-14* alleles occurred because KCNK12 is normally a dimeric protein.

**Future Direction**

We are creating worms that are heterozygous for the *twk-14(tm2522)* and *twk-14(syb6863)* alleles to assess α-syn-induced DA neurodegeneration. We plan to assess the impact of neurodegeneration over the course of aging.

## 20. Six-Month Change in Brain Care Behaviors in a Primary Care Registry: The BHAM Registry

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**Introduction**
Dementia and stroke share modifiable vascular and lifestyle risk factors often addressed in primary care, yet scalable brain health prevention approaches remain limited. The Brain Health Advocacy Mission (BHAM) Registry integrates structured brain health counseling into primary care using the Brain Care Score (BCS), a multidomain measure of modifiable brain health factors. This analysis evaluated short-term change in a telephone-administered partial BCS focused on lifestyle and socioemotional domains.

**Methods**
Analyses included the first 100 BHAM participants who completed 6-month follow-up with paired baseline and 6-month partial BCS data. Change was assessed using a paired-samples t-test with 95% confidence intervals (CI). A Wilcoxon signed-rank test evaluated consistency and characterized individual-level change.

**Results**
Mean partial BCS increased from 9.86 (SD 2.19) at baseline to 10.63 (SD 1.83) at 6 months, a mean improvement of 0.77 points (95% CI 0.49 to 1.05; $t(99)=5.39$, $p<.001$; Cohen's $d=0.54$). Wilcoxon signed-rank testing confirmed significant change ($Z=-4.89$, $p<.001$). At the participant level, 51 improved, 18 declined, and 31 showed no change.

**Conclusions**
Among the first 100 BHAM follow-up completers, partial BCS improved over six months, with improvements more common than declines. These findings provide early longitudinal evidence that a pragmatic primary care-embedded registry model may support measurable near-term improvements in brain health relevant behaviors.

**Future Directions**
Ongoing follow-up will evaluate durability of change, examine which domains change most over time, and link partial BCS change to 12 and 24-month outcomes including the full BCS and clinical risk factors. Additional work will refine retention strategies to improve reach and generalizability.

**Acknowledgements:** This research was funded by the McKnight Brain Research Foundation.

## 21. Untangling Tau's Role in a Multimodal Analysis of Functional Network Health

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**Introduction**
Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by the accumulation of amyloid-β and neurofibrillary tau, which leads to widespread cognitive decline. Emerging evidence suggests that AD pathology disrupts the organization and health of largescale brain networks, such as the default mode network and visual network. Tau accumulation has been linked to changes in functional network activity and connectivity patterns, but the mechanisms linking network-level tau pathology to systems-level dysfunction remain unclear.

**Methods**
Using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, our goal was to find subjects with completed Flortaucipir (AV-1451) Tau PET, resting state blood-oxygen level dependent (BOLD) fMRI, T1-weighted structural MRI, APOE genetic screening, Clinical Dementia Rating scale, and Mini Mental Status Examination. Because this data is crosssectional, to maintain that people were captured in uniform pathologic time courses, participant selection was filtered only to keep subjects whose diagnosis was consistent prior to, during, and one visit after the collection of data. All sequences and collection needed to be completed within 60 days. As a result, our sample includes 329 subjects (168 Female, Mean Age = 73.38 years). Brain networks were anatomically labeled using the Gordon 13-Network parcellation framework, reduced to 10 networks with sufficient volume for comparison across all subjects.

**Results**
Network health measures were defined to be Network Tau, Network Cortical Thickness, Within-Network Connectivity, and Network Segregation, determined as (1 - [BetweenNetwork/ WithinNetwork]). To test the hypothesis that network health metrics significantly correlate to each other inside of a given network compared to any other, we performed a Spearman's Rho Correlation analysis to identify these relationships. This correlation revealed that the CinguloOpercular Segregation decreases had significant negative correlations to Tau deposition in all networks of interest (Rho Range: (-0.247, -0.307), FDR-P Range: (4.09e-05, 8.72e-08)). Additionally, thickness decreases and tau increase in the Retrosplenial Temporal network correlated significantly with thickness decreases and tau increases in all networks, except for the somato-motor networks.

**Future Directions**
Currently, we are working to support these findings in a longitudinal analysis with subjects from ADNI and the Open Access Series of Imaging Studies (OASIS). Our goal is to further describe the relationships between connectivity and functional changes, tau accumulation patterns, and the eventual atrophy and behavioral findings characteristic of Alzheimer's Disease.

**Acknowledgements**
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## 22. Cell type specific mitophagy in the heart in a heart failure model

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**Background**
Cardiac aging is tightly linked to chronic pressure overload from hypertension and aortic stenosis, which accelerates hypertrophy, fibrosis, microvascular dysfunction and inflammatory remodeling. Mitochondrial quality control is central in these age-associated changes, yet it remains unclear how mitophagy changes across cardiomyocytes, endothelium, and macrophages during pressure-overload.

**Methods**
Using MitoQC reporter mice, we quantified mitophagy as red-only puncta and mapped these events specifically within Desmin-positive cardiomyocytes, CD31-positive microvasculature, and CD68-positive macrophages. Analyses were performed at day 4 following transverse aortic constriction (TAC) versus sham, across left-ventricular regions (LV1 baso-equatorial, LV2 equatorial, LV3 apico-equatorial) and stratified by sex. Mitophagy event count, size, and intensity were compared between groups, with statistical significance defined as Welch $p<0.05$.

**Results**
TAC increased mitophagy versus sham, with the largest shift in Desmin+ cardiomyocytes, with higher red puncta count, size, and intensity. This response showed a clear gradient (LV1 > LV2 > LV3) and was stronger in males than females. CD31+ endothelium also experienced increased mitophagy, with an ~2-fold rise in endothelial-associated events that were larger and brighter. CD68+ macrophages showed a significant increase of red-only puncta in both small and large CD68+ cells, again stronger in males, while large CD68+ macrophages are more frequently colocalized with the brightest red-only puncta compared to small CD68+ cells.

**Conclusions**
Pressure overload elevates mitophagy not only in cardiomyocytes, but also in endothelial cells and macrophages. The magnitude of induction differs by cell type, with the strongest macrophage-associated signal concentrated in enlarged CD68+ cells compared with smaller CD68+ cells. These data establish a cell-type–resolved framework to test geroprotective strategies that preserve mitochondrial quality control under aging-relevant afterload stress.

**23. Disruption of the growth hormone receptor in pancreatic alpha-cells, but not beta-cells, recaptures the growth hormone resistant phenotype**

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**Introduction**
Interrupting growth hormone (GH) signaling is one of the most robust avenues for extending lab rodent lifespan, yet the mechanisms for this effect remain unclear. Although classical GH-responsive tissues such as liver, adipose, and muscle have been extensively targeted, GH receptor (GHR) deletion in these organs fails to recapture the effect of global GHR knockout or GH-deficiency. This gap suggests that noncanonical GH-targets drive key features of this phenotype. Here, we show that pancreatic alpha-cell GHR deletion recaptures GH-interrupted physiology, indicating a key role for alpha-cell GH signaling in aging.

**Methods**
Cre/loxP mediated recombination was used to produce alpha-cell specific and beta-cell specific GHR knockout (aKO and bKO, respectively) mice. Body weight, body composition, glucose/insulin tolerance testing, and indirect calorimetry were carried out to determine metabolic consequences of these cell-specific deletions *in vivo*.

**Results**
aKO mice weighed less than control littermates, while bKO weights were unaffected. Body composition was unchanged in aKO or bKO mice after accounting for body weight. Glucose tolerance and insulin sensitivity were improved in aKO mice while bKO glucose tolerance was impaired and insulin sensitivity was unchanged. Metabolic rate was elevated in aKO males, reduced in aKO females, and unchanged in bKO mice. Respiratory quotient (RQ) was reduced in aKO males, indicating preferential lipid oxidation, while no differences were observed in female aKO or bKO mouse RQs.

**Conclusions**
Our data indicates that alpha cell GH interruption plays a previously unappreciated role in reproducing the GH-interrupted phenotype, defined by reduced body weight, improved insulin sensitivity, and preferential lipid metabolism to meet organismal energy demands, while beta-cell GH interruption is dispensable for this phenotype.

**Future Directions**
Future work will evaluate the consequences of alpha-cell or beta-cell GHR knockout on overall lifespan and will evaluate transcriptional changes within the endocrine pancreas mediating our observations.

## 24. Home-Based, Remotely-Delivered Exercise Training to Improve Physical Function of Middle-aged and Older Sepsis Survivors – the HEAL Sepsis Trial

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**Background**
Sepsis survivors frequently experience post-discharge physical function decline and encounter logistical barriers to participation in traditional outpatient rehabilitation. This pilot study examined the feasibility, safety, and preliminary efficacy of a remotely delivered, home-based exercise program on physical function in middle-age and older sepsis survivors.

**Methods**
In this single-blinded, randomized controlled trial (RCT), we included sepsis survivors aged ≥55 years old and randomized them to 12 weeks of avatar-guided, progressive exercise training group (EX) or to a standard care control group (CO). Primary outcomes were feasibility (retention, adherence) and safety (adverse events), whereas secondary outcomes were changes in the 30-second Sit-to-Stand (30SSTS), 4-Stage Balance Test (4SBT), Timed Up-and-Go tests, and Eastern Cooperative Oncology Group/Zubrod's (ECOG/Zubrod) performance status score. Secondary outcomes were summarized as mean change, standard deviation, and effect sizes.

**Results**
Twenty-one participants were randomized to either EX (n=10, mean age=69.6±8.5 years, 40% females) or CO (n=11, mean age=72.3±7.9 years, 45% females). Mean retention in the study was 95% and adherence to exercise training was 76%. Thirty-four adverse events (AEs) occurred (EX=12; CO=22 events), including four serious AEs that were unrelated to the study. The EX group demonstrated positive direction of change in lower-extremity strength (30SSTS: 1.14±2.91 repetitions, Cohen's d=0.393) and balance (4SBT: 5.07±4.75 seconds, d=1.07). In contrast, the CO group showed minimal change in balance on the 4SBT (0.01±4.38 seconds, d=0.003) and a negative direction of change in lower-extremity strength on the 30SSTS (−0.88±0.99 repetitions, d=−0.883). Timed Up-and-Go performance showed modest reductions in completion time in both groups (EX: −1.42±6.58 seconds, d=−0.216; CO: −1.27±2.73 seconds, d=−0.466). ECOG/Zubrod scores also showed a positive direction of change in the EX group.

**Conclusions**
This pilot RCT demonstrated that a 12-week, remotely delivered exercise program was safe and feasible for middle-aged and older sepsis survivors. Preliminary signals of positive change in lower-extremity strength, balance, and functional status were observed, supporting the need for evaluation in a fully powered Phase IIb RCT targeting individuals at risk for post-discharge physical function decline.

**25. Microbiome Integrity Protects Against Glial-Mediated Tau and Amyloid Pathology Through Circadian and Autophagy Homeostasis**

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**Abstract**

Alzheimer's disease (AD) pathology extends beyond tau and amyloid aggregation, involving systemic disruptions in sleep–circadian rhythms, gut–brain communication, and metabolic homeostasis that intensify neuroinflammation. Because glial cells are key regulators of protein clearance and inflammatory signaling, we investigated how glial dysfunction interacts with the gut microbiome to influence AD progression using *Drosophila melanogaster* expressing humanized wild-type and mutant tau or amyloid specifically in glia. Both models exhibited significant shifts in microbiome composition, notably in *Lactobacillus* and *Acetobacter*, suggesting a compensatory microbial response to AD-associated stress. Strikingly, microbiome depletion exacerbated disease phenotypes, including disrupted circadian rhythms, impaired memory, and reduced locomotion. These behavioral deficits were accompanied by heightened neuroinflammation (*Upd, Dome, Hop, Stat92e*), increased apoptotic signaling (*Hid, Reaper*), elevated lipid accumulation, tau, phospho-tau, Aβ42, and ubiquitinated proteins, and reduced levels of synapsin and the autophagy marker Ref2p. Together, our innovative findings reveal that removing the gut microbiome amplifies glia-driven inflammation, disrupts circadian and metabolic homeostasis, impairs autophagy, and accelerates cognitive and motor decline. This work highlights a previously underappreciated protective role of the gut microbiome in restraining glial dysfunction and mitigating AD-like pathology, positioning microbial homeostasis as a critical modulator of neurodegenerative disease progression.

**Keywords:** Alzheimer's disease, Gut microbiome, Circadian homeostasis, Autophagy, Memory impairment, Gut-brain axis, Neuroinflammation.

## 26. Comparative epigenetic aging between rhesus and Japanese macaques

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**Abstract**
Characterizing patterns of biological aging across species is important for comparing and contrasting environmental or evolutionary processes that regulate lifespan and age-related health. Non-human primates, particularly macaques, are valuable models for aging research because of their close evolutionary relationship to humans, well-characterized variable life histories, and robust research infrastructure. In this study, we examine both shared and species-specific patterns of epigenetic aging in Japanese macaques (*Macaca fuscata*) and rhesus macaques (*M. mulatta*) using genome-wide DNA methylation data. We analyzed DNA methylation profiles spanning the full adult lifespan in both species to estimate epigenetic age and evaluate differences in the rate of biological aging between species. We trained epigenetic clocks using elastic net penalized regression models and assessed model performance and generalizability using leave-one-out (LOOCV) and leave-one-species-out cross-validation (LOSOCV). Results showed a strong relationship between chronological age and DNA methylation age estimates in both species (LOOCV: Pearson's r = 0.918; $R^2$ = 0.84), with mean absolute error of 1.8 years across the age range. We are currently identifying genes and biological pathways that show both age and species-divergenic patterns of epigenetic aging.

Additionally, to understand evolutionary differences in epigenetic aging, we are in the process of extending this framework to include a wider variety of macaque species (including pig-tailed, long-tailed, and Tonkean macaques). Taken together, these studies are enhancing our knowledge of how evolution and environment shape biological aging in primates, yielding novel insights into the molecular underpinnings of health and age-related disease in our lineage.

## 27. tRNAome Remodeling in Aging

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### Introduction
Aging is associated with progressive loss of proteostasis. Transfer RNAs (tRNAs) play a central role in translation and have recently emerged as dynamic regulators of gene expression. However, whether systematic changes in tRNA abundance, integrity, or modification occur during aging remains largely unexplored.

### Methods
We applied Nanopore-based direct tRNA sequencing (Nano-tRNA-seq) to profile native tRNAs from young and replicatively aged Saccharomyces cerevisiae. We generated in vitro–transcribed (IVT) tRNAs lacking endogenous modifications as a baseline for sequencing error. tRNA abundance, 3' CCA-end integrity, and base-calling error signatures were quantified to assess age-dependent changes in tRNA expression and modification patterns.

### Results
Replicative aging was associated with modest but significant changes in the abundance of a subset of tRNAs. Strikingly, we observed a global reduction in coverage at the terminal adenosine of the 3' CCA tail, indicating widespread age-associated cleavage of mature tRNAs. In parallel, analysis of sequencing error signatures revealed selective remodeling of tRNA modifications during aging. Notably, $tRNA^{Lys\text{-}CTT}$ exhibited pronounced age-dependent changes at T-loop positions corresponding to $m^5U_{54}$, $\Psi_{55}$, and $m^1A_{58}$. Genes enriched for the corresponding AAG codon were associated with ribosome structure and function, suggesting modification changes may preferentially affect translation of ribosome-associated proteins.

### Conclusions
Our findings demonstrate that the tRNAome undergoes coordinated remodeling during replicative aging. Global CCA-end cleavage and selective modification changes in $tRNA^{Lys\text{-}CTT}$ point to tRNA-mediated regulation as an important layer of translational control during aging.

### Future Directions
Future studies will investigate the enzymatic mechanisms underlying age-associated CCA-end cleavage and determine how specific tRNA modification changes influence translation efficiency and ribosome biogenesis across aging models.

### Acknowledgements
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## 28. Treatment with Tetracycline and Rifampicin antibiotics improves survival of Flock House virus infection in young and old *Drosophila melanogaster*

**Justin McGee**[1], Dean Bunnell[1], Maddie Buhl[1], Grace Milas[1], Sanjay Saini[1], Atulya Iyengar[1], and Stanislava Chtarbanova[1]

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### Introduction

Host metabolism and immunity are intricately linked in both health and disease. Aging can significantly influence this interplay, often leading to increased susceptibility to infections. Identifying interventions that mitigate age-associated decline in immune function and improve survival outcomes from viral infections is of primary importance. We have previously shown that following infection with an RNA virus (Flock House Virus, FHV), aging *Drosophila* display stronger regulation of genes whose products function in metabolic processes and mitochondrial respiration. Oxygen consumption rate measurements as a proxy for metabolic rate and mitochondrial function, identified significant age-dependent changes linking decreased metabolic rates to improved survival. We hypothesize modulation of host metabolism using antibiotics that disrupt mitochondrial translation (tetracycline, TTC) and transcription (rifampicin, RIF) would affect survival outcomes of FHV infection.

### Methods

Young (5 days-old) and aged (30 days-old) control- or FHV- injected *Oregon-R* flies were placed on vehicle or antibiotic-supplemented food following injection. A luminescence-based assay was used to measure ATP. Survival measured by recording the number of surviving flies every 24h. RT-qPCR was used to measure virus load. Axenic animals were obtained by bleaching *Drosophila* embryos.

### Results

We show antibiotic treatment significantly decreases ATP levels. Compared to vehicle-treated flies, TTC and RIF significantly improve survival of FHV in young and aged flies. TTC-treated axenic, FHV-infected flies also showed significantly improved survival. No significant differences in viral load were observed between age and treatment groups.

### Conclusions

Our findings suggest antibiotic treatment targeting mitochondrial function can mitigate FHV susceptibility in both young and aged flies, further investigation is needed to fully understand the underlying mechanisms.

### Future Directions

Determine whether mitochondrial dysfunction in electron transport chain mutants (e.g. *ND23*$^{60114}$*)* results in UPR$^{mt}$ activation and protects against FHV infection.

### Acknowledgements

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**29. Association Network Segregation and Cortical GABA in the Oldest-Old Evidence from the McKnight Brain Aging Registry**

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**Introduction**
Age-related alterations in large-scale functional brain organization are well documented, yet the neurochemical mechanisms supporting network stability in advanced aging remain incompletely understood. Gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the human cortex, is hypothesized to support functional network segregation, but evidence in the oldest-old remains limited.

**Methods**
Participants were 86 community-dwelling adults aged 85 years and older enrolled in the McKnight Brain Aging Registry. Tissue-corrected cortical GABA concentration was quantified using proton magnetic resonance spectroscopy processed with Gannet version 3.3.1. Resting-state functional magnetic resonance imaging was used to estimate within-network and between-network functional connectivity across five canonical large-scale networks. Network-specific segregation was computed as the normalized difference between within- and between-network connectivity, and a global segregation index was derived as the average across networks.

**Results**
Global segregation was highly correlated with association-network segregation, indicating that association networks accounted for the majority of variance in the global metric. Cortical GABA concentration was not associated with global segregation. In contrast, higher tissue-corrected GABA concentration was significantly associated with greater association-network segregation. This relationship was not moderated by age.

**Conclusions**
These findings indicate a network-specific association between cortical inhibitory tone and functional organization, with GABA relating preferentially to the segregation of association networks in advanced aging.

**Future Directions**
Ongoing work will examine the cognitive relevance of association-network segregation and evaluate whether inhibitory tone contributes to individual differences in cognitive performance in the oldest-old.

**Acknowledgements:** This work was conducted using data from the McKnight Brain Aging Registry. We thank the participants and study staff for their contributions.

**30. Improving Patient Centered Care for Underserved Older African American Patients with Cardiovascular Comorbidities: A pilot study of the Patient Priorities Care Approach**

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**Introduction**
Cardiovascular comorbidities (CVCs), defined as multiple co-occurring chronic conditions in adults with cardiovascular disease, are common and exacerbate symptoms and treatment complexity, particularly among older African Americans (AAs) in the southern United States, who face the highest burden of CVCs. This leads to higher cardiovascular mortality and earlier death compared to other racial groups. Effective communication with clinicians is crucial for managing symptoms and treatment planning; however, older AAs frequently struggle to express their values and preferences, resulting in care that is misaligned with their goals. This misalignment contributes to poorer quality of life, greater distress, delayed treatment, and persistent disparities in health outcomes. This pilot study evaluates the Patient Priorities Care (PPC) Approach to address these communication challenges among older AAs with CVCs at Cooper Green Mercy Health Services Authority (CGMHSA).

**Methods**
A community advisory group consisting of three primary care clinicians, three older AA patients with CVCs, and three AA caregivers was developed. We are conducting a single-arm pilot study with 20 older African American patients with CVCs. Data collection includes acceptability interviews, feasibility indicators, and validated measures of perception of care, treatment burden, and patient–clinician communication.

**Results**
The study is ongoing. Primary outcomes focus on feasibility, acceptability, cultural appropriateness, and completion rates of study procedures measures.

**Conclusion**
This pilot addresses a significant gap in culturally responsive communication interventions for older African Americans with complex CVC and informs refinement of the PPC Approach to better align care with patients' values and priorities in under-resourced settings.

**Future directions**
Findings inform a future randomized controlled trial evaluating the efficacy of a culturally adapted PPC approach among under-resourced older AAs with CVCs.

**Acknowledgments**
This work is supported by a UAB Forge AHEAD Center pilot grant and conducted in partnership with CGMHSA. We thank the participating patients, caregivers, and clinicians.

## 31. Serine and Glycine Sensing and Signaling in Skeletal Muscle Progenitor Cells

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### Introduction

Skeletal muscle development and regeneration in response to injury uses myogenesis to establish homeostasis. Myogenesis is driven by a specialized population of muscle specific stem cells (MuSCs) that self-renew or commit to muscle progenitor cells (MPCs). In various pathogenic states, including in older individuals, the number and function of MuSCs decline, impairing the myogenic capacity of MuSCs. To understand the age-related impairment in older adults, our lab demonstrated that serine and glycine (ser/gly), two nutritionally non-essential amino acids, are reduced endogenously in older adults (human and mice). Further, we demonstrated that ser/gly are essential for MuSC/MPC proliferation. How ser/gly impact the proliferative capacity of MuSCs has yet to be defined.

### Methods

To fill this gap in knowledge, MPCs, cultured in ser/gly sufficient or deficient media will be used. We will measure the spatial distribution of ser/gly biosynthetic pathway enzymes using immunocytochemistry. Ser/gly availability, through one-carbon metabolism, can modify proteins (e.g., histones) with methylation; we will measure chromatin accessibility using ATAC-seq coupled with qRT-PCR for associated differential expression of myogenic regulatory factors (MRFs). Changes in ser/gly metabolism are thought to be linked to the glycolytic enzyme PKM2, which has been shown to localize in the nucleus under nutrient stress conditions. Thus, we will measure, using immunocytochemistry and subcellular fractionation coupled with immunoblot, the subcellular localization of PKM2 under ser/gly conditions.

### Results

We expect to identify changes in the spatial distribution of the ser/gly biosynthesis pathway with ser/gly depletion. Further, we expect these changes will be associated with changes in chromatin accessibility and expression of MRFs. Additionally, we suspect that nuclear changes will be related to nuclear localization of PKM2.

### Conclusions

Completion of this research would identify a novel molecular pathway that is likely impaired in older adults and individuals with reduced ser/gly availability.

### Acknowledgements

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## 32. Cognitive Testing of a Deprescribing Evaluation and Quality Improvement Instrument with Older Veterans

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**Introduction**
The Deprescribing Evaluation and Quality Improvement (DEQI) instrument is being developed as a Patient Reported Outcomes Measure and Experience Measure for deprescribing in older adult (OA) veteran populations. Previous phases of this study involved veterans and deprescribing experts in developing the constructs, dimensions, and items for the DEQI. This phase aims to refine the DEQI instrument through cognitive interviews with OA Veterans.

**Methods**
A draft DEQI Instrument was tested in two rounds of cognitive interviews, four weeks apart, with a total of 16 Veteran adults ≥65 years with polypharmacy. Interviews lasted approximately 90 minutes. The think-aloud and verbal probing cognitive interviewing techniques were employed to elicit participants' cognitive processes as they responded to the questions. The interviews were analyzed using interaction coding and the cognitive coding scheme to evaluate the clarity and appropriateness of respondents' DEQI responses.

**Results**
The classification coding scheme identified 102 problem-related items in the first round, approximately 70% of which pertained to comprehension and communication, and approximately 14% to response selection. After the items were modified and readministered, there was a remarkable decrease (from 102 to 21) in the number of identified problems. OA Veteran participants provided a high proportion of immediately codable answers in both rounds. However, in the second round, the proportion of immediately codable answers increased significantly after the items were modified and readministered, while the proportions of uncodable answers and items requiring clarification decreased significantly.

**Conclusions**
Older adults' participation supported the refinement of the DEQI instrument to enhance its clarity.

**Future Direction**
Findings will be used to refine the DEQI instrument for psychometric assessment and inform deprescribing initiatives aimed at improving patient-provider communication and advancing evidence-based policies that promote safe and effective medication management among OA Veterans.

**33. The Effect of Exercise on Triple-Transgenic Model of Alzheimer's Disease Mouse Brain**

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Alzheimer's disease (AD) is the main cause of dementia and is quickly becoming one of the most expensive and devastating diseases. Although there are pharmacological treatments include anti-amyloid β, anti-tau, and anti-inflammatory strategies at clinical trials stage, so far, no effective treatment to attenuate disease progression. Low levels of physical activity are a risk factor associated with Alzheimer's disease. Research has shown that people who take regular exercise may be up to 20% less likely to develop dementia than those who don't take regular exercise. We used the triple-transgenic model (3xTg-AD), which develops amyloid plaques and neurofibrillary tangles in a manner that mimics the progression observed in human AD patients, and compared exercised mice versus sedentary controls. We found Inflammatory and stress markers Gfap and Iba1 weren't changed significantly but had a trend of decreasing in exercised cortices. There were no significant changes in autophagy and lysosomal markers Lamp1, Lc3, msSQSTM1 (p62), Cathepsin D. There were no significant changes in mitochondria complex marker Cox1 (Complex V), Ndufa1 (Complex I) and mitophagy marker Rab9a. However, AD biomarkers ThioS, which stains amyloid plaques and tau aggregates, decreased in the cortex of exercised group compared control group. Unexpectedly, both somatostatin (SST)-positive inhibitory neurons and parvalbumin (PV)- positive inhibitory neurons displayed a trend of increasing in the hippocampus and amygdala of exercised mice. More interestingly, ThioS stained inside the SST-positive inhibitory neurons decreased after exercise. From those results, we confirmed that exercise modulated protein aggregate turnover in this animal model. Importantly, our results suggested that such turnover might be through decreasing the aggregate load inside specific types of inhibitory neurons.

## 34. Bacterial Infection Induces Hallmarks of Cellular Senescence in Skeletal Muscle of Old Mice

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**Introduction**
Aging is associated with heightened vulnerability to skeletal muscle dysfunction and impaired recovery following stress. Bacterial infection is a life-threatening disease that can cause debilitating reductions in skeletal muscle mass and function. Cellular senescence has emerged as a source of skeletal muscle dysfunction, yet its role in infection-induced muscle pathology remains unclear. This study aimed to evaluate cellular senescence as a mediator of muscle dysfunction following bacterial infection.

**Methods**
Young and old wild-type mice were injected with lipopolysaccharide (LPS) or vehicle, and skeletal muscle samples were collected at 6 hours, 24 hours, and 7 days post-injection. Skeletal muscle samples were flash-frozen and stored at −80°C for downstream analyses via RNA-seq, RT-qPCR, long-range PCR, and western blotting. Additional skeletal muscle samples were frozen in liquid nitrogen-cooled isopentane and stored at −80 °C for histochemical analysis.

**Results**
LPS-treated mice exhibited a robust inflammatory response during the initial phase of infection, as evidenced by the upregulation of key inflammatory mediators. LPS increased the expression of DNA damage markers, powerful inducers of cellular senescence, and anti-apoptotic factors at 6 and 24 hours. Mitochondrial biogenesis markers were reduced in both age groups post-infection. RNA-seq revealed higher enrichment of senescence-related and atrophy-associated pathways, and downregulation of oxidative phosphorylation at 6 and 24 hours in old LPS-treated mice. Mitochondrial DNA damage increased in LPS-treated mice, with old mice showing persistent damage at 7 days post-infection. LPS-treated old mice showed reduced muscle cross-sectional area and increased centronucleation, and fibrosis at 7 days post-infection.

**Conclusions**
LPS-induced bacterial infection activates a senescence program in skeletal muscle, characterized by inflammatory signaling, mitochondrial dysfunction, and enrichment of atrophy pathways. Aging amplifies hallmarks of cellular senescence, contributing to muscle pathology during recovery.

**Future directions**
Future studies will evaluate whether senescence-targeted therapies can mitigate senescent signatures and improve muscle recovery following bacterial infection.

**35. Yeast phenomic analysis of mitochondrial DNA escape**

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**Abstract**

Mitochondrial DNA (mtDNA) escape from the mitochondrial compartment is a significant cellular process that impacts innate immunity, inflammation, nuclear genome mutagenesis, cancer, and cellular senescence. Release of mtDNA, particularly in senescent cells, can cause chronic inflammation with increasing age of the cells, a process known as 'inflammaging'. YME1 (Yeast Mitochondrial Escape) encodes an evolutionarily conserved protease of the mitochondrial outer membrane, named after the discovery in *S. cerevisiae* for its involvement in regulating mtDNA escape. Other factors involved in regulating mtDNA release are also highly conserved, and to help characterize this genetic network we are leveraging a unique reporter and the power of yeast genetics to discover other genes involved in regulating mtDNA escape. This mtDNA-reporter has the nuclear TRP1 gene integrated into the mtDNA and contains elements for extra-mitochondrial replication and segregation, such that the escape of this construct out of the mitochondrial compartment and into the nucleus can be detected in a trp1 auxotrophic background. We used synthetic genetic array (SGA) technique to introduce this reporter into the yeast gene deletion strain (YGDS) library to systematically assess mtDNA escape. Our phenomic screen identified over one hundred genes showing growth on tryptophan-dropout media, suggesting mtDNA release, mapping them to human homologs and further validating the genes for reproducibility and categorizing the phenotype based on high/low frequency of escape and high/low frequency of integration. Ongoing efforts include validation of YME genes by tetrad analysis, assess meiotic segregation of mtDNA escape with the candidate gene. Further, we aim to perform quiescence profiling on tetrads of the YME genes validated from our screen to assess their role in aging as we endeavor to better understand these genes in the context of human aging, disease and cellular pathways regulating inflammation and senescence.

## 36. Sex Differences in Estrogen Receptor Alpha Expression in Glucagon-like Peptide-1 (Glp-1) Releasing Neurons

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**Introduction**

Menopause is significantly linked to increased risk of obesity and diabetes due to hormonal shifts and metabolic syndrome. Glucagon-like peptide-1 (Glp-1) is centrally produced by preproglucagon (Gcg) neurons in the nucleus of the solitary tract (NTS) and plays a key role in suppressing appetitive behaviors. Preclinical studies suggest estradiol, the primary ovarian estrogen, also suppresses feeding and enhances Glp-1's anorexigenic effects. Although previous studies have identified estrogen receptor alpha (ERα) within male NTS-Gcg neurons, the extent of this relationship in females and contribution of local estradiol synthesis from testosterone through the aromatase enzyme has remained unclear.

**Methods**

Immunofluorescence staining was performed in adult male and female Gcg reporter mice to examine the colocalization of estrogen receptor alpha (ERα) and Gcg neurons and expression of aromatase within the nucleus of the solitary tract (NTS).

**Results**

Overall densities of Gcg neurons and ERα-expressing cells within the NTS did not differ significantly between sexes. However, females exhibited a higher proportion of Gcg neurons expressing ERα, as well as a higher proportion of ERα-positive cells coexpressing Gcg. In contrast, males displayed significantly higher aromatase expression within the NTS compared to females.

**Conclusions**

These findings reveal sex-specific mechanisms underlying estradiol and Glp-1 interactions in the NTS. In females, estradiol's anorexigenic effects may be more directly mediated through ERα signaling within Gcg neurons. In males, increased aromatase expression suggests greater reliance on local estradiol synthesis to modulate Glp-1 signaling.

**Future Directions**

Ongoing studies are investigating how ERα colocalization and aromatase expression change after cessation of ovarian hormones. Additional studies will explore peripheral actions of estradiol, Glp-1, and its regulatory enzymes across the rodent estrous cycle and aging. Understanding how ERα signaling or compensatory local estradiol synthesis contributes to a menopausal mouse model may identify novel targets for age-related obesity and identify potential links with loss of ERα.

**37. Defining Ubiquitous and Sex-Biased Aging Biomarkers Using Transcriptome Data Across Evolutionarily Diverse Model and Non-Model Organisms**

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**Introduction**
Sex-biased differences in lifespan are observed across many species. In mammals, females tend to outlive their male counterparts. This trend also appears in fish but reverses in birds, where males tend to outlive females. Regardless of which sex lives longer, these lifespan differences between sexes are indicators of underlying sex specificity in aging, raising the question of whether conspecific lifespan differences between sexes may share common gene signatures across species.

**Methods**
We analyzed sex-specific transcriptome data from skeletal muscle comparing young and old individuals from seven model and non-model species spanning diverse evolutionary lineages: *Drosophila melanogaster*, *Plodia interpunctella*, *Xiphophorus maculatus*, *Nothobranchius furzeri*, *Rattus norvegicus*, *Mus musculus*, and *Homo sapiens*.

**Results**
A key finding across all species was the age-related upregulation of heat shock protein (HSP) genes in both sexes. These chaperone proteins are important in maintaining proper protein homeostasis. Thus, their expression increase with age, indicates loss of proteostasis occurring in all animals assayed, which is one of the hallmarks of aging for which very little data outside model organisms exist. Sex-biased gene signatures were also detected. These signatures were more prevalent in one sex over the other, such as the dysregulation of genes that encode for sarcoplasmic/endoplasmic reticulum Ca(2+)-ATPase (SERCA) proteins. Dysregulation of SERCA is an indicator of muscle atrophy and weakening. Interestingly, all females displayed significant age-related down-regulation of many SERCA genes. In contrast, this was not observed in male *H. sapiens* or male *X. maculatus*.

**Conclusion**
These results suggest that skeletal muscle breakdown with age is a female-biased trait, which males do not always experience. These results also confirm that sex-biased gene signatures are identifiable in transcriptome data and are common across multiple clades, offering insights into both the shared and divergent molecular mechanisms of aging between sexes and lineages.

## 38. From mouth to brain: How *Porphyromonas gingivalis* infection turns microglia into lipid-loaded driver of Alzheimer's disease progression

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### Introduction
The key pathogen in chronic periodontitis, known as *Porphyromonas gingivalis* (*Pg*), was detected in the brains of Alzheimer's disease (AD) patients. In neurodegenerative disorders such as AD, the microglia are often characterized by increased lipid droplet (LD) accumulation, heightened activation, and impaired functionality.

### Methods
Murine BV2 microglial cells were treated with *Porphyromonas gingivalis* (*Pg*; ATCC 33277), and LD accumulation was assessed by confocal microscopy and flow cytometry. Triacsin C was used to inhibit *Pg*-induced LD and evaluate its role in ROS production and microglial function. In vivo, *APP* knock-in mice were treated with Triacsin C and infected with *Pg* via retro-orbital injection to assess the impact of microglial LD accumulation on the progression of AD.

### Results
In this study, we investigated whether *Pg*, a major periodontal pathogen, induces LD accumulation in microglia and alters their functional status. We observed significant LD accumulation in *Pg*-infected BV2 microglial cells and in the microglia from the *Pg*-infected *App KI* mouse brains, suggesting that the *Pg* infection promotes the LD accumulation both in in-vitro and in-vivo. Our findings demonstrate that *Pg*-induced LD accumulation correlates with increased reactive oxygen species (ROS) production, leading to a compromise in microglial functionality, including impairment of phagocytosis ability. Furthermore, our results indicated that the *Pg*-induced LD contributed to impairment of microglia functionality by downregulating TMEM119 (a homeostatic microglial marker) and upregulating MHC-II (an activation marker), indicating a loss of resting microglia identity and a transition toward an activated and dysfunctional phenotype. Importantly, treatment with **triacsin C**, a triglyceride synthesis inhibitor, effectively reversed *Pg*-induced LD accumulation, ROS production, and phagocytosis defects, highlighting the mechanistic role of lipid metabolism in microglial dysfunction.

### Conclusions
Together, our results underscore the role of *Pg* infection in driving microglial lipid dysregulation and functionality impairment, suggesting that the lipid dysregulation contributes to the link between periodontal diseases and AD.

### Future Directions
Building on our findings that *Pg* drives LD accumulation and microglial dysfunction, future studies will focus on defining the precise molecular mechanisms linking *Pg* infection to altered lipid metabolism. Specifically, we aim to investigate the signaling pathways regulating triglyceride synthesis, fatty acid oxidation, and ROS generation in *Pg*-infected microglia.

**Keywords:** Porphyromonas gingivalis, Periodontitis, Alzheimer's disease, Lipid droplet, microglia

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## 39. A Fourfold Male-Specific Lifespan Extension via Canonical Insulin/IGF-1 Signaling

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**Abstract**

The insulin/IGF-1 signaling (IIS) pathway is an evolutionary conserved regulator of longevity, and its modulation is a hallmark of aging research. The 1993 ground-breaking report of a *daf-2* mutation (e1370) that reduced IIS and doubled *C. elegans* lifespan in hermaphrodite worms paved the way for molecular approaches to modulating aging. However, the impact of that mutation on the male sex has remained largely unstudied. Here we report that the same mutation extends male lifespan by a staggering fourfold, to over 110 days. This extreme longevity is coupled with a dramatic extension of healthspan as well, characterized by the robust maintenance of youthful morphology and preserved metabolic homeostasis deep into old age. Daf-2 male muscle motility displayed higher movement in day ten adults in comparison to hermaphrodites when functional assays were performed. The male daf-2 also displayed higher lipid content compared to wildtype males when using Oil Red O staining. These findings establish sex not as a secondary variable but as a primary determinant of longevity potential, capable of amplifying the output of a core aging pathway to an astonishing degree. This work provides a powerful new tool for dissecting the interplay between sex and aging and suggests that sex-specific interventions may be critical for developing future anti-aging therapeutics. The next step would be to sequence for genetic expression to determine how this extreme longevity is occurring and perform lipidomics/metabolomics to determine which molecules affect the processes for aging in the mutant model. We would like to thank the Austad lab, and Biology department for letting us use their equipment, and we would like to thank Haoseng Sun for lending us our wildtype (N2) model.

## 40. The Effect of Pulse Pressure on Cognitive Decline Among Older Adults: Variations Based on Blood Pressure Status

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**Introduction**
Elevated pulse pressure (PP), calculated as the difference between systolic and diastolic blood pressure (BP), is a vascular risk factor for cognitive decline and Alzheimer's Disease. However, the predictive utility of PP in relation to BP status remains unclear. This study, therefore, examines the effect of PP on cognitive decline and whether this effect is influenced by BP status.

**Methods**
This 10-year longitudinal study from the ACTIVE (Advanced Cognitive Training for Independent and Vital Elderly) cohort included 2,787 older adults (65+). Based on baseline measurements, the sample was stratified into normal (n=979) and elevated (n=1808) BP groups. Elevated BP was defined with ACC/AHA guidelines (SBP>=130 and/or DBP>=80). Cognitive function was longitudinally assessed using neuropsychological tests, with standardized global cognitive composite and domain-specific composites calculated for memory, reasoning, and processing speed. Linear mixed-effects models assessed the relationship between PP, BP, and cognition.

**Results**
Higher PP was associated with faster global cognitive decline (b= −0.003, 95% CI [−0.004, −0.001]) after adjusting for covariates. This effect was consistent for the memory and reasoning domains. The effects remained significant after adjusting for BP status. Interaction and stratified analyses revealed a differential effect of PP based on BP status. Specifically, the negative effect of PP on global cognitive decline was observed only among participants with elevated BP (b = −0.005, 95% CI [−0.005, −0.002]), not in those with normal BP. This pattern was consistent across the three cognitive domains.

**Conclusion**
PP is associated with accelerated cognitive decline among older adults, but this relationship is moderated by BP status. PP monitoring could improve cognitive risk assessment in older adults with elevated BP. This underscores the importance of managing BP to mitigate the risk of cognitive decline associated with increased PP.

**Future Directions**
Future research investigating PP's effect on cognition must account for BP status.

## 41. Using ATP6V0A1 genetics and biology to understand dopaminergic neuron vulnerability in Parkinson's disease

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**Introduction**
Parkinson's disease (PD) is characterized by progressive degeneration of dopaminergic neurons and accumulation of α-synuclein pathology, yet the mechanisms underlying selective dopaminergic vulnerability in idiopathic PD remain unresolved. ATP6V0A1 is a neuron-enriched subunit of the lysosomal vacuolar ATPase (v-ATPase) that is critical for vesicular acidification and protein degradation. This study examines the role of ATP6V0A1 in maintaining dopaminergic neuron viability and function in vivo.

**Methods**
To assess the impact of ATP6V0A1 expression on dopaminergic neuron integrity, complementary loss- and gain-of-function approaches were used in adult mice. Cre-mediated deletion and adeno-associated virus (AAV)–mediated overexpression were employed to selectively manipulate ATP6V0A1 levels in dopaminergic neurons. One month following manipulation, motor behavior was evaluated using the pole test and wire suspension assay to assess bradykinesia, coordination, and neuromuscular endurance. Brain tissue was processed for immunostaining to quantify dopaminergic markers and terminal density, and striatal dopamine levels were measured using high-performance liquid chromatography (HPLC).

**Results**
Conditional deletion of ATP6V0A1 in dopaminergic neurons resulted in significant motor impairments, including prolonged pole test descent times and reduced wire suspension latency. Immunohistochemical analysis revealed reduced tyrosine hydroxylase labeling in the striatum, and HPLC confirmed decreased striatal dopamine content, indicating impaired dopaminergic signaling. In contrast, ATP6V0A1 overexpression was well tolerated, loss of dopaminergic markers was lessened, and changes in dopamine levels over the same timeframe were decreased.

**Conclusions**

These findings demonstrate that ATP6V0A1 is required for normal dopaminergic neuron function and viability, supporting a critical role for lysosomal acidification in maintaining dopaminergic integrity and resilience during aging.

**Future Directions**

Future studies will evaluate whether ATP6V0A1 overexpression confers neuroprotection in models of α-synuclein pathology and lysosomal stress, and will examine downstream effects on lysosomal function, autophagic flux, and long-term neuronal survival.

## 42. Inflammation as a Mediator of Organ Damage and Lifespan Reduction in Short-Lived Mouse Models

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### Introduction

Aging is orchestrated by complex interactions between metabolic and immune pathways. One defining feature is chronic, low-grade inflammation ("inflammaging"), which contributes to physiological decline and the progression of age-related diseases. Here, we examined how distinct biological stressors influence inflammaging and lifespan in two short-lived mouse models.

### Methods

We studied liver-specific glucagon receptor knockout (LKO) mice and PS19 tau transgenic mice. Lifespan analysis, glucose and insulin tolerance tests, indirect calorimetry, body composition analysis, Western blotting, and histological staining (H&E, Masson's Trichrome, and Oil Red O) were used to evaluate metabolic status, inflammatory signaling, and organ damage across age and sex.

### Results

LKO mice showed improved metabolic health, including reduced adiposity, enhanced glucose tolerance, and increased insulin sensitivity, yet male lifespan did not improve, and female LKO mice exhibited a 19% decrease in lifespan. In aged female LKO mice, we observed pronounced activation of pro-inflammatory pathways, including elevated cGAS-STING signaling in liver and kidney tissue, accompanied by significant glomerular damage, collagen deposition, and immune cell infiltration. PS19 mice, previously established as a short-lived model, also displayed marked physiological decline, including weight and fat loss, glucose intolerance, and organ-level inflammation. Histological analysis revealed severe glomerular disruption and fibrotic remodeling in kidneys from PS19 females. Both models demonstrated sex-specific vulnerability and shared features of sustained inflammatory activity and organ damage.

### Conclusions

Despite originating from distinct mechanisms—metabolic dysregulation in LKO and neurodegeneration in PS19—both models converged on a common phenotype of chronic inflammation and multi-organ pathology. These findings suggest that inflammaging may act as a unifying process contributing to reduced lifespan across diverse aging contexts.

### Future Directions

Targeting pathways like cGAS-STING may provide therapeutic opportunities to limit inflammation-induced tissue degeneration. Further studies will determine how immune modulation influences longevity and whether targeted interventions can restore tissue resilience in these models.

## 43. Role of succinylation in skeletal muscle regeneration in aging

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**Purpose**
With advancing age there is a decline in the number and function of skeletal muscle progenitor cells (MPCs), which are necessary for tissue regeneration (i.e., myogenesis) and maintenance. Myogenesis is a coordinated process involving the proliferation and differentiation of MPCs. Little is known regarding the mechanisms by which nutrient availability and metabolism impact MPCs during myogenesis. Post-translational modifications (PTM) link to metabolism, alter cellular pathways, and MPC state (proliferation, differentiation and fusion); however, succinylation, the addition of a succinyl group from succinyl-CoA to a protein lysine residue, has not been examined in myogenesis.

**Methods**
Using immortalized C2C12 MPCs we measured the protein succinylome using untargeted proteomics during differentiation. To identify metabolic pathway (branched chain amino acid [BCAA]) carbons entering the TCA cycle, we used stable isotope tracing. We measured methylmalonic acid (MMA) to test the activity of methylmalonyl-CoA mutase (MUT).

**Results**
We demonstrated a decrease in protein succinylation as MPCs advanced through myogenesis. Differentially succinylated proteins were enriched in BCAA catabolism pathways, with MPC differentiation. Additionally, protein levels of catabolic enzymes for BCAAs, isoleucine and valine, increased with MPC state change (proliferation to differentiation). Because catabolic products of isoleucine and valine enter the TCA cycle through the enzyme MUT, which synthesizes succinyl-CoA, we next measured BCAA carbons entering into the TCA cycle, but found no enrichment. Intriguingly, we identified higher levels of extracellular MMA at late differentiation (vs. proliferation), suggesting impaired MUT activity, which supports our BCAA isotope tracing.

**Conclusions**
In conclusion, we demonstrated that succinylation modifications decline with myogenic differentiation, in line with a decrease in MUT activity. We hypothesize that another enzyme (MTR) is sequestering a cofactor (B12) necessary for MUT activity, which could explain the elevated MMA.

**Future Directions**
Next, we will quantify MTR activity during differentiation.

**Acknowledgements:** UAB CDIB, Nathan Shock Center

## 44. Ketone supplementation ameliorates age-dependent deficits in the TgF344AD rat model of Alzheimer's disease

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### Introduction

Alzheimer's disease (AD) and related dementias impair the ability to reduce learned fear response (i.e., fear extinction), thus exacerbating symptoms of fear-related disorders in late life such as anxiety, hypervigilance, and emotional dysregulation. Accordingly, there is a greater prevalence of fear-based disorders in those with AD. The basolateral amygdala (BLA), a part of central medial lobe structures, serves as an early epicenter of AD pathology and is involved in fear-based circuitry. We have previously shown fear extinction impairments in TgF344-AD (AD) rats that are associated with BLA hyperexcitability and inflammation. One promising intervention is the ketogenic diet, which has been shown to reduce epileptiform activity and inflammation as well as ameliorate symptoms of fear disorders and AD. However, strict adherence remains a challenge. Ketone supplements offer an alternative, replicating the anxiolytic, antiepileptic, and anti-inflammatory effects of ketosis while being easily administered as a dietary supplement.

### Methods

To determine if the extinction memory impairments can be ameliorated by a ketone supplement, we orally gavage young and aged WT and TgAD rats ketone diester or saline (control). We began our daily supplementation twenty-eight days prior to fear memory acquisition and extinction to observe extensive systemic changes.

### Results

Importantly, our preliminary data show that ketone supplementation rescues fear extinction deficits and reduces markers of inflammation in this model.

### Conclusions

We hypothesize that ketone supplementation can rescue fear extinction deficits as well as mechanistically reduce hyperexcitability and/or neuroinflammation in AD rats.

### Future Directions

Current experiments include employing calcium imaging via fiber photometry during fear behavior in ketone and saline supplemented rats. Determining the efficacy of ketones to reduce hyperexcitatory activity as well as rescue behavioral deficits will pave the way for wholistic treatments for aging disorders and AD.

**45. Development of a novel analytical approach for quantification of Advanced Glycation End Products in *Drosophila* hemolymph and assessment of dietary polyphenol interventions**

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Advanced Glycation End Products (AGEs) are irreversible and non-enzymatic modifications of biomolecules. They accumulate with age, sedentary lifestyle, and consumption of hyperglycemic diets. They contribute to metabolic dysfunction, chronic inflammation and pathogenesis of aging-related non-communicable diseases (NCDs). Current AGE-detection methods are non-specific and inapplicable for small model organisms owing to sample volume limitations. This project aims to overcome this challenge, by developing a high-resolution analytical assay capable of detecting low-abundance AGEs in complex biological matrices using Orbitrap-bases top-down Mass Spectrometry approach. *Drosophila melanogaster* provides an ideal model system to investigate AGEs. It is tractable, has a short lifespan, shares~70% conserved genes with humans, including metabolic and inflammatory pathways central to AGE biology. Here, I use high-sugar diets (HSD) to induce glycation and accelerate aging-related metabolic stress in flies, using hemolymph which serves as an apt matrix to detect and define a candidate AGE biomarker in flies, akin to glycated hemoglobin in humans. I also aim to evaluate dietary polyphenols, a class of naturally occurring antioxidant and anti-inflammatory compounds, extensively present in geroprotective diets. To help find safer, non-pharmaceutical options to mitigate aging processes I plan to screen a library of polyphenols to determine their ability to reduce AGEs accumulation, under HSD-induced metabolic and systemic stress. Lastly, I aim to investigate varying efficacy and mechanism of anti-AGE action of these polyphenols by comparing flies maintained on diets supplemented with polyphenols, with flies sustained on dietary extract of natural polyphenol rich diets. This work integrates analytical chemistry, nutrition, and gerosciences to develop a robust AGE-detection and quantification pipeline and identify dietary polyphenols as AGE-intervention candidates. This knowledge could help guide the design of diet-based strategies to assist healthy aging across species. This project is supported by National Institutes of Health (NIH).

## 46. Epigenetic Aging Biomarkers and Cognitive Performance in Older Adults

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**Introduction**
Aging is the strongest non-modifiable risk factor for cognitive decline, yet biological aging varies across individuals. Epigenetic clocks derived from DNA methylation provide a promising biomarker of biological aging, but their relationships with cognitive function is not well understood. In this study, we examined associations between multiple established epigenetic clocks and cognitive function in older adults using The National Health and Nutrition Examination Survey (NHANES) data.

**Methods**
We analyzed data from the DNA methylation subsample of NHANES 1999–2000 and 2001–2002. Cognitive function was assessed using the Digit Symbol Substitution Test (DSST) among participants aged ≥60 years. Raw epigenetic clock measures including, GrimAgeMort, GrimAge2Mort, HannumAge, HorvathAge, PhenoAge, SkinBloodAge, Vidal-BraloAge, WeidnerAge, ZhangAge, and LinAge, were evaluated as primary exposures. Survey-weighted linear regression accounted for NHANES' complex sampling design and was sequentially adjusted for chronological age (Model 1); sociodemographic factors (Model 2); and cardiometabolic factors (Model 3). Physical activity was examined in secondary analyses (Model 4).

**Results**
Several epigenetic clocks were inversely associated with cognitive performance. In fully adjusted models, GrimAgeMort ($\beta = -0.39$), GrimAge2Mort ($\beta = -0.37$), HannumAge ($\beta = -0.37$), and PhenoAge ($\beta = -0.17$) were significantly associated with DSST scores. Rank-order analyses showed GrimAge-based clocks were strongest predictors in less adjusted models, whereas HannumAge remained consistently highly ranked after sociodemographic and cardiometabolic adjustment. After inclusion of physical activity, most associations were attenuated; however, HannumAge remained significantly associated with cognition ($\beta = -0.32$, $p = 0.04$).

**Conclusion**
Epigenetic clocks were differentially associated with cognitive performance in older adults, highlighting heterogeneity in biological aging processes relevant to brain health.

**Future Directions**
Longitudinal studies are needed to determine whether specific epigenetic clocks predict cognitive decline and to clarify the role of physical activity in modifying these associations.

## 47. Voices and Smiles: A Community Snapshot of Older Adults' Oral Health Perceptions and Clinical Assessment Findings

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### Introduction

Among older adults, oral diseases are prevalent and have been associated with multiple systemic diseases. Overall quality of life (QOL) can be adversely affected by potential sequelae of oral disease (i.e., pain, infection, and tooth loss) resulting in decreased chewing capacity which could negatively impact diet and nutrition. Poor nutrition is associated with increased risk for frailty. Prevention and early diagnosis of oral disease can mitigate morbidity and improve overall QOL; however, the literature is lacking regarding information specific to the older adults in Alabama. This study explorators oral health factors associated with perceived oral health QOL (OHQOL) among older adults in Alabama.

### Methods

Oral health assessments were made by UAB third- and fourth-year dental students and clinical faculty. Data were collected from male and female participants (N=192) screened at living facilities (n=26) and senior centers (n=166), with an average age of 75.3 (SD=9.5). Participants had visually obvious dental problems if untreated caries, severe dry mouth, severe gingival inflammation or need for periodontal care were identified. OHQOL is considered poor for those experiencing challenges with flavor, pain, chewing, daily life, or personal appearance. Number of natural teeth were grouped (0, 1-19, 20-32). Association between OQOL and number of teeth was evaluated with Cochran-Mantel-Haenszel.

Statistical analyses were performed in SAS v9.4, under $\alpha=0.05$.

### Results

Of non-edentulous participants, 46.9% had visually obvious dental problems. 63.5% had poor OQOL; there was no association between OQOL and visually obvious dental problems and OQOL (all $p>0.05$) or number of teeth ($p=0.4277$).

### Conclusion

The preliminary analysis points to the need to further explore the association of tooth loss and perceived QOL among older Alabamaians.

### Future Directions

Initial results can be used in planning for future programs and services. Future studies to assess associations between oral health disease and function, systemic disease, and overall QOL.

## 48. Exploring Cardiorespiratory Fitness as a Modifier of Social Risk and Arterial Stiffness in Postmenopausal Women

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**Introduction**
Arterial stiffness, measured by carotid-femoral pulse wave velocity (cf-PWV), is an independent predictor of cardiovascular disease. Social determinants of health, including neighborhood deprivation (ND), and Black race are associated with increased cf-PWV. However, the potential protective role of cardiorespiratory fitness ($VO_2$peak) in mitigating these effects is poorly understood in women. This study examined whether $VO_2$peak moderates the relationship between ND, race, and cf-PWV in postmenopausal women.

**Methods**
We analyzed data from 91 postmenopausal women (52% Non-Hispanic Black; age: 63±8 years; body mass index: 28±5 kg/m$^2$; blood pressure: 131±17/73±9 mmHg). Cf-PWV was measured using SphygmoCor® XCEL. ND was quantified using Area Deprivation Index scores. $VO_2$peak was determined via graded exercise tests. Multivariate linear regression models examined associations between cf-PWV, ND, race, and $VO_2$peak. Covariates included age, body mass index, and mean arterial pressure. Interaction terms tested whether $VO_2$peak buffered the effects of ND and Black race on cf-PWV.

**Results**
In adjusted models, age, BMI, mean arterial pressure, race, ND, and $VO_2$peak were not independently associated with cf-PWV (all $p > 0.1$). Interaction terms were directionally consistent with the hypothesis: higher $VO_2$peak attenuated associations between ND and cf-PWV ( $\beta = -0.152$, $p = 0.15$) and between Black race and cf-PWV ($\beta = -0.193$, $p = 0.20$). Although not significant, effect sizes suggest potential buffering effects of cardiorespiratory fitness.

**Conclusions**
While main effects of age, BMI, mean arterial pressure, race, and ND were nonsignificant, trends in interaction terms suggest higher cardiorespiratory fitness may mitigate the vascular consequences of social adversity in postmenopausal women. These findings highlight the potential of improving fitness as a strategy to reduce the cardiovascular impact of adverse social determinants of health.

**Future Directions**
Future studies should examine whether improving cardiorespiratory fitness can buffer the vascular effects of social adversity in a larger, longitudinal cohort of postmenopausal women.

## 49. Effects of ROCK Inhibitor Ripasudil on the Mitochondria in Human iPSC-differentiated Neuro-spheroids and the *App*$^{NLGF}$ Mouse Model of Alzheimer's Disease

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**Abstract**

Alzheimer's disease (AD) pathologies not only include brain amyloid β protein (Aβ) plaques and hyperphosphorylated tau (p-tau) tangles, but also metabolic dysregulation and mitochondrial dysfunction. Prior studies have demonstrated that Ras homolog (Rho)-associated kinases (ROCK) activities are elevated in AD, and that fasudil, a ROCK inhibitor, alleviates neuroinflammation and p-tau in the P301S tau transgenic mouse line PS19 that models neurodegenerative tauopathy and AD, while mitochondrial protein levels and activities were decreased after 2 weeks of daily i.p. dosing at 100 mg/kg/day. In the current study, we investigated effects of a fasudil derivative, ripasudil, which is a much more potent ROCK1/2 inhibitor (>10 times $IC_{50}$), on mitochondrial protein levels and activities in human iPSC-differentiated neuro-spheroids as well as the *App*$^{NLGF}$ mouse model of Alzheimer's disease. We observed that neuro-spheroids exposed to 10 μM ripasudil for 24, 48, and 72 hrs exhibited increase in several mitochondrial electron transport chain complex (ETC) protein levels without decreasing p-tau (Ser202/Thr205). Autophagy flux as assessed by LC3-II levels with and without chloroquine did not find any changes in response to ripasudil, while there was a slight downregulation of p62 and upregulation of Lamp1 with ripasudil compared to sole chloroquine treatment. Western blot analyses found increased mitochondrial ETC proteins after *App*$^{NLGF}$ mice i.p. injected with 30 mg/kg ripasudil. Western blot analyses also found a decrease of full-length APP (Amyloid precursor protein), and increased CTFα (C-terminal α fragment) with 1 dose ripasudil treatment. Our results provide insights into effects of ripasudil on mitochondrial remodeling in the context of development of AD therapeutics.

**50. Impact of Mirabegron on Urinary Incontinence Management in adult women with cognitive impairment at a long-term care facility**

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**Introduction**

Overactive bladder (OAB) is an understudied subtype of urinary incontinence, a geriatric syndrome disproportionately affecting up to 70% of women with cognitive impairment (CI) in long-term care (LTC). It is often erroneously considered an inevitable part of dementia progression due to limited behavioral interventions and older anticholinergic pharmacological options that carry cognitive side effects. To address this, we evaluated the efficacy of mirabegron, a bladder specific β-3 agonist that is evidence-based for OAB in community dwelling adults, in LTC residing women with CI.

**Methods**

In this pilot study, a convenience sample of 5 women with moderate to severe OAB and mild to moderate CI were identified using the OAB Severity Score (OABSS) and SLUMS and received mirabegron 25mg daily for 7 weeks. 24-hour wet diaper counts and weights and OABSS were measured pre and post treatment. Demographics and routine pelvic exam findings were obtained from chart reviews.

**Results**

Two black and three white women (mean age 60 years, BMI 37.8) with average SLUMS score 17.6 were studied. At baseline, average OABSS score was 9 with 3.2 wet diapers weighing 1593.8 g over 24h. After 7 weeks of mirabegron 25mg daily, average OABSS score was 10 with wet diaper use was 3/day with a total diaper weight reduction of 27%. Pelvic exams revealed at least a grade 1 or 2 urethrocystocele.

**Conclusion**

Low dose mirabegron was well tolerated but has not yet demonstrated efficacy in this population. It has shown potential for clinical use for patients with urinary incontinence and cognitive impairment in long-term care facilities but needs further study.

**Future Directions**

Increasing the dose to 50mg, studying vibegron 75mg and including men in the future would help establish data for larger studies to form guidelines for urinary incontinence in CI among LTC dwelling adults.

## 51. Ketone Supplementation Reduces BLA Pathology in the TgF344AD Rat Model

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### Introduction

Alzheimer's Disease (AD) is associated with accumulated amyloid beta(Aβ) plaques and hyperphosphorylated tau protein which are correlated with neuronal inflammation and cell death. The transgenic Fisher-344 AD(TgF344AD) rat model was developed to simulate this neurodegeneration. We have identified the basal lateral amygdala(BLA) as a site of early inflammation. When used as a supplement, ketone bodies decrease inflammation throughout the body and provide anxiolytic effects. Immunohistochemistry(IHC) can be used to stain and quantify several characteristics of AD including amyloid-beta(Aβ) plaques, inflammation(Iba1, GFAP), alive neuronal nuclei(NeuN), and phosphorylated tau protein(Ser202/Thr205, Thr231). My hypothesis is that a ketone supplemented diet will reduce pathological protein expression in the BLA across sexes, genotype, and age.

### Methods

TgF344AD and WT rats at young adult (5-6 months) and older adult (21-22 months) ages were orally gavaged ketone supplements and given a normal chow diet for 31 days. Glucose and ketone levels in the blood were tested weekly. Rats were perfused using paraformaldehyde. Brains stained with Aβ, Iba1, NeuN, and AT8 antibodies were quantified.

### Results

Preliminary results show a decrease in Aβ signal in the ketone supplemented TgF344AD rats compared to saline supplemented rats. Blood testing reveals that ketone bodies are consistently present in a rat's blood stream within an hour of ketone supplementation.

### Conclusions

Decrease in Aβ in ketone supplemented TgF344AD rats indicates that ketone supplementation decreases the accumulation of Aβ plaques. Consistent elevated ketone levels indicate systematic effects that correspond to these pathological changes.

### Future Directions

We are currently performing IHC on other neurometabolic markers (GLUT3, Thr231, MCT2) to further reveal the role of ketone bodies in the prevention of neurodegenerative diseases.

## 52. B12 supplementation improves mitochondrial biology in aged skeletal muscle

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### Introduction
The age-related decline of skeletal muscle (SkM) mass, function, and strength (i.e. sarcopenia) is associated with increased disability, decreased independence, and even mortality. The underlying cause for sarcopenia is multifactorial and includes a hallmark of aging, mitochondrial dysfunction. The etiology of mitochondrial dysfunction is also multifactorial and minimally understood. A potential underlying, yet overlooked, cause could be changes to nutrient availability, such as vitamin B12 (B12); B12 absorption declines with advancing age, independent of dietary intake, and is the co-factor for two mitochondria-related enzymes. The objective for this study was to assess the impact of B12 supplementation on mitochondrial biology in aged skeletal muscle.

### Methods
Aged (20-22 months) C57BL/6N female mice received a defined, AIN93G diet. They were randomized to weekly (12 weeks) intramuscular injections of either (i) vehicle control (saline) or (ii) B12 supplementation. At 12 weeks, SkM was collected and analyzed for: mass (quad mass normalized to femur length); mitochondria morphology (transmission electron microscopy on tibialis anterior SkM; and global proteomics, select enzymatic activity, and oxygen consumption rate (snap frozen SkM). Complementary redox assays (ROS and glutathione) were conducted on female primary myoblasts.

### Results
With B12 supplementation (vs. control), SkM mass was significantly greater and mitochondrial morphology visually improved. Proteomics analysis revealed enrichment of proteins related to mitochondrial respiration with supplementation. SkM citrate synthase activity was significantly higher in B12 supplemented mice, indicating increased mitochondrial content, and ROS was lower in B12 treated myoblasts. Oxygen consumption was similar between treatments.

### Conclusions
We demonstrated that B12 supplementation improves mitochondrial biology and SkM mass in older adults, which could improve SkM function.

### Future Directions
Assess impact of B12 supplementation on organismal function.

### Acknowledgements
Funded by the UAB Nathan Shock Center and NIH Pathobiology and Rehabilitation Medicine T32

## 53. Dgat2 modulates lipid dysmetabolism and neuroinflammation associated with Alzheimer's Disease

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**Presenter**
Archana Yadav, PhD
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**Introduction**
Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive cognitive decline, amyloid-β (Aβ) accumulation, lipid dysregulation, and chronic neuroinflammation. Age is the primary risk factor for AD, yet the molecular mechanisms linking aging, amyloid toxicity, lipid metabolism, and neuroinflammation remain poorly defined. Understanding how aging-associated metabolic changes contribute to AD pathogenesis is critical for developing therapeutic interventions.

**Methods**
Using *Drosophila* models expressing neuronal $App^{NLG}$ and Aβ42, we assessed age-dependent progression of locomotor decline, memory impairment, sleep disruption, lipid accumulation, synaptic degeneration, and neuroinflammatory activation across the lifespan. We performed panneuronal knockdown (KD) of diacylglycerol O-acyltransferase 2 (Dgat2), a critical enzyme in triglyceride synthesis. Findings were validated in the $App^{NLG-F}$ knock-in mouse model to confirm conserved aging mechanisms.

**Results**
Neuronal expression of $App^{NLG}$ and Aβ42 in *Drosophila* led to accelerated aging phenotypes including locomotor and memory deficits, abnormal sleep patterns, progressive lipid accumulation, synaptic degeneration, and neuroinflammatory activation. Similar age-related lipid and inflammatory alterations were observed in $App^{NLG-F}$ mice, supporting conserved mechanisms. Panneuronal *Dgat2* KD significantly reduced age-associated lipid accumulation and restored neuronal lipid homeostasis in aged flies. This intervention preserved synaptic integrity during aging, improved age-related locomotor decline, enhanced cognitive function, and reduced neuroinflammatory markers. Notably, *Dgat2* modulation normalized sleep fragmentation and circadian dysfunction, suggesting broader benefits on health span and metabolic balance.

**Conclusion**
Our findings reveal that Dgat2 plays a pivotal role at the intersection of aging, amyloid toxicity, lipid metabolism, and neuroinflammation, establishing *Drosophila* as a powerful model to dissect age-related lipid-neuroimmune interactions in neurodegeneration.

**Future direction**
These results provide evidence that targeting Dgat2-mediated lipid pathways could serve as a promising therapeutic approach for promoting healthy brain aging and mitigating age-related neurodegenerative processes in AD. Future studies will explore whether early-life Dgat2 modulation extends health span and prevents age-associated cognitive decline.

**Acknowledgement:** Stocks obtained from the Bloomington Drosophila Stock Center were used in this study.

## 54. Nuclear DLST orchestrates progressive catabolic memory in aged and injured muscle

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### Introduction
Skeletal muscle catabolic stress, that occurs with advancing age and injury, is associated with disrupted nutrient metabolism and impaired muscle regeneration driven in part by reduced regenerative capacity of muscle progenitor cell (MPC). Glutamine (Gln), though considered non-essential, becomes conditionally essential during catabolic stress (e.g., age-related skeletal muscle deterioration) and is critical for MPC proliferation. Gln disruption affects the activity of the TCA cycle including the α-ketoglutarate dehydrogenase complex (OGDHC). We have demonstrated that the OGDHC E2 subunit, dihydrolipoyl succinyltransferase (DLST), regulates histone succinylation in response to Gln deficiency. However, whether catabolic stress drives aberrant nuclear DLST localization in vivo remains unknown.

### Methods
In vivo models examined tibialis anterior muscle from young, aged, and aged-injured (day 3 post cardiotoxin injury) female C57BL/6N mice. To model nutrient (Gln) stress independently of age, young mice received glutaminase inhibitor (GLSi; CB839) injections. DLST subcellular localization was assessed by immunohistochemistry, confocal imaging. Mitochondrial distribution patterns were evaluated to assess subsarcolemmal versus intermyofibrillar populations.

### Results
Nuclear DLST accumulation increased progressively from young mice (minimal) to aged mice (moderate) to aged-injured mice (maximal). GLSi-treated mice exhibited nuclear DLST levels similar to aged-injured mice, demonstrating that acute nutrient stress recapitulates age-related DLST mislocalization. Notably, catabolic stress conditions were associated with increased subsarcolemmal mitochondrial accumulation and mitochondria positioning in proximity to nuclei.

### Conclusions
Catabolic stress from aging, injury, and Gln-depletion triggers aberrant nuclear DLST accumulation and subsarcolemmal mitochondrial repositioning, with progressive exacerbation in aged and aged-injured muscle. This mislocalization may establish a "catabolic memory" that links metabolic dysfunction to epigenetic reprogramming and impaired muscle regeneration.

### Future Directions
We will determine whether nuclear DLST accumulation persists following metabolic recovery, representing a sustained catabolic memory that impairs myogenic capacity even after Gln restoration. Using PKmito imaging, we will characterize mitochondrial dynamics and subsarcolemmal accumulation patterns in aged and nutrient-stressed muscle.

### Acknowledgment
We acknowledge the UABHSF and UAB-UCEM/ICAR for financial support.

**55. Amygdalar Dysfunction in Aging and Chronic Fear Contributes to PTSD and ADRD Neuropathological Changes**

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Post-Traumatic Stress Disorder (PTSD) is a psychiatric condition triggered by trauma, characterized by fear, hyperarousal, and emotional dysregulation. It has been shown to exacerbate age-related cognitive decline and double the risk of developing Alzheimer's disease and related dementias (ADRD). PTSD also shares overlapping pathological features with both normative aging and ADRD. Our study focuses on the amygdala, a region critical for emotional processing, and often dysregulated in both PTSD and age-related neurodegenerative conditions. In prior work using a rat model of normative aging, we demonstrated that aging and AD-like pathology impair fear extinction which is the ability to suppress learned fear responses when a stimulus is no longer threatening, resulting in chronic, maladaptive fear responding. Specifically, aged wild-type rats express dysregulated fear as measured by excessive freezing to non-threatening stimuli show elevated immunoreactivity for Iba1 (a microglial marker), pTau (Thr231), and GFAP (an astrocyte marker) compared to young adult wild-type rats. Building on these findings, we hypothesized that similar pathological changes would be observed in human amygdala tissue from older adults with PTSD. To test this, we employed JESS Simple Western technique using PTSD human postmortem amygdalar tissue to quantify ADRD-related markers (amyloid beta, pTau, GFAP, Iba1, S100β, NeuN, CD68) and excitatory/inhibitory synaptic proteins, including AMPAR1, vGlut, vGAT, GAD, GABA B1/B2, and mGluR2/3/5/7. Preliminary results show an increase in phosphorated tau, amyloid beta, AMPAR, mGluR2-3 in PTSD human amygdala tissue compared to control, suggesting an elevation of ADRD and excitatory signaling markers in PTSD amygdala. This supports my hypothesis that PTSD associates with ADRD through similar amygdalar neuropathology. Future studies will measure proteins localization in the amygdalar via immunohistochemical staining of human amygdala tissue.