afar american federation for aging research

GLENN FOUNDATION FOR MEDICAL RESEARCH

THE PAUL F. GLENN/AFAR CONFERENCE ON THE BIOLOGY OF AGING
THE 35TH ANNUAL AFAR GRANTEE CONFERENCE

JUNE 13 – 15, 2022
Ritz-Carlton Bacara
Santa Barbara, CA

#AFAR2022 @AFARorg

MONDAY, JUNE 13

3:30 – 4:00 p.m.	**Registration/reception**	*Santa Ynez Terrace*
4:00 – 4:10 p.m.	**Welcome** **Stephanie Lederman** Executive Director American Federation for Aging Research	*Santa Ynez*
4:10 – 5:10 p.m.	**BIG Presentations** **The Dynamic Epigenome - Challenges and Opportunities for Healthy Aging** Peter Adams, PhD **(2018 BIG)** Professor Sanford-Burnham Prebys Medical Discovery Institute **Electroencephalogram-based Brain Age and its Relation with Cognitive Function and Sleep Quality** M. Brandon Westover, MD, PhD **(2018 BIG)** Associate Professor, Neurology Massachusetts General Hospital and Harvard Medical School	
5:10 – 5:30 p.m.	**Break**	
5:30 – 6:00 p.m.	**Geroscience Interventions: The Path to Translation** James Kirkland, MD, PhD President, AFAR Professor of Medicine and Physiology, Mayo Clinic Rochester	
6:00 – 6:30 p.m.	**Establishing Biomarkers for Geroscience Prevention Trials** Stephen Kritchevsky, PhD Professor, Gerontology and Geriatric Medicine Wake Forest University School of Medicine	

6:30 – 7:00 p.m.	**Mapping Molecular Pathways that Link Aging to Alzheimer's Disease** Veronica Galvan, PhD Professor, Department of Biochemistry and Molecular Biology Donald W. Reynolds Endowed Chair of Aging Research Co-Director, Center for Geroscience and Healthy Brain Aging University of Oklahoma Health Sciences Center	
7:00 – 8:30 p.m.	**Dinner**	*Rotunda Terrace*
TUESDAY, JUNE 14	**GLENN WORKSHOP ON THE BIOLOGY OF AGING** Joint meeting of the AFAR Grantee Conference and Glenn Workshop participants Moderator: **Kevin Lee, PhD**	
7:30 – 8:30 a.m.	**Breakfast**	*Santa Ynez Terrace*
8:30 – 8:40 a.m.	**Welcome and Opening Remarks** **Kevin Lee, PhD** Senior Scientific & Programmatic Advisor Glenn Foundation for Medical Research	*Santa Ynez*
8:40 – 9:00 a.m.	**Mark Collins** President Glenn Foundation for Medical Research	
9:00 – 9:30 a.m.	**Introducing the Hevolution Foundation** **Felipe Sierra, PhD** *(virtually)* Chief Scientific Officer, The Hevolution Foundation	
9:30 – 10:00 a.m.	**Gamma Oscillations: Mechanisms, Function and Human Diseases** Li-Huei Tsai, PhD Picower Professor of Neuroscience, Massachusetts Institute of Technology	
10:00 – 10:30 a.m.	**The Dog Aging Project** Daniel Promislow, PhD Professor, University of Washington	
10:30 – 11:00 a.m.	**Break**	
11:00 – 11:30 a.m.	**Clinical Studies to Improve the Function of the Aging Immune System: Lessons Learned** Joan Mannick, MD CEO, Tornado Therapeutics	

11:30 a.m. – 12:00 p.m.	**Involvement of Retrotransposons in Aging and Age-Related Diseases** **John Sedivy, PhD** Hermon C. Bumpus Professor of Biology, Brown University	
12:00 – 1:30 p.m.	**Lunch**	*Santa Ynez Terrace*
1:30 – 2:00 p.m.	**Mitochondrial Dysfunction With Aging and its Effect on Sarcopenia and Mobility Loss** **Luigi Ferrucci, MD, PhD** Scientific Director, National Institute on Aging, NIH	
2:00 – 2:30 p.m.	**Regenerative Medicine and Aging: Barriers to Repair** **Jennifer Elisseeff, PhD** Morton Goldberg Professor, Johns Hopkins University	
2:30 – 3:00 p.m.	**Targeting the Integrated Stress Response to Reverse Cognitive Deficits in Aging and Traumatic Brain Injury** **Susanna Rosi, PhD** Principal Investigator, Altos Labs Bay Area Institute	
3:00 – 5:00 p.m.	**Free time**	
5:00 – 5:45 p.m.	**Reception**	*Rotunda Terrace*
5:45 – 6:15 p.m.	Dinner Speaker **Neurobiology of the World's Most Dangerous Animal** **Leslie B. Vosshall, PhD** Robin Chemers Neustein Professor, The Rockefeller University Vice President, Chief Scientific Officer, Howard Hughes Medical Institute	*Rotunda*
6:15 – 8:00 p.m.	**Dinner**	*Rotunda Terrace*

WEDNESDAY, JUNE 15

7:30 – 9:00 a.m.	**Breakfast**	*Santa Ynez Terrace*
	ADJOURN	

PAUL F. GLENN

Founded by Paul F. Glenn in 1965, the mission of the Glenn Foundation For Medical Research is to extend the healthy years of life through research on mechanisms of biology that govern normal human aging and its related physiological decline, with the objective of translating research into interventions that will extend healthspan with lifespan.

GLENN FOUNDATION
FOR MEDICAL RESEARCH

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BEACHES & POOLS

Set on 78 acres, the resort offers a two-mile natural beach, and three zero-edged saline, heated pools with private cabana rentals. Learn more about cabana rentals by dialing Ext. 43012.

GOLF

Santa Barbara's three 18-hole championship golf courses include Sandpiper Golf Club, located next door to the resort. Tee times at all courses can be arranged by dialing Ext. 0.

OUTDOOR ADVENTURE

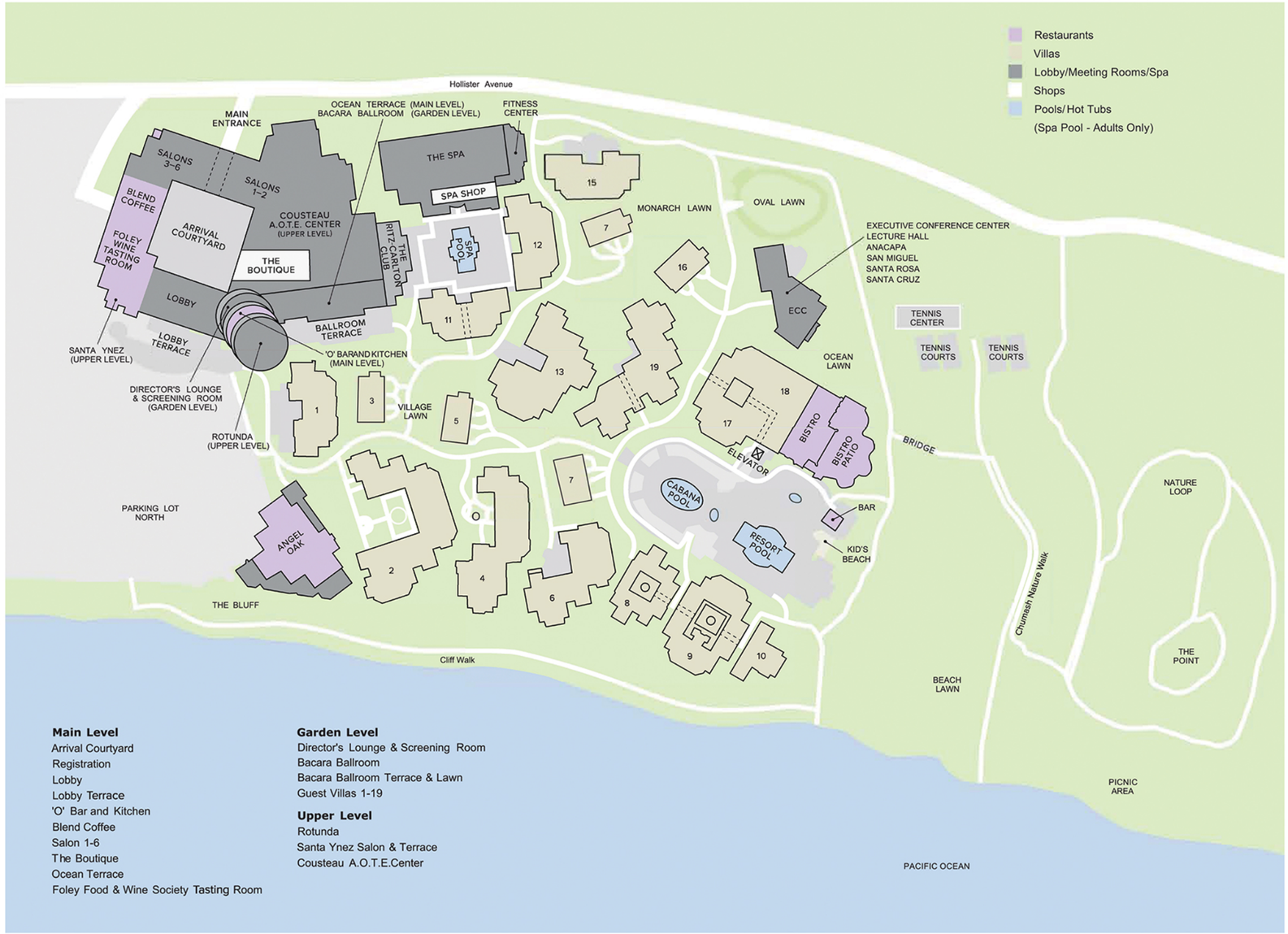
Santa Barbara offers horseback riding, biking, hiking and other activities. Pick up a hiking map. or book activities, including complimentary two-hour bike rentals at the front desk.

WINE COUNTRY

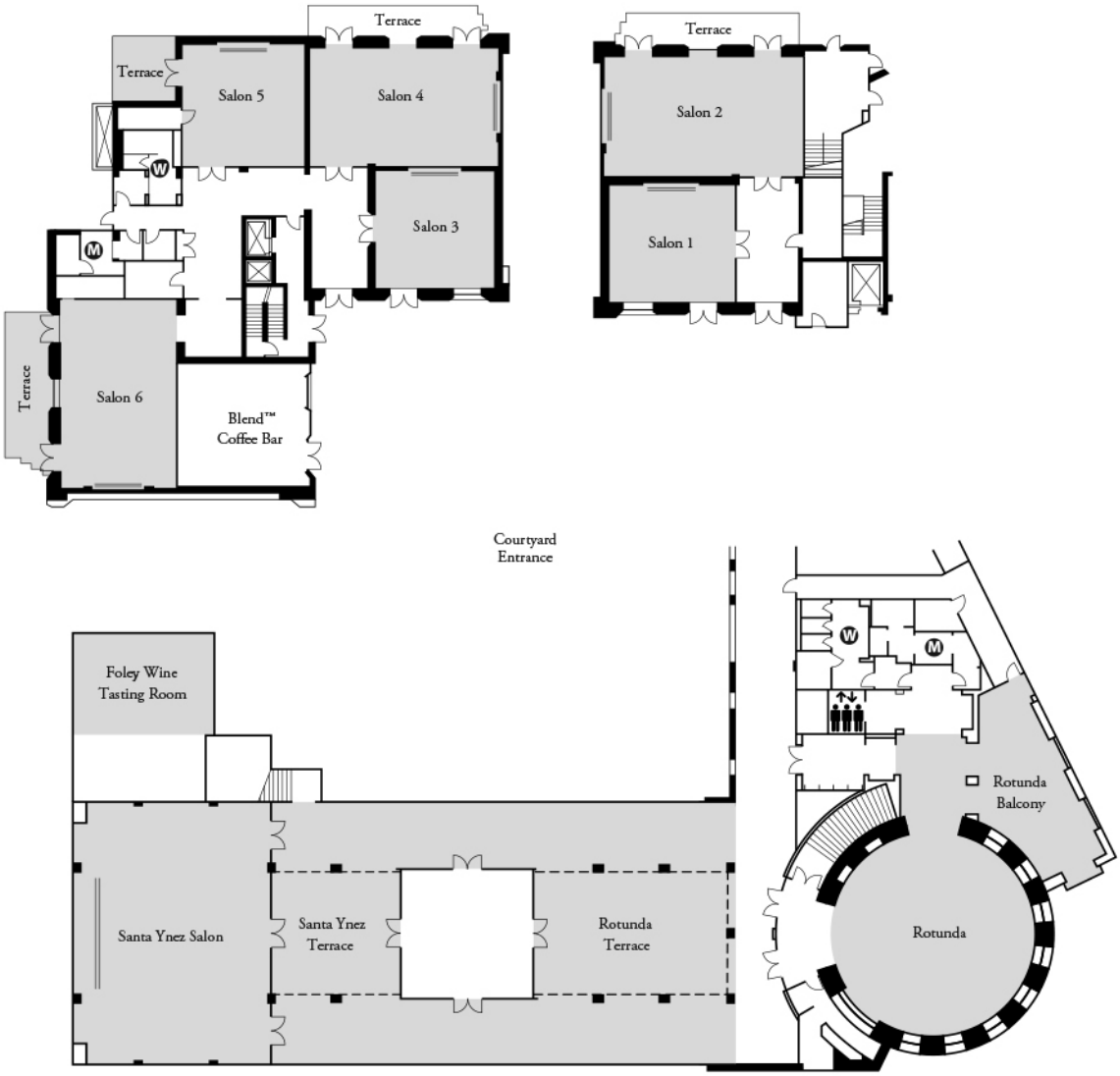
We encourage you to explore the wineries and tasting rooms located near historic State Street and throughout the diverse Santa Ynez region. Our relationship with select local wineries allows complimentary wine tastings to Resort guests with their room key. For a winery map or more information about the Santa Ynez Wine Country and Urban Wine Trail, see the Concierge.

DINING GUIDE

Each of the resort's six restaurants offers its own twist on a successful pairing: ocean views and local flavors. From a modern steakhouse with seasonal sides at Angel Oak, to rustic California cuisine at 'O' Bar and Kitchen, our dining showcases the best of Santa Barbara. For restaurant recommendations, reservations or a copy of our Dining Guide, please see the Concierge in the main lobby or dial Ext. 44220.



Rotunda, Santa Ynez Terrace & Salons



THE RITZ-CARLTON

BACARA, SANTA BARBARA

2022 AFAR Grantee Conference and Glenn Workshop

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Advances in medicine and public health increase average life span and survival of patients with chronic diseases, contributing to a gradual and continuous shift toward older adults in the US population. As our lifespan increases, maintaining active lifestyle with age and diseases will become increasingly important part of our life and society. I am interested in finding ways to contribute to healthy and active lifespan in the elderly and diseases. My lab uses animal models to elucidate mechanistic insights of muscle weakness and wasting, while testing interventions that can be translated to the elderly and cancer patients in parallel. We use animal models to elucidate mechanistic insights of muscle weakness and wasting, while testing interventions that can be translated to the elderly and cancer patients. First, I am interested in the role that free radicals play in the progression of loss of muscle mass and function with age. I and others have demonstrated that reactive oxygen species from the mitochondria is an early event prior to muscle weakness and loss. Using gain-of-function and loss-of-function mouse models of antioxidant enzymes, I test causal effect of oxidative stress in sarcopenia. Also, we are seeking for interventions that can delay muscle wasting and weakness in the elderly and chronic diseases. I am currently testing the therapeutic potential of unacylated ghrelin in sarcopenia and cancer cachexia. The overarching goals of my research program are to find ways to extend active and functional lifespan in the elderly and patients with chronic diseases.

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Dr. Jenna Bartley's multidisciplinary research uses geroscience approaches to bridge the bench and the bedside to uncover common pathways among the aging process and to develop potential interventions to prevent age-related declines in immune responses and overall health. Older adults are at increased risk for morbidity and mortality from infections due to immune system declines. Influenza (flu) infection remains a significant burden on older populations, with 9 out of 10 flu deaths occurring in individuals 65 years and older. While flu and COVID-19 vaccines are available, impaired immune responses with aging reduce vaccine efficacy, leaving older adults less protected than their young counterparts. Current methods to improve vaccination efficacy in older adults, however, target singular deficits in immune responses, and fail to completely rescue responses. Robust immune responses to infection and vaccination require a complex coordination of multiple cells and tissues. Thus, an approach that targets the biology of aging as a whole, rather than specific cell types or pathway, is in line with the geroscience hypothesis and likely is more suitable to improve overall immune responses and vaccine efficacy in older adults.

Metformin is a safe FDA-approved diabetes drug that modulates AMPK/mTOR pathways. In mice, metformin increases CD8+ T cell memory formation—which is impaired with age. Furthermore, metformin enhances B cell vaccine responses in diabetics compared to other oral hypoglycemics. Notably, metformin reverses hallmarks of aging including pro-inflammatory signaling and the senescence-associated secretome phenotype. However, how metformin affects flu vaccine responses in healthy nondiabetic older adults has not previously been studied. Thus, I completed a proof-of-concept pilot study, Vaccination Efficacy with Metformin in Older Adults (VEME), that examined the effect of metformin on flu vaccine responses in healthy older adults. Eligible participants were randomized to metformin (n = 8, 1500mg Extended-Release/day) or placebo (n=7) for 20 weeks. At week 10 of treatment, participants were vaccinated with high dose Fluzone vaccine. Blood was drawn prior to treatment, prior to vaccination, and 1-, 5-, and 10-weeks post vaccination. Peripheral blood mononuclear cells (PBMCs) were isolated using density gradient centrifugation and cryopreserved in liquid nitrogen, whereas plasma and serum were immediately stored at -80C. Despite the small cohort size (n=15) in the VEME study of older adults, metformin treatment had trending increases antibody fold changes and circulating T follicular helper cells (cTfh) post flu vaccination while reducing the CD57 exhaustion marker on CD4 T cells. Ongoing research in my lab is utilizing stored samples to better understand the effect of metformin on immune responses in healthy nondiabetic older adults with more sensitive and mechanistic approaches.

Age-related frailty and diseases carry a heavy societal burden, making it key to decipher the networks and processes that deteriorate during aging. Although the use of short-lived non-vertebrate model systems in experimental aging research has many advantages, this experimental pragmatism has hampered our understanding of vertebrate-specific mechanisms in aging. **In our AFAR-funded project, we aimed at generating a genome-to-phenome toolkit in a powerful emerging model organism that we have helped develop, the naturally short-lived African turquoise killifish, the shortest-lived Vertebrate that can be bred in captivity.** We have generated an unbiased atlas of cell types in 4 key vertebrate tissues from healthy male and female killifish: blood, kidney, spleen and liver. Across 3 cohorts of animals, we have generated data on >150,000 cells across the 4 tissues and both sexes. We are analyzing this data to identify (i) cell type markers in this species, to allow precise analysis of immune-related aging processes in the killifish, and (ii) identify potential differences in female and male killifish, which may drive sex differences in aging. Once complete, this atlas and compendium of curated cell type markers in the African turquoise killifish, together with its unique compressed lifespan, will provide new unique opportunities to understand age-related functional decline in vertebrates. This will also help transform thisemerging model organism into a powerful mainstream experimental system in the field of aging research.

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My lab is broadly interested in how the autophagy-lysosome system governs health and disease. We are studying many types of autophagy (including aggrephagy, mitophagy, pexophagy, and ER-phagy) with the goal of understanding how lysosome function and plasticity ultimately control animal physiology, aging, and rejuvenation. We are also attempting to clarify how organelle activity is altered in animal disease models, and whether natural products can be harnessed to improve cellular function during aging.

As part of our AFAR-funded studies, we are investigating the regulation of mitophagy in germ-cell development. We are interested in understanding whether lysosomal degradation of dysfunctional mitochondria plays a role in transgenerational rejuvenation in animal species. We have evidence that mitochondrial homeostasis is revamped just prior to fertilization as part of the oocyte maturation process, and this coincides with and requires lysosome activation. We are developing fluorescent markers to track mitophagy in real time in developing oocytes and testing whether any clean-up by this mechanism may be altered in older mothers, potentially contributing to age-related infertility.

Sebastian Brandhorst, Dr. rer. Nat
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My scientific training is based on a vast background in cell biology, molecular biology, medicine, and biochemistry, all of which are highly relevant for my focus on biogerontology research to identify the mechanisms underlying cellular protection, as well as health- and lifespan-regulation, and their translation into clinical applications. I have performed research related to aging with focus on mouse models to study the role of growth hormone/Insulin-like growth factor 1 (IGF-1) signaling as a major regulatory pathway that modulates lifespan and age-associated diseases/pathologies; including cancer. My research provided significant contributions in demonstrating that fasting can protect organisms from the toxic side-effects of commonly prescribed chemotherapy drugs while simultaneously sensitizing many types of malignant cells. Subsequently, I extended my research from pre-clinical to clinical studies to investigate the application of nutrition-based interventions, such as short-term starvation, low calorie and/or low protein diets, so called fasting-mimicking diets, to improve healthspan and extend longevity. A major focus of my ongoing research is focused on nutrition-induced cellular resilience, systemic regeneration and rejuvenation, and lifespan/healthspan extension ranging from model organisms of aging to humans.

Abigail (Abby) Buchwalter, PhD
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My research program is focused on the cell biology of the genome. We week to define how the organization of genome within the nucleus promotes establishment and maintenance of cell-type-specific gene expression programs, and to illuminate how this exquisite nuclear and genome organization is disrupted by aging and disease. Current projects in my laboratory focus on three main themes: (i) defining the essential functions that the nuclear lamina plays in nuclear organization; (ii) exploring how disruption of nuclear organization leads to aging and disease; and (iii) determining how dynamic regulation of components of the nuclear periphery shapes function.

I bring an innovative perspective to the genome organization field by integrating my cell biology background with genomic and proteomic approaches. My laboratory uses dynamic proteomic approaches as a powerful discovery tool to reveal new biological regulatory mechanisms. For instance, we have used protein turnover measurements to uncover a novel degradation pathway for an unstable nuclear membrane protein (Buchwalter et al., 2019) and to reveal a dramatic shift in protein synthesis regulation in an accelerated aging syndrome (Buchwalter & Hetzer, 2017). In recently published work, we have begun to quantify protein lifetimes *in vivo* and have observed broad variation across tissues, hinting that proteome maintenance is influenced by tissue context (Hasper et al., BioRXiV 2022). For example, we found that the nuclear lamins are an order of magnitude more long-lived in the heart than in the liver. The molecular control of this extreme difference in protein lifetime across tissues is completely unknown. Enticingly, this finding suggests a reason why mutations to Lamin A/C selectively affect the cardiovascular system and cause cardiomyopathy.

These studies demonstrate how protein turnover measurements can reveal basic gaps in our understanding of proteostasis as well as illuminate disease mechanisms. Along with a network of collaborators, we intend to extend these analyses to build a multimodal atlas of mammalian tissue homeostasis. To accomplish this goal, we have developed a method to extract both proteome and cellular turnover rates from *in vivo* 15N labeling of proteins and DNA, respectively. We will use these parallel measurements to define protein and cellular lifetimes across mouse tissues. By defining the lifetimes of cells and their component proteins, we can understand how cells and tissues are maintained over a lifetime.

Wei-Wen Chen

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Dr. Wei-Wen Chen is a physical chemist who is trying to solve a long existing technical issue in the field – the limited ability of currently available biochemical approaches to determine chemical composition within anatomically defined spaces in living biological systems. This is because methods that retain anatomical integrity, such as histochemical assays, do not provide compositional data, while biochemical methods, which provide detailed chemical information, lack information on spatial distribution of the metabolites as these methods rely on tissue or cell extractions. The uncoupled spatial and spectral information obtained by current biochemical methods remains one of the biggest challenges in biological research.

Wei-Wen's project combined a novel label-free optical technology called broadband coherent anti-Stokes Raman scattering (BCARS) imaging, machine-learning analysis, and aging-related *C. elegans* mutants to quantitatively assess lipid composition in intact tissue and to investigate how beneficial and harmful lipids affect the aging process. BCARS can rapidly detect the intrinsic molecules via collection of optically enhanced Raman signal without any labeling, which is about 1000 faster than traditional Raman microscopy. More importantly, BCARS can be used to study living, intact specimens over extended periods of time, providing direct insight in the dynamics of metabolic processes. The relevant work [1] has been highlighted in a "News & Views'' overview published in *Nature Chemical Biology* [2]. Currently, the project is still ongoing. The results up to now show that BCARS can not only allow for quantitative characterization of heterogeneous lipid rich particles even in the absence of previously defined protein markers but also simultaneously detect multiple biochemical species based on the unique Raman peaks of these molecules (Fig. 1). These results also lead to a hypothesis that aging process could be modulated by the production of lipoprotein and specific lipids such as unsaturated lipids can play a critical role in aging as well. Nevertheless, the results so far demonstrates that BCARS combined machine-learning analysis can potentially provide new avenues for biomedical research, particularly in lipid utilization and longevity.

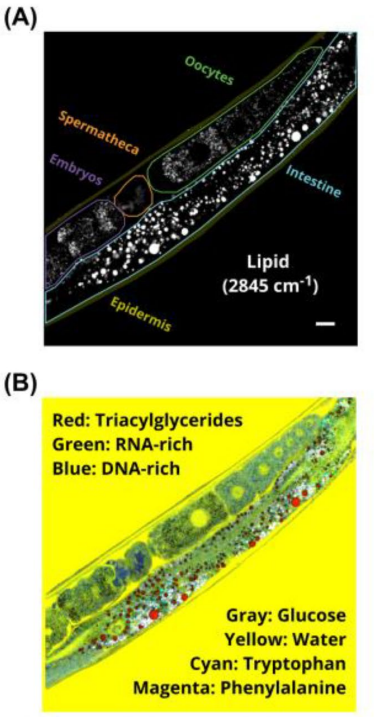

Fig. 1 BCARS image of **(A)** lipid (2845 cm-1) **(B)** RNA (811cm-1), DNA (784 cm-1), glucose (1125 cm-1), tryptophan (760 cm-1), phenylalanine (1002 cm-1), and water (3200-3400 cm-1)

References

[1] *Nature Chemical Biology* 16, 1087-1095

[2] *Nature Chemical Biology* 16, 1039-1040

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Cellular senescence, a stable proliferation arrest caused by a range of cellular stresses, is a bona fide cause of cell and tissue aging. As well as proliferation arrest, cell senescence is associated with a potent pro-inflammatory phenotype, the senescence-associated secretory phenotype (SASP). Recent studies have shown the importance of cytoplasmic DNA and chromatin, either reverse transcribed retrotransposons or cytoplasmic chromatin fragments (CCF) expelled from the nucleus, in activation of nuclear SASP gene expression via the cGAS/STING cytoplasmic DNA-sensing pathway. As a source of chronic inflammation, over the long term SASP promotes tissue aging and disease. Thus, it is important to better define the mechanism of SASP activation in senescence. We show here that both the Promyelocytic Leukemia (PML) protein and HIRA histone chaperone are required for SASP expression in senescent cells. PML protein is the key organizer of PML nuclear bodies, nuclear features up to 1□M in diameter, containing many proteins and previously implicated in diverse cellular processes, including control of cell senescence and cellular intrinsic anti-viral immunity. HIRA is a histone chaperone best known for its ability to incorporate histone variant H3.3 into nuclear chromatin in a DNA replication-independent manner, including in non-proliferating senescent cells. HIRA localizes to PML nuclear bodies in senescent cells. We show that both HIRA and PML are required for NF-kB activation to induce SASP. We found that HIRA regulate cytoplasmic NF-kB signaling in senescent cells through interaction with autophagy cargo receptors. In mouse models, conditional knock out of HIRA also suppresses inflammation and tissue damage caused by senescence-inducing irradiation in liver. Overall, our findings point to functions for HIRA and PML in coordination of cytoplasmic signaling and nuclear gene expression to regulate inflammation during cell senescence and aging.

Dibyadeep Datta, PhD
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The overarching focus of my research is to elucidate the molecular alterations and understand the etiology underlying the neurobiology of Alzheimer's Disease (AD) that contribute to cognitive dysfunction with advanced age. Our research has illuminated how calcium dysregulation contributes to aberrant tau phosphorylation leading to neurofibrillary tangle pathology and cognitive impairment with advancing age in sporadic AD using non-human primates. The research is particularly translationally relevant as we are able to test novel pharmacotherapies to ameliorate age-related cognitive deficits. Our results suggest that suppressing calcium "leak" through phosphorylated ryanodine receptors might provide a novel therapeutic strategy for protecting higher-order cortical circuits required for cognition.

During my postdoctoral fellowship, I am using a plethora of techniques, involving iontophoresis with pharmacology to alter physiology/behavior in monkeys during working memory tasks, in conjunction with high spatial-resolution ultrastructure to explore the interaction of various proteins that regulate the dynamic activity pattern in PFC microcircuits. My research is explicating how layer III PFC pyramidal cells that provide top-down control of thought are distinctly regulated at the synaptic level, where network activity can be acutely dampened by feedforward, calcium-cAMP-K^+ channel signaling during stress and advancing age by activation of neuroinflammatory cascades, due to dysregulation of phosphodiesterase signaling. My current research is also explicating the role of pT217-tau in aged monkey cortex, a tau phosphorylation species that might track AD pathology in humans and exciting arena of discovery crucial for biomarker development and therapeutics.

Skin is the largest organ in human body, harboring a plethora of cell types and serving as the organismal barrier. Skin aging such as wrinkling and hair graying is graphically pronounced, accompanied with many hallmarks of aging, such as stem cell exhaustion, genotoxic stress, metabolic deregulation, and epigenetic erosion. My lab studies molecular mechanisms that regulate stem cell function and lineage plasticity, and how they contribute to skin aging when going awry.

Our previous work identified the essential role of Kruppel like factor KLF5 in regulating hair follicle stem cell plasticity. We recently found KLF5 specifically marks the epidermis, and its deletion leads to skin dysfunction *in vivo*. KLF5 binds to and transcriptionally controls genes encoding rate-limiting sphingolipid metabolism enzymes. Lipid envelopes and secretory lamellar bodies are defective in *Klf5*-deficient skin, accompanied by preferential loss of complex sphingolipids. Remarkably, skin barrier defects elicited by KLF5 ablation can be rescued by dietary interventions. Of significance, KLF5 is widely suppressed in human pathologies with disrupted epidermal secretion including aged skin. Altogether, we established KLF5 as a master secretory lineage factor governing skin sphingolipid metabolism and barrier integrity, which is highly relevant to maintaining epidermal function during aging.

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As a postdoctoral fellow in Tom Carmichael's lab at UCLA, my research has focused on how astrocytes respond to stroke and how those responses are shaped by astrocytes' proximity to the injury and the location of the injury. Using mouse models of cortical and white matter stroke, I have identified zones of reactive astrocytes after stroke and developed transcriptomic datasets of the changes occurring in astrocytes within these zones. These analyses have revealed both interesting similarities and differences in astrocytic responses to stroke in different brain regions; I am leveraging some of these differences to influence tissue repair after stroke.

With AFAR support, I extended these studies to aged mice. I have completed phenotypic studies to map astrocytic zones after stroke in aged animals, and am using this analysis to inform transcriptomic studies. I have also mapped the spatial expression patterns of candidate gene systems and identified several key genes whose expression post-stroke is altered by age. I developed a dual virus system to selectively knockout expression of one of these genes, Thbs2, in astrocytes in the peri-infarct cortex of aged mice. Thbs2 is upregulated after stroke in young adult mice, further upregulated in aged mice, and has roles in both promoting synaptogenesis and inhibiting angiogenesis. Neuronal plasticity and angiogenesis are both critical processes in post-stroke neural repair and recovery. Therefore, I am evaluating how this astrocyte-specific knockout of a gene differentially regulated by age, in both young adult and aged mice, influences both angiogenesis and synapse number.

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I am an assistant professor in the Department of Aging and Geriatric Research at the University of Florida. I have extensive experience in mitochondrial biology, axon regeneration and degeneration, and the *C. elegans* genetic model system. My long-term research goal is to understand how the nervous system maintains its unique structures and function throughout an animal's lifetime and further explorer how it regulates the health and aging of the whole organism. For me, it is a critical unmet question because neurons are susceptible to damage, and most neurons are not replaced and must be maintained throughout the animal's lifetime. In particular, our current research goal is to identify the mechanisms regulating mitochondrial location and function in two critical conditions: damage (regulation of axonal regeneration) and aging (maintaining normal synaptic function during aging), and elucidating their physiological significance. This research goal is built on the growing evidence that mitochondria undergo dynamic changes in morphology, localization, and activity in the subcellular area in neurons to meet demand. Incorrect mitochondrial localization of neurons can lead to functional defects and degeneration of neurons. Our study also revealed that mitochondria act as key determinants of axon regeneration. However, the underlying mechanisms regulating mitochondrial localization and how mitochondrial subcellular localization supports specific neural functions during aging are incompletely understood.

To meet these research goals, we utilize the nematode *C. elegans* as an *in vivo* model that allows for mitochondria analysis in a single neuron/axon resolution over a wide range of genetic backgrounds during aging *in vivo*. Our first project aims to reveal the underlying mechanisms that regulate the age-related decline in axon regeneration ability of neurons by understanding the role of age-related changes in mitochondria in injured neurons. The second project, kindly supported by AFAR, aims to dissect the molecular pathways regulating mitochondrial localization and homeostasis at the synapse, which is challenged by aging and pathological conditions. We generated *in vivo* model system that enables visualization of mitochondria at the synapse and genome-wide genetic screening. We identified several genes required to maintain normal mitochondrial positioning at the synapse. In addition to this essential role of mitochondria in neurons, our third project investigates how mitochondrial stress in specific neurons affects organismal aging and health. This is in line with recent findings suggesting that neuronal mitochondrial stress can trigger changes in mitochondrial stress response activity in peripheral tissues through non-cell-autonomous signaling.

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2020 Glenn Foundation for Medical Research Postdoctoral Fellowship

Title: Single-cell omics analysis of the aging methylome and transcriptome

To better understand why some people are able to become very old I wanted to investigate whether cells of these exceptionally old people are more resistant to DNA damage than cells of people with an average lifespan. For my study, I used T-cells from young and old donors, as they are abundant in blood and can be easily sampled. While DNA damage can be repaired, the errors in genome and epigenome, called mutations and epimutations, that occur during the repair process are irreversible, which make them good candidates as the basic causes of aging. Since mutations and epimutations during aging occurs more or less randomly I used a study design for analyzing both single cells and bulk RNA and DNA. To set up conditions for my experiments I used human primary fibroblasts, which I irradiated to mimic the effect of DNA damage during the aging process. I then isolated both single cells and RNA and DNA from bulk cells and established a pipeline for processing preparing libraries for simultaneous mRNA and DNA methylation analysis. This allows us to cell-to-cell heterogeneity within a population and determine the impact of DNA methylation on gene expression.

Together with Einstein's core facility for cytogenetics we were able to establish a protocol for cell culture and isolation of T-cells. Currently, I am comparing gene expression of T-cells from young, old and centenarian people to establish baseline levels before moving on to irradiated T-cells. First experiments show a dose-dependent delay in proliferation after irradiation and an overall effect of the age of the donors. Next, I hope to find differences in the responses of cells from young, old and very old donors to the radiation damage in terms of changes in DNA methylation and gene expression. Since cells will change their gene expression and the regulation thereof in response to DNA damage, I hypothesize that the general ability to respond is less and more variable in cells from older individuals than from younger ones, yet better and more coordinated in exceptionally old people, which might explain their old age.

Research Synopsis

Seokjo Kang earned her doctoral degree from Seoul National University in South Korea. As a predoctoral student with Dr. Inhee Mook-Jung, her research focused on defining mechanisms underlying the pathogenesis of Alzheimer's disease (AD), demonstrating that microglia are metabolically defective during Aβ-induced chronic inflammation, which indicated that modulating microglial cellular metabolism might be a new therapeutic strategy for AD.

She subsequently joined Dr. Helen Goodridge's Lab at Cedars-Sinai Medical Center to study molecular mechanisms controlling functional changes in innate immune cells during aging and in aging-related diseases, including their impacts on cognitive health and peripheral immunity. Currently, she is defining how changes in microglial energy metabolism during aging alter microglial function, and determining how sex differences impact microglial function and brain aging. Investigating these mechanisms could facilitate the development of novel approaches to slow human aging and treat aging-associated diseases.

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Abstract:

Macrophages are key players in white adipose tissue (WAT) biology in health and disease. The role of ATMs in metabolic disease is often discussed based on the M1/M2 paradigm, however ATMs are a heterogeneous population composed of multiple subsets with unique functions that can associate with different tissue structures such as adipose parenchyma, vessels, and nerves. While the heterogeneity of ATMs in the context of obesity has begun to emerge, the specific changes in ATM subsets that occur with age remain to be addressed. Nerve-associated macrophages (NAMs) belong to a unique neural niche within WAT, yet we know very little about their characteristics and function at homeostasis and in aging. To gain insight on the transcriptional identity of NAMs, we performed single cell RNAseq of rATMs from young and aged WAT. We describe 9 transcriptionally distinct rATM subsets and find a unique ATM population that only emerges with aging. By combining high-resolution imaging such as electron microscopy, confocal and two-photon microscopy, we define two closely related, but distinct subsets of NAMs, perineural and intraneural NAMs, in the adipose tissue based on their localization, morphology, ontogeny, and transcriptional program. We show that similarly to other rATM subsets, NAMs increase their pro-inflammatory status with age. Finally, we show that NAMs are a phagocytic population capable of internalizing myelin components and likely play a role in the maintenance of the adipose peripheral nervous system integrity during lifespan, linking age-associated inflammation with defective myelination in aging.

A mitochondrial membrane-bridging machinery mediates signal transduction of intramitochondrial oxidation

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My research focuses on understanding brain aging and how brain disease develops as we age. I am specifically interested on the energy factory of the cells; mitochondrial function and kinetics. Mitochondria are the main site for generating reactive oxygen species, which are key players in diverse biological processes. However, the molecular pathways of redox signal transduction from the matrix to the cytosol are poorly defined. I discovered an inside-out redox signal of mitochondria. Cysteine oxidation of MIC60, an inner mitochondrial membrane protein, triggers the formation of disulfide bonds and the physical association of MIC60 with Miro, an outer mitochondrial membrane protein. I found the increased binding of MIC60 with Miro in aged flies, flies overexpressing alpha-synuclein and flies with frataxin deficiency. The oxidative structural change of this membrane-crossing complex ultimately elicits cellular responses that delay mitophagy, impair cellular respiration and cause oxidative stress. Blocking the MIC60–Miro interaction or reducing either protein, genetically or pharmacologically, extends lifespan and health-span of healthy fruit flies, and benefits multiple models of Parkinson’s disease and Friedreich’s ataxia. My data provides a molecular basis for common treatment strategies against oxidative stress.

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The genome is under attack. This assault comes from exogenous mutagens like UV light and polycyclic aromatic hydrocarbons present in tobacco smoke, and from endogenous forces such as reactive oxygen species, mobile DNA elements, and errors during normal cell division. This damage is often transient due to the activity of DNA damage repair pathways. Still, repair failure or misrepair can result in permanent genetic changes in cells of the body, called somatic mutations. As a result of somatic mutations, each of us is a genetic mosaic, with each cell likely having a unique genome, different from every other cell in the body.

Since mosaic mutations exist in only some cells in a tissue, or could even be limited to a single cell, they are too rare to be studied comprehensively using standard genome sequencing techniques. Therefore, our group has used single-cell sequencing techniques to characterize the rates, characteristics, and consequences of somatic mutations in the human brain. We applied single-cell DNA sequencing to aging in the human brain, showing that indeed in two areas of the human brain, the prefrontal cortex (PFC) and dentate gyrus of the hippocampus (DG), somatic SNVs accumulate over time (Lodato et al., 2018, Science). Importantly, mutation types were not random but comprised specific signatures that displayed age, brain region, and disease status specificity. More recently, we applied single-cell DNA sequencing to Alzheimer's disease, showing the excitatory neurons in the AD brain show increases in some classes of somatic mutation (Miller et al., 2022, Nature). In contrast, other mutation classes were identical in AD neurons and age-matched controls. This analysis thus nominated some DNA damage and repair pathways for Alzheimer's therapeutic intervention while deprioritizing others. Currently, our lab is investigating how the activity DNA damage and repair genes changes during aging in the brain using single-cell transcriptomics and *in vitro* modeling.

Microglia and Astrocytes Promote Neurodegeneration in Human and Mouse with *GRN* Mutations

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Dominant mutations in the *Progranulin* (*GRN*) gene are a leading cause of frontotemporal lobar degeneration (FTLD). While previous studies implicate aberrant microglial activation as a cause for degeneration in the thalamocortical circuit in *Grn*$^{-/-}$ mice, what promotes neurodegeneration in FTLD-*GRN* remains unclear. Here, we perform comparative single-cell transcriptomics using thalamus and frontal cortex from FTLD-*GRN* cases and 19 months-old *Grn*$^{-/-}$ mice. This approach confirms the shared transcriptomic and phenotypic changes in disease microglia in human and mouse. Furthermore, this study uncovers highly conserved astroglial pathology across species that disrupts glia-vascular coupling and synaptic organization. The glial pathology in FTLD-*GRN* is accompanied by widespread transcriptomic changes in cortical and thalamic neurons that affect synaptic signaling and axo-dendritic growth. Consistent with these results, iPS-derived Progranulin-deficient astrocytes when transplanted into cortical organoids promote synaptic degeneration and TDP-43 proteinopathy in neurons. Together, these results support that conserved glial pathology and neuronal vulnerability are key drivers of neurodegeneration in FTLD-*GRN*.

The McCormick Lab studies the basic biology of aging. We use multiple model systems to look for conserved biology that will help us understand and delay aging, and the onset of age-related diseases, in humans.

In recent work, we have identified drugs that greatly extend the lifespan of two organisms used to study aging: the budding yeast *S. cerevisiae*, and the nematode *C. elegans*. These drugs increase levels of a transcription factor called Gcn4 in yeast, and if we remove this gene (*GCN4* in yeast or *atf-5* in worms), the drugs no longer extend lifespan. In mice and humans *GCN4* is called ATF4, and several types of longlived mice have been shown to have elevated ATF4 levels. In work supported by a Glenn Foundation / American Federation for Aging Research Junior Investigator Grant, we have now shown that these same drugs do raise ATF4 levels in a dose-dependent manner in mouse cells in culture. We have also now measured changes in *all* other genes when we add these drugs using RNASeq, in normal mouse cells, and in mouse cells without ATF4. Based in part on these new AFAR-supported findings, we have now obtained additional funding to test the effects of some of these compounds on mouse lifespan. We hope through this ongoing work to uncover conserved effects that could lead to treatments to offset or delay the onset of diseases of aging in humans.

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Microglia are implicated in aging and Alzheimer's disease, however their role in the progression of cognitive decline in humans is not clear. While multi-cellular interactions in the human brain are best studied by in situ imaging, traditional imaging methods fall short of capturing these interactions as they suffer from low multiplexing capabilities, low sensitivity and high background signals. We utilized Multiplexed Ion Beam Imaging (MIBI) and machine learning to map the cellular niches across the human brain and define a spectrum of phenotypic profiles in microglia which varies between healthy human brain regions and is altered around the pathology of Alzheimer's disease.

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My long-term career goal is to identify novel therapeutic approaches for geriatric patients by using "big data" from single-cell datasets to decode molecular mechanisms underlying age-related diseases. Armed with molecular biology and machine learning techniques from my Ph.D. and postdoctoral trainings, I am developing robust multidisciplinary research programs to integrate single-cell datasets with experimental data to advance geriatric research in the following areas:

1. *Single-Cell Transcriptome Analysis to Identify Molecular Mechanisms Underlying Resilience to Diet-Induced Obesity in Aged Mouse Pancreatic Islets.* Aging is a major risk factor for the development of type 2 diabetes (T2D). Aging is known to cause pancreatic islet dysfunction, but very little is known about the underlying connection to date. Using single-cell transcriptomics profiling, my group has examined the effect of aging and obesity on islet dysfunction by single-cell RNA-sequencing of samples across different age groups, from young (1 month), middle (13 months) to old (24 months) age groups. By applying single-cell western blot, we further verified that aged mice had increased islet beta-cell percentage, which was accompanied by an increased insulin secretion *in vivo*. Young and old groups were fed with a six-month high-fat diet. Surprisingly, aging significantly enhanced insulin secretion which prevented old mice from diet-induced glucose intolerance. Together, this single-cell atlas allows a comprehensive exploration of all transcriptional states in the aging islets and provides insight into the pathogenesis of human T2D. More importantly, our findings demonstrate that age-dependent hyperinsulinemia protects diet-induced obesity, leading to resilience of aged islets to nutritional stress.

2. *GLP-1 Agonists to Prevent mTOR-induced Metabolic Dysfunction.* Inhibition of mammalian target of rapamycin (mTOR) complex 1 with rapamycin is an effective intervention to slow down aging. However, clinical administration of rapamycin may have several potential side-effects, including hyperlipidemia and hyperglycemia. Semaglutide is one of the agents in the glucagon-like peptide 1 (GLP-1) receptor agonist class that is highly effective in lowering glucose level and improving lipid metabolism. Before assessing the effectiveness of rapamycin to slow down aging in humans, it is necessary to mitigate its potential side-effects. We will test the hypothesis whether a combination therapeutic approach using rapamycin and semaglutide will diminish some of the metabolic defects caused by rapamycin treatment in common marmoset (*Callithrix jacchus*), including beta-cell dysfunction, glucose intolerance, and hyperlipidemia.

3. *Single-Nucleus RNA Profiling of Aged Human Adipose Tissues to Identify Senescence Population.* Human adipose tissues display a remarkable ability to adapt to the age and body mass index (BMI) status. However, a detailed single cell map among human adipose tissue that include the age-related phenotypes in mature adipocytes has not been investigated. Here, we have applied single-nucleus RNA-seq to human subcutaneous white adipose tissue across middle to older age groups in lean to obese subjects. We identified two major different mature adipocytes that has different origination: permeant lipid storage adipocytes (PLA), which is derived from committed preadipocytes, and temporary lipid storage adipocytes (TLA), which only differentiate from adipocyte progenitors. Moreover, aging leads to the disappearance of the PLA, not the TLA. Interestingly, the TLA population exhibits the senescence phenotype during aging. Taken together, these data demonstrate vital elements that allows adipose tissue to adapt the aging environment and provide a first-time differential trajectory map between progenitors and mature adipocytes.

My future research interests include 1) investigate islet function at a single organoid level and identify the heterogeneity of islets in various aged human populations. 2) measure biologic age of human adipose tissue by applying machine learning deep neural networks. 3) discover the crosstalk between different adipose tissue cell types/subtypes during aging by computational model to identify novel therapeutic targets. 4) propose new rapamycin combination treatments to extend the longevity lifespan studies of human populations.

Mechanisms of longevity factor klotho and platelet activation to counter cognitive aging

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Cognitive aging is one of our biggest biomedical challenges with no effective medical treatments. Klotho is a longevity factor and reverses cognitive impairments in the aging brain through systemic treatment. Recently, we found that klotho treatment increased platelet factors in the blood, suggesting a novel biological action of klotho in platelet activation. This research focuses on determining i) whether and how klotho activates platelets throughout the lifespan – and testing ii) whether platelet factors are messengers of klotho in attenuating deficits of cognitive aging in mice. The impact of the proposed studies will deepen our understanding of how the body signals to the brain to affect aging, unravel a new role for platelets in the aging brain, provide a link between klotho, platelets, and cognitive aging, and may open a new therapeutic path to treatment of cognitive aging.

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Even a small piece of brain tissue can contain dozens of subtypes and neurons, each with their own distinct role the neural circuits underlying complex behaviors and neurological disorders. The goal of the Pfenning group is to disentangle this complexity by building a set of computational and genomic tools to study how genome sequence influences neural cells, neural circuits, disease, and behavior. The group is conducting research on the epigenetics of aging, the genetics of Alzheimer's disease, the genetics of addiction, and the evolution of behavior. To attack these questions, the lab uses an interdisciplinary approach that combines machine learning with high-throughput genomic experiments. Our current and previous support includes an AFAR Grant, a National Institute on Drug Abuse Avenir Award, a grant from the CureAlzheimer's foundation, and an NSF CAREER award.

The Pfenning laboratory is studying how DNA damage is at the center of aging by looking both within the human population and across species. Within the human population, the lab is studying differences in how distinct subtypes of neurons respond to DNA damage that can accumulate with age and Alzheimer's disease. In parallel, the laboratory is taking an evolutionary approach, studying how different components of the response to DNA may have adapted in species with longer life spans. The long-term goal of the Pfenning laboratory is to draw parallels between aging-associated genetic variation within the human population and across species.

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The Sudmant Lab studies the evolution and diversity of aging, genome structure, and mutation. We use genomics, sequencing, computational, and statistical approaches to interrogate these topics across a wide array of species, systems, and contexts. Our aging work focuses on both *the comparative genomics of aging* as well as *profiling the fidelity of molecular processes through aging*.

Understanding the interplay between tryptophan and NAD metabolism during aging

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Metabolic dysregulation increases with age and is a major cause of age-associated functional decline and disease. Nicotinamide adenine dinucleotide (NAD) is an essential cofactor that plays a critical role in many enzymatic redox reactions and in mitochondrial energy production. NAD levels decrease with age in a variety of tissues. This decline has been implicated as a driving factor in the pathophysiology of several categories of age-associated disease, including metabolic and neurodegenerative disease. Elevating physiological NAD by administering NAD precursors, such as nicotinamide riboside (NR), have been reported to extend lifespan and improve health the roundworm, *Caenorhabditis elegans*. In contrasting preliminary data, we find that inhibiting *de novo* NAD synthesis through the tryptophan-kynurenine metabolic pathway robustly extends lifespan in *C. elegans*. In particular, knockdown of the kynurenine pathway gene *haao-1*, encoding the enzyme 3-hydroxyanthranilic acid dioxygenase (HAAO), extends *C. elegans* lifespan by ~30% in a manner that is mediated by physiological upregulation of the HAAO metabolic substrate, 3-hydroxyanthranilic acid (3HAA). The original goal of this project is to understand the role of altered NAD metabolism in lifespan extension from kynurenine pathway inhibition. Given previous reports of lifespan extension from elevating physiological NAD, we were specifically interested in determining whether the lifespan extension from *haao-1* knockdown could be synergistically enhanced by simultaneously supplementing worms with an NAD precursor. Unfortunately, we were unable to consistently replicate the previously reported lifespan extension resulting from NAD or several precursor molecules (NAM, NMN, and NR). Our inability to replicate these studies parallels the story of dietary NR in mice. Dietary NR started at 23 months of age was reported to extend lifespan in male C57BL/6J mice by one group, but this observation did not replicate in UM-HET3 mice fed NR starting at 8 months of age in the Interventions Testing Program (ITP). There are numerous potential explanations for these discrepancy (e.g. environment, dose and dose schedule) and we are still troubleshooting this issue in *C. elegans*.

In lieu of NAD precursors, we tried an alternative method to elevate physiological NAD, namely inhibition of several of the NAD-consuming enzymes. In this case, we find that knockdown of *parp-2*, encoding a poly-ADP ribose polymerase, or *parg-2*, encoding a poly ADP-ribose glycohydrolase, extends lifespan in *haao-1* knockout animals, providing some evidence that indirectly rescuing the lack of *de novo* synthesis in *haao-1* mutants can further increase lifespan. We have further examined processes regulated by NAD in the context of 3HAA supplementation or *haao-1* knockdown. We find that animals with reduced *haao-1* expression have more fragmented mitochondria and are slower to change oxygen consumption rate in response to FCCP treatment than control animals during aging. Mitochondrial fragmentation has also been reported in response to NR treatment in *C. elegans*, suggesting that the mitochondrial phenotypes observed in *haao-1* knockdown animals are not a result of reduced NAD content. More strikingly, we find that *haao-1* interacts with several enzymes involved in iron homeostasis, and 3HAA produces synergistic toxicity in both bacteria and human cell culture. There is some evidence for cross-regulation between iron homeostasis and NAD metabolism; however, whether NAD levels mediate the interaction between *haao-1*/3HAA and iron homeostasis in our models is currently unknown.

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Research Synopsis

Declines in adult stem cell number and function are hallmarks of aging. This is especially true in the aged hair follicle, where stem cells suffer from prolonged dormancy and progressive exhaustion. Accumulating evidence has implicated a deteriorating exchange with microenvironmental cues that normally govern hair follicle stem cell (HFSC) behavior. To identify the root causes of aging and improve tissue fitness, it will be necessary to dissect the relative contributions of HFSCs from their specialized niches. However, the study of aged HFSC-niche interactions to date is hampered by a lack of tractable, timely, and physiologically relevant models. I have overcome this hurdle by leveraging our discovery that cultured HFSCs, removed from their niche, exhibit a wound-like epigenetic signature. Through the systematic manipulation of conditions aimed at eliminating this signature, I identified critical niche signals that lie at the intersection between homeostatic regeneration and wound-enabled lineage plasticity. When reintroduced in culture, these signals serve to meet the minimal requirements necessary for the acquisition of a full suite of hair cell types, establishing a novel platform for the interrogation of HFSC biology.

Critically, this platform can be adapted for exchange with the dermal niche, an age-affected signaling hub that coordinates hair cycling. To isolate the deleterious effects of aging on niche interactions from autonomous HFSC deficits, I employed heterochronic HFSC-dermal co-cultured and found that aged HFSCs retained the ability to appropriately respond to niche-derived growth factors. Instead, the aged dermal niche's ability to provide key growth factors supporting HFSC self-renewal was impaired. Moving forward, I plan to use this system to functionally define the HFSC niche signals most affected by age. If successful, this work has the potential to accelerate efforts to understand how aging impacts HFSC biology through their local microenvironment, as well as find application in regenerative approaches designed to ameliorate the age-associated decline of hair maintenance and growth.

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The role of dorsomedial hypothalamic neurons in mammalian aging and longevity

Recent studies have revealed that the inter-tissue communications play a critical role in the regulation of aging and longevity in model organisms. In mammals, the hypothalamus functions as a high-order “control center of aging,” counteracting age-associated pathophysiological changes and thereby promoting longevity. Adipose tissue communicates with the hypothalamus by secreting extracellular nicotinamide phosphoribosyltransferase (eNAMPT), which enhances NAD^+ biosynthesis and the activity of SIRT1, the mammalian NAD^+-dependent protein deacetylase, in the hypothalamus and its function.

We have successfully identified new neuronal subpopulations in the hypothalamus which may be involved in mammalian aging/longevity control. One of them is Ppp1r17, Protein Phosphatase 1 Regulatory Subunit. We have extensively characterized Ppp1r17-positive neurons in the dorsomedial hypothalamus ($DMH^{Ppp1r17}$ neurons), and found that $DMH^{Ppp1r17}$ neurons regulate white adipose tissue function, most likely through the sympathetic nervous system. Based on these findings, we hypothesize that $DMH^{Ppp1r17}$ neurons drive a critical feedback loop between the hypothalamus and white adipose tissue through the regulation of the sympathetic nervous system, promoting lipolysis and secretion of eNAMPT. By maintaining this feedback loop, $DMH^{Ppp1r17}$ neurons counteract age-associated physiological decline and promote lifespan in mammals. The anticipated outcome of this study will make a significant impact to our understanding of the systemic regulatory network of mammalian aging/longevity control.

The Vivas Lab

Our team is interested in understanding the mechanisms behind the modulation in the excitability of autonomic neurons in health and disease as we age. Why the autonomic nervous system? As we age, we perceive a decline in our ability to maintain constant internal conditions (homeostasis) at rest and under stressful conditions. Here are some examples. Thermoregulation is challenging, blood pressure is hardly controlled, heart rate decreases and cannot keep up with vigorous activity, and even simple tasks like salivation and urination become challenges. The autonomic nervous system innervates every organ; hence, it controls the physiological processes in charge of thermoregulation, blood pressure, and so on. In other words, the autonomic nervous system's function is to coordinate the homeostatic mechanisms. The deterioration caused by aging leads to the detriment of the coordination of homeostatic mechanisms necessary to keep constant conditions at rest and under stress. Moreover, further deterioration can lead to age-related pathologies. Our team attempts to find answers to the following questions: Is aging a perturbation factor for which the autonomic nervous system can respond? When does aging become a stressor for which the autonomic nervous system cannot compensate? What are the cellular and molecular properties of the autonomic neurons altered by aging?

Current Project: hyper-excitability of the sympathetic nervous system

It is known that aging leads to an overactive autonomic system. This is observed as increased noradrenaline levels in plasma and as more frequent electrical firing from sympathetic nerves. Autonomic overactivity is involved in the development of hypertension, cardiovascular diseases, and urinary dysfunction. Nevertheless, the underlying changes that lead to an overactive autonomic system are not understood. Using electrophysiology, we discovered that isolated sympathetic motoneurons from old mice are hyperexcitable, as they fire more action potentials both spontaneously and evoked. We aim to determine which ion channels are underlying this hyperexcitability and characterize their differential biophysical properties. A second aim is to establish the effect that hyperexcitable postganglionic neurons have on the autonomic output and organ function. A third aim is to determine the mechanism by which aging alters ion channels. Addressing these aims will provide insight into the biology of aging and will offer potential therapeutics to treat age-related disorders.

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My name is Ming Xu. I am currently an Assistant Professor in University of Connecticut Health Center.
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Cellular senescence is one of the major players contributing to the fundamental aging process. My lab is leveraging novel mouse models and primary human cells as tools to examine the role and underlying mechanism of senescent cells in various conditions in mammals, and we aim to find new drugs to target senescent cells in order to alleviate a range of diseases as a group.

We are interested in understanding the heterogeneity of cellular senescence, investigating the role of senescent cells in various pathological conditions, and developing drugs to target these cells.

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Systemic depletion of the DNA repair endonuclease ERCC1-XPF causes the accelerated accumulation of spontaneous, oxidative DNA damage and senescent cells in mice, leading to their premature aging. Now we can begin to ask to what extent is their senescence and aging due to cell autonomous events (*i.e.,* DNA damage driving senescence in every cell?) or non-autonomous events (*i.e.,* senescent cells driving secondary senescence in non-damaged cells) by creating a series of tissue-specific mutants. We knocked-out *Ercc1* in differentiated myocytes, hepatocytes, podocytes, renal tubular epithelial cells, hematopoietic cells, lens epithelia, skin keratinocytes and CNS neurons to determine the impact on targeted cells/tissues and non-targeted tissues. I helped to characterize each of these novel strains of mice. The most interesting to pursue are the *Vav-iCre*$^{+/-}$*;Ercc1*$^{-/fl}$ mice, missing ERCC1-XPF in hematopoietic lineages. Not only do the mice rapidly develop characteristics seen in age-related immunological decline, but the mice are also the only tissue-specific mutant in which senescence and loss of tissue homeostasis occurs robustly in non-targeted tissues. Currently we are characterizing the *Vav-iCre*$^{+/-}$*;Ercc1*$^{-/fl}$ mice and the role of senescent immune cells in driving cell non-autonomous aging in this project. Recently, we have shown that pre-existing senescent cell burden conferred poor survival after coronavirus infection. Elimination of senescent cells either genetically or pharmacological treatment with senolytics improved survival.