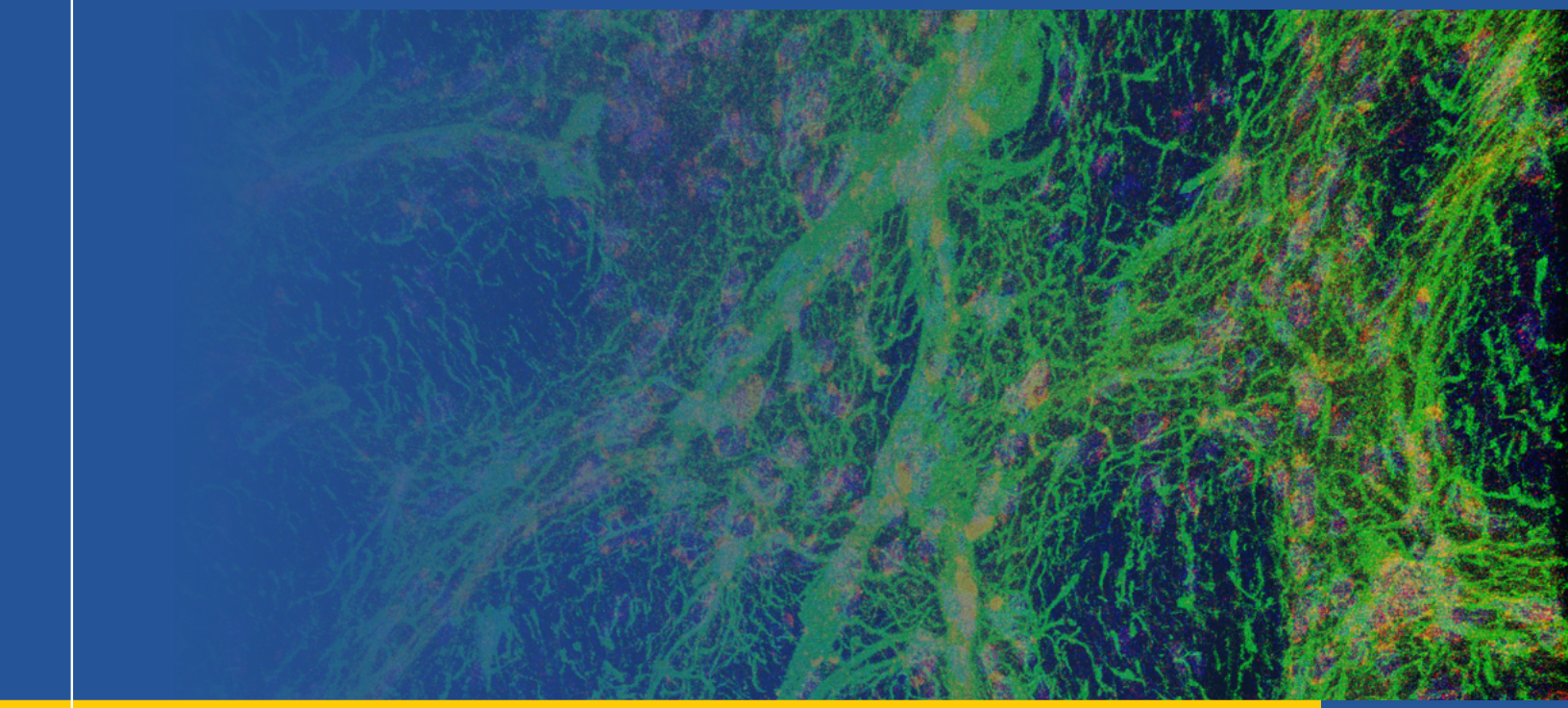
UC Irvine
Center for Neural Circuit Mapping

MARMO-AD
Marmosets as Research Models of Alzheimer's Disease

UNIVERSIDAD DE CHILE



2ND INTERNATIONAL CONFERENCE

# Unconventional Animal Models of Alzheimer's Disease and Aging (UAMAA)

## February 9 – 11 , 2026

8:30 a.m. – 5:00 p.m. PT

Sue & Bill Gross Nursing & Health Sciences,
Sue Gross Auditorium, UC Irvine, Irvine, CA

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# Code of Conduct

The CNCM and organizers are committed to providing a professional, welcoming, and safe environment free from harassment and discrimination of any kind so that all participants can take part in advancing science through research, education, and professional development in safe fashion. All participants in attendance need to comply with this Code of Conduct Policy and in doing so also agree to conduct themselves in a professional manner. Harassment includes verbal, written, or physical conduct that denigrates or shows hostile behavior to others, which (1) has the purpose or effect of creating an intimidating, hostile, or offensive environment; (2) has the purpose or effect of interfering with an individual's performance or ability to participate in events; or (3) otherwise affects an individual's ability to participate in events due to unwelcomed verbal or physical conduct which can adversely affect the environment, or results in a decision adversely affecting the individual based upon the their rejection of such conduct.

Violations of this Policy will be taken seriously and may result in appropriate action, including removal from the event.

UC Irvine School of Medicine
Center for Neural Circuit Mapping
2026 UAMAA CONFERENCE

# Welcome Message

On behalf of the Organizing Committee, it is our great pleasure to welcome you to the Second Unconventional Animal Models in Aging and Alzheimer's Disease (UAMAA) Conference, co-hosted by the University of California, Irvine Center for Neural Circuit Mapping (CNCM), MARMO-AD, and the University of Chile. We are delighted to have you join us in Irvine for what we anticipate will be an exciting meeting.

The inaugural UAMAA conference in 2023 was established to address a critical gap in aging and Alzheimer's disease research: the need to move beyond traditional laboratory models and to embrace a broader range of unconventional animal systems that capture essential biological features of aging, neurodegeneration, and resilience. By bringing together investigators working across species, disciplines, and methodological approaches, this conference series seeks to foster new conceptual frameworks, comparative insights, and collaborative opportunities.

This year's program showcases cutting-edge research spanning natural aging models, species-specific circuit and molecular organization, behavior and cognition, and disease-relevant phenotypes, alongside emerging technologies that enable cross-species comparisons at cellular, circuit, and systems levels. Through invited lectures, selected talks, and poster sessions, we aim to promote open dialogue around both the opportunities and challenges inherent in studying unconventional models of aging and Alzheimer's disease.

A central goal of UAMAA is to cultivate an inclusive and collaborative environment that supports early-career investigators, trainees, and interdisciplinary exchange. We hope this meeting will not only highlight exciting scientific advances, but also serve as a catalyst for mentorship, networking, and the development of new research partnerships that extend well beyond the conference itself.

We sincerely appreciate the encouragement and support provided by the National Institute on Aging program leadership throughout the preparation of this meeting. We gratefully acknowledge the strong institutional support that has made this meeting possible, including leadership and backing from the UC Irvine School of Medicine and the UC Irvine Office of Research, as well as the many faculty members, staff, and trainees who contributed to the organization of this event. In particular, we thank the CNCM leadership and administrative team for their dedication and attention to detail in planning and executing the conference.

Thank you for being part of UAMAA 2026. We look forward to stimulating discussions, new ideas, and lasting collaborations throughout the meeting.

Sincerely,

*Afonso Silva, Stacey J. Rizzo, Patricia Cogram, Bing Ren, and Xiangmin Xu*

# Meet Our Organizers

**Afonso Silva, PhD**
Endowed Chair in Translational Neuroimaging
Professor, Departments of Neurobiology & Bioengineering
Associate Member, Aging Institute
University of Pittsburgh School of Medicine

**Bing Ren, PhD**
Scientific Director and CEO, New York Genome Center
Professor of Genetics & Development
Biochemistry & Molecular Biophysics, Systems Biology
Columbia University Irving Medical Center

**Patricia Cogram, PhD**
Professor of Genetics
Institute of Ecology and Biodiversity
University of Chile, Chile

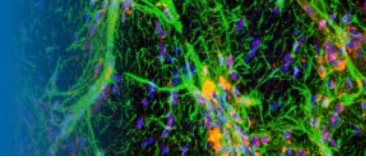
**Stacey Sukoff Rizzo, PhD**
Associate Professor
Departments of Neurobiology and Medicine, Aging Institute
University of Pittsburgh School of Medicine

**Xiangmin Xu, PhD**
Director, UCI Center for Neural Circuit Mapping
Chancellor's Professor, Department of Anatomy &
Neurobiology, School of Medicine
University of California, Irvine

# UAMAA 2026 Conference Schedule

Organizers: Afonso Silva, Stacey J. Rizzo, Patricia Cogram, Bing Ren, and Xiangmin Xu

| Day 1 - Monday, February 9 | |
|---|---|
| 7:45 – 8:30 a.m. | Breakfast and Registration |
| 8:30 – 8:35 a.m. | Introduction: Todd Holmes, PhD, Professor, Physiology & Biophysics (University of California, Irvine) |
| 8:35 – 8:50 a.m. | Opening Remarks: Aileen Anderson, PhD, Vice Chancellor for Research (University of California, Irvine) |
| **Session 1: Genetics and Genomics Research** | |
| 8:50 – 8:55 a.m. | Introduction: Xiangmin Xu *Session Chair* |
| 8:55 – 9:30 a.m. | Bing Ren, PhD *Co-Organizer* |
| 9:30 – 10:00 a.m. | Trygve Bakken, MD, PhD |
| 10:00 – 10:30 a.m. | Gregory Carter, PhD |
| 10:30 – 10:50 a.m. | Break |
| 10:50 – 11:05 a.m. | Nathan Zemke, PhD |
| 11:05 – 11:20 a.m. | Max Garduño |
| 11:20 – 11:50 a.m. | Christopher Glass, PhD |
| 12:00 – 1:00 p.m. | Lunch and Poster Session |
| 1:00 – 1:10 p.m. | Speaker Group Photo (Auditorium) |
| 1:00 – 1:30 p.m. | Poster Session Continued |
| **Session 2: New Models & Technologies I** | |
| 1:30 – 1:35 p.m. | Introduction: Patricia Cogram, PhD *Session Chair* |
| 1:35 – 2:10 p.m. | Patricia Cogram, PhD *Co-Organizer* |
| 2:10 – 2:40 p.m. | Vera Gorbunova, PhD |
| 2:40 – 3:10 p.m. | Ewan St. John Smith, PhD |
| 3:10 – 3:30 p.m. | Break |
| 3:30 – 4:00 p.m. | Donna M. Wilcock, PhD |
| 4:00 – 4:30 p.m. | George Perry, PhD |
| 4:30 – 5:00 p.m. | Adrian Oblak, PhD |
| 5:00 – 7:30 p.m. | On-site welcome reception for all attendees |



## Day 2 - Tuesday, February 10

| | |
|---|---|
| 7:30 – 8:30 a.m. | Breakfast |

### Session 3: New Models & Technologies II

| | |
|---|---|
| 8:30 – 8:35 a.m. | Introduction: Bing Ren, PhD *Session Chair* |
| 8:35 – 9:05 a.m. | Mathew Blurton-Jones, PhD |
| 9:05 – 9:35 a.m. | Jing Liu, PhD |
| 9:35 – 10:05 a.m. | Amantha Thathiah, PhD |
| 10:05 – 10:25 a.m. | Break |
| 10:25 – 10:55 a.m. | Christine Charvet, PhD |
| 10:55 – 11:25 a.m. | Elizabeth Head, MA, PhD |
| 11:25 – 11:40 a.m. | William Van Nostrand, PhD |
| 11:40 – 11:55 a.m. | Kiho Lee, PhD |
| 12:00 – 1:00 p.m. | Lunch and Poster Session |
| 1:00 – 1:30 p.m. | Poster Session Continued |

### Session 4: Neuroscience, Behavioral Biomarker & Intervention Development

| | |
|---|---|
| 1:30 – 1:35 p.m. | Introduction: Stacey Rizzo, PhD *Session Chair* |
| 1:35 – 2:05 p.m. | Kim Green, PhD |
| 2:05 – 2:35 p.m. | Bogdan Bintu, PhD |
| 2:35 – 3:10 p.m. | Xiangmin Xu, PhD *Co-Organizer* |
| 3:10 – 3:30 p.m. | Break |
| 3:30 – 4:05 p.m. | Stacey Rizzo, PhD *Co-Organizer* |
| 4:05 – 4:35 p.m. | Bernard Schreurs, PhD |
| 4:35 – 5:05 p.m. | Frank Longo, MD, PhD |
| 5:05 – 5:20 p.m. | Poster Presentation Awards |

## Day 3 - Wednesday, February 11

| | |
|---|---|
| 7:30 – 8:30 a.m. | Breakfast |
| **Session 5: AD Pathological Models** | |
| 8:30 – 8:35 a.m. | Introduction: Kim Green, PhD *Session Chair* |
| 8:35 – 9:05 a.m. | John Morrison, PhD |
| 9:05 – 9:35 a.m. | Jeffrey Kordower, PhD |
| 9:35 – 10:05 a.m. | Emilio Kropff, PhD |
| 10:05 – 10:25 a.m. | Break |
| 10:25 – 10:55 a.m. | Marina Emborg, MD, PhD |
| 10:55 – 11:25 a.m. | Kuo-Fen Lee, PhD |
| 11:30 – 1:00 p.m. | Lunch |
| **Session 6: Geriatrics and Aging Process Research** | |
| 1:00 – 1:05 p.m. | Introduction: Afonso Silva, PhD *Session Chair* |
| 1:05 – 1:40 p.m. | Afonso Silva, PhD *Co-Organizer* |
| 1:40 – 2:10 p.m. | Dirk Keene, MD, PhD |
| 2:10 – 2:40 p.m. | Roberta Marongiu, PhD |
| 2:40 – 3:00 p.m. | Break |
| 3:00 – 3:30 p.m. | Natalia Chermont PhD |
| 3:30 – 4:00 p.m. | Carol Shively, PhD |
| 4:00 – 4:15 p.m. | Hong-Wei Dong, MD, PhD |
| 4:15 – 4:30 p.m. | Marcelo P. Coba, PhD |
| 4:30 – 4:40 p.m. | Closing Remarks |

# UAMAA 2026 Conference Attendee Demographics

UC Irvine: 63 (46.7%); Non-UCI: 65 (48.1%); International: 7 (5.2%);

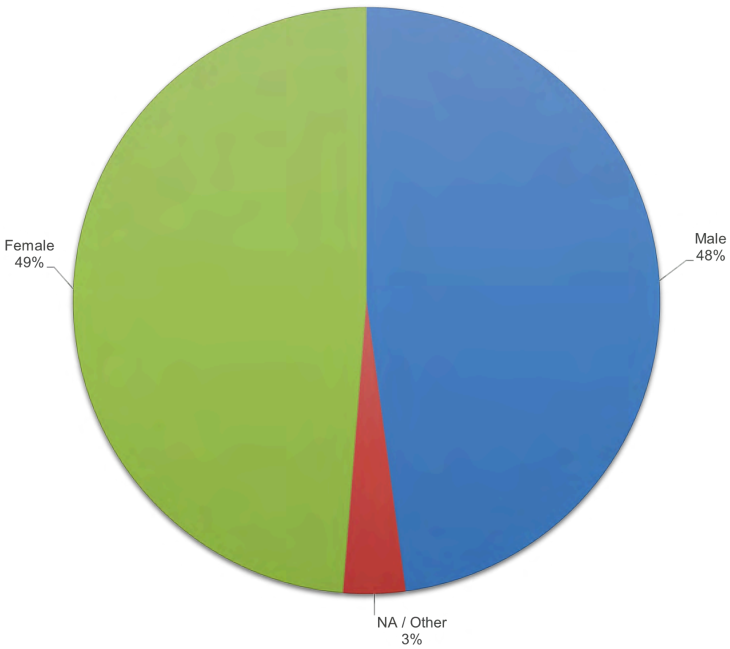
## Institutions / Organizations

Allen Institute for Brain Science
Apellis Pharmaceuticals
Arizona State University
Auburn University
City of Hope Beckman Research Institute
Complete Genomics
George Washington University
Guangzhou Institutes of Biomedicine and Health
Chinese Academy of Sciences
Icahn School of Medicine at Mount Sinai
Indiana University
Leloir Institute
Massachusetts Institute of Technology
Mayo Clinic
National Institute on Aging (NIA)
National Institutes of Health (NIH)
New York University Grossman School of Medicine
Quanterix
Saint Louis University
SRI International
Springer Nature
Stanford University
The George Washington University
The Jackson Laboratory
The Salk Institute for Biological Studies
The University of Texas MD Anderson Cancer Center
TissueVision
University of California (Davis, Irvine, Los Angeles, Riverside, San Diego, and Santa Barbara)
University of Cambridge
University of Chile
University of Massachusetts
University of Michigan
University of Missouri
University of Pittsburgh
University of Rhode Island
University of Rochester
University of Southern California
University of Texas at San Antonio
University of Washington
University of Wisconsin
University of Zurich
Wake Forest University
Weill Cornell Medical College
West Virginia University
Western University of Health Sciences

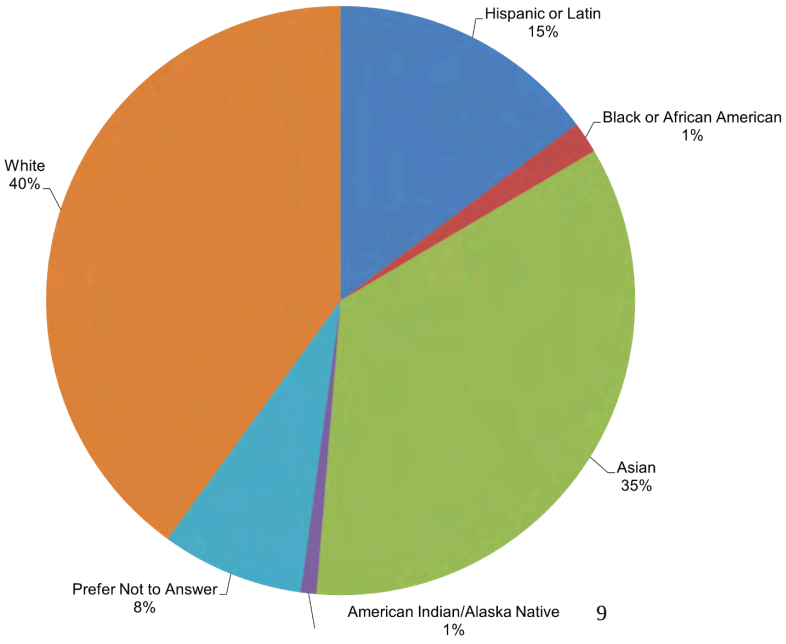
## Countries

Argentina
Chile
China
Germany
Switzerland
United Kingdom
United States

### Gender




### Ethnicity/Race

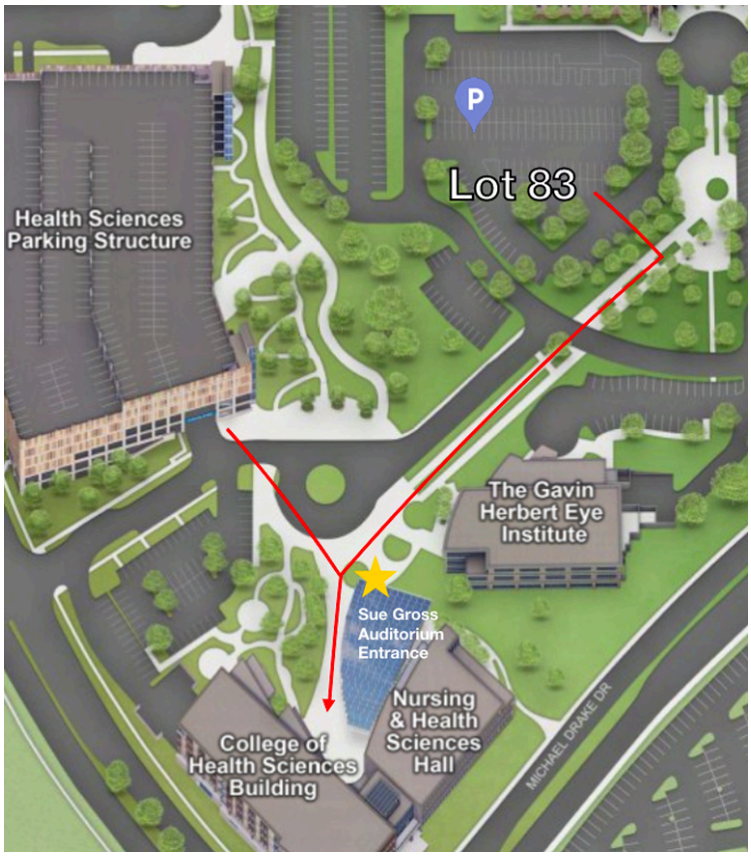


# Conference Venue

We are pleased to have this conference at The UC Irvine Susan & Henry Samueli College of Health Sciences (COHS) on the University of California, Irvine Main Campus. COHS is translating its tripartite mission to Discover. Teach. Heal. into the diverse healthcare workforce of the future and groundbreaking scientific discoveries. In robust synergy with UCI Health, the only university-based health system in Orange County, the college is transforming education, discovery, and patient care to benefit the region, state and nation. The main lectures will take place in Sue Gross Auditorium.


## Directions:

854 Health Sciences Rd, Irvine, CA 92617




## Parking

Parking is available via Park-by-Plate at the Health Sciences Parking Structure, located directly across from the Sue & Bill Gross Auditorium. UC Irvine also honors UC faculty/staff permit reciprocity for infrequent visits; please print and display your permit, or visit https://parking.uci.edu/permits/visitor/ for visitor parking details.

## Shuttle

The hotel offers a complimentary shuttle to and from John Wayne Airport (SNA), operating daily from 6:00 AM to 10:00 PM. Shuttle pick-up is at the Airport Transportation Center, located across from pillars 5 and 6.

*Important: Please be sure to board the "Sonesta Irvine John Wayne Airport Hotel"* shuttle*, as there are multiple hotel shuttles serving the airport.*

# Session 1:

# Genetics and Genomics Research


## Bing Ren, PhD

New York Genome Center & Columbia University Irving Medical Center


# “Single-cell insights into brain aging and Alzheimer’s disease – an epigenomic perspective”


Aging is the dominant risk factor for cognitive decline and Alzheimer’s disease (AD), yet how age-related molecular changes in the brain drive disease vulnerability remains poorly understood. In this presentation, I will discuss recent single-cell epigenomic studies that reveal how gene regulatory programs, chromatin architecture, and cellular states are rewired in the hippocampus. Using integrative single-cell transcriptomic, chromatin accessibility, DNA methylation, and 3D genome profiling of human hippocampi spanning the adult lifespan, we identify coordinated, cell-type-specific aging trajectories marked by neuroinflammation, mitochondrial dysfunction, and global erosion of higher-order chromatin organization. Aging is accompanied by profound remodeling of glial populations, including loss of synapse-regulating astrocytes and a dramatic switch of cellular state in microglia with inflammatory signatures. Extending these insights to Alzheimer’s disease, single-cell multimodal profiling of aging AD mouse models uncovers hyperactivation of the cGAS–STING pathway in microglia as a key mechanistic link between aging, amyloid pathology, and cognitive decline. Pharmacological STING inhibition restores regulatory programs, reduces amyloid burden, and improves memory. Together, these studies highlight aging-driven epigenomic reprogramming of brain cell types as a central driver of cognitive decline and AD, and point to innate immune pathways as promising therapeutic targets.

## Trygve Bakken MD, PhD

Allen Institute for Brain Science

# “Primate whole brain atlas for cross-species cell typing and tool design”

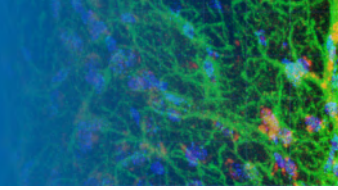
We are building a whole brain consensus cell type atlas for human, macaque, and marmoset using large scale single nucleus RNA seq, ATAC seq, and spatial transcriptomics. The atlas defines homologous cell types across major structures, including cortex and basal ganglia, and captures conserved spatial organization and regulatory programs. By combining these maps with validated enhancer-AAV tools, we identify conserved enhancer grammar that supports cross species genetic targeting. This framework links human cell types to primate and mouse models and enables selective access to shared and divergent neuronal classes for experimental and therapeutic studies.


## Gregory Carter, PhD

The Jackson Laboratory


# “Genetic and multi-omic analysis of marmosets as a model of aging and dementia”


The common marmoset provides a platform for translational studies of molecular, behavioral, anatomical, and neuropathological aging in an outbred laboratory animal. The MARMO-AD project is designed to track over 200 marmosets across lifespan, including both wild-type and genetically engineered animals that carry variants associated with Alzheimer’s disease in humans. Here we report on multi-omics analysis of postmortem brain tissue and genetic association studies of blood and imaging biomarkers. These findings potentially represent early molecular biomarkers of Alzheimer’s disease to be tracked longitudinally in an aging primate model.




## Nathan Zemke, PhD

University of California, San Diego


# “Single Cell Epigenome Profiling of the Aging Dog Brain Reveals Gene Regulatory Programs Associated with Neurodegeneration”


Aging is the primary risk factor for neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis. Yet, the most widely used model organism—mice—does not naturally develop Alzheimer’s-like pathology, underscoring the need for alternative models. Unlike mice, dogs spontaneously accumulate amyloid plaques and hyperphosphorylated tau with age, accompanied by cognitive decline that becomes prominent after 11 years of age. To define the aging gene regulatory programs in the dog brain, we generated single-nucleus profiles of gene expression, chromatin accessibility, DNA methylation, and 3D genome organization across three brain regions—the prefrontal cortex (PFC), temporal cortex (TC), and ventral hippocampus (vHIP)—from 24 animals spanning the canine lifespan (1–14 years). Aging was marked by sharp declines in GABAergic and glutamatergic neurons, astrocytes, oligodendrocyte precursors, and endothelial cells. Thousands of genes showed age-associated dynamics, including reduced expression of cell type–specific functions and increased neuroinflammatory signatures. Epigenomic analysis revealed age-dependent accessibility of bZIP transcription factor motifs, including AP-1 and CEBP, alongside widespread reprogramming of DNA methylation in glial cells of the TC and vHIP. 3D genome analysis across age revealed widespread restructuring that corresponded to age-dynamic transcriptional signatures. Strikingly, aging microglia exhibited robust activation of senescence-associated gene programs. Together, our multi-omic profiling of the aging dog brain reveals cell type– and region-specific transcriptomic, epigenomic, and genome organizational changes that parallel hallmarks of human neurodegeneration, establishing the dog as a powerful natural model for age-related cognitive dysfunction.

**Max Garduño**

University of California, Irvine

# "Amyloid-ß Neuropathology Across the *Octodon degus* Lifespan and it's Correlation to *Apoe* Genomic Variants"

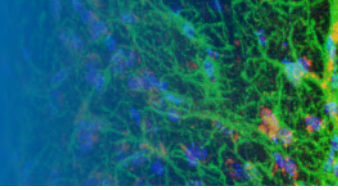
Alzheimer's disease (AD), the most common form of dementia, afflicts over 55 million people worldwide and has no cure. Despite substantial efforts from the scientific community, most AD clinical trials have failed, and treatments for this cognitively debilitating condition are limited. In response to this, the field has encouraged the investigation of organisms that naturally develop neuropathological features akin to those seen in human AD—something that does not naturally occur in mice without genetic engineering. The degu (Octodon degus), a long-lived rodent endemic to Chile, naturally exhibits key hallmarks of human AD, including amyloid-β plaques, phosphorylated tau, and neuroinflammation. Here, we quantified amyloid-β levels in the brains of degus across their lifespan (3 – 96 months). Cognitive states were gauged via burrowing behavior performance, an ethologically relevant test for degus due to the underground tunnels they inhabit in the wild. The resulting burrowing and neuropathological profiles were correlated to variants in the degu Apoe Mt4 locus. Our data show degus exhibit variable drifts into AD-like profiles as they age, similar to what is seen in humans. Upon further analysis, we find that by classifying degus according to their Apoe Mt4 genotype we are able to parse animals into three subpopulations exhibiting distinct temporal progression of AD-like features across their lifespan: the AD-like, intermediate, and Non-AD degus. These findings begin to untangle the degu's AD-like profile and identify naturally occurring subpopulations that could be used for AD and aging research. Our results emphasize the importance of utilizing genetically diverse (outbred) animal populations when studying polygenically-invoked diseases and highlight the promise of the degu as a translationally-relevant model for sporadic AD.

## Christopher Glass, MH, PhD

University of California, San Diego

# “Decoding microglia responses to amyloid pathology”

Microglia, the innate immune cells of the brain, adopt diverse phenotypes in the context of Alzheimer’s Disease that are alternatively linked to protective or pathogenic roles. A population of microglia associated with amyloid plaques, referred to as disease associated microglia (DAMs) or microglia-neurodegeneration (MGnD), are proposed to exert protective effects dependent on signaling by the triggering receptor expressed on myeloid cells 2 (TREM2). In mice, acquisition of the DAM/MgND phenotype in response to amyloid pathology has been proposed to progress from Trem2-independent to Trem2-dependent stages but the mechanisms driving these transitions at a transcriptional level have remained enigmatic. Here, we address this problem by intersecting the amyloid-responsive epigenomic landscapes of mouse and human microglia with transcriptional and epigenetic responses of macrophages to an in vivo model of sterile inflammation that induces core features of the DAM/MgND phenotype. We provide evidence for a general model in which activation of a common set of transcriptional regulators that includes members of the MITF/TFE and ATF3/AP-1 families functions to both establish the Trem2-independent phase of gene expression and to mediate a large fraction of the downstream transcriptional effects of Trem2 signaling. In parallel, we intersect the disease associated microglia phenotype associated with amyloid pathology in mice with age related changes in microglia gene expression in Degu.



# Session 2:

# New Models & Technologies I


## Patricia Cogram, PhD

University of Chile


# “Towards a Translational Model of Alzheimer's Disease: Advancing the Octodon degus as a Natural Platform for Drug Discovery”


This talk will explore how moving beyond traditional laboratory models and embracing animals that naturally develop Alzheimer’s disease–like pathology can transform our understanding of late-onset Alzheimer’s disease (LOAD). Species that show age-dependent cognitive decline and neuropathological features similar to humans offer not only greater translational validity, but also a unique opportunity to identify what is missing from current mechanistic models of Alzheimer’s disease and why many therapeutic strategies fail to translate. A central focus will be apolipoprotein E (APOE), the strongest genetic risk factor for LOAD in humans, and how natural variation in this gene across species can illuminate its pleiotropic roles in aging, lipid metabolism, and neurodegeneration. I will present recent work on the South American rodent Octodon degus, a long-lived species that spontaneously develops amyloid pathology, tau alterations, neuroinflammation, and age-dependent cognitive impairment. We have identified and published naturally occurring variants in degu Apoe at position 213 (E213E, E213Q, and E213K), revealing a new evolutionary dimension to APOE biology. I will integrate genetic, structural, and functional analyses of these variants, including comparative modeling of human and degu Apoe, their predicted effects on lipid handling. Decentering humans as the sole reference for Alzheimer’s disease and instead using natural models such as degus as evolutionary replicatescan reveal why certain deleterious variants persist, how aging reshapes the force of natural selection, and how these insights can be leveraged to build more predictive preclinical platforms for therapeutic discovery.

**Vera Gorbunova, PhD**

University of Rochester

# "Methionine sulfoxide reductase deficiency in Octodon degus and in humans with sporadic Alzheimer's disease"

Alzheimer disease (AD) and related dementias are devastating age-related proteinopathies. One of the main difficulties in developing treatments is the lack of animal models that accurately recapitulate sporadic human disease. Thus, despite enormous resources being committed to studying these diseases, there remains no effective cure. In this study, we set out to continue the development of Octodon degus as a potential model for sporadic AD. We observe that degus are systemically prone to amyloidosis and develop highly penetrant age-related conditions that closely resemble human disease. On peripheral histology, all aged degu pancreases had distorted and disrupted islets due to extensive filling with Congo-red-positive proteinaceous material. We also make similar findings in brain, where we observe reactive cellular changes and large aggregates of Aβ, particularly surrounding the cerebral vasculature. To identify causal contributors to this proteostatic decline, we performed a DIA-proteomics screen and found distinct abundance profiles of the methionine sulfoxide reductases (Msrs) between mouse and degu cortices. To further validate this finding, we used the fluorescent probe, MsrBlue, and found that Msr-activity is ubiquitously highest in mouse (cells, tissues, and brain), and that this difference becomes exacerbated with age. Subsequent analysis of tissues and cells from sporadic AD patients versus those of control patients demonstrated comparable deficits across and within species. Using Methionine Oxidation by Blocking (MObB), we confirmed global accumulation of in vivo methionine sulfoxide (MetO), and further find that MetO accumulation is particularly enriched on exposed methionines and known aggregation-prone proteins like APP. Overall findings provide key comparative insight into how different mammalian species maintain proteostasis, demonstrate the value of non-conventional models in studying human age-related disease, and provide novel avenues for therapeutic development in human AD and T2DM.


## Ewan St. John Smith, PhD

University of Cambridge


# “The (non-)ageing naked mole-rat cortex”


Naked mole rats (NMRs, Heterocephalus glaber) exhibit numerous signs of healthy ageing throughout their 35+ year lifespan, from maintained cardiac to displaying high resistance to conditions for which age is a risk factor, such as cancer and neurodegenerative disease. With an ever-ageing human population, the prevalence of neurodegenerative diseases is becoming more common, but our ability to prevent and treat such conditions is limited. Here, we sought to gain insight into how the cortex ages healthily by employing a multi-omic analysis of young and old NMR brains, combining proteomics, transcriptomics and single-nuclei RNA sequencing. Our results reveal unique age-related changes in the NMR brain. For example, comparing young and old NMR cortex, we observed minimal changes in senescence- and inflammation-associated genes, whereas in other species senescent cells accumulate with ageing and there are also signs of microglial activation and an inflammatory phenotype. By contrast, we did observe signs of neuronal ageing in NMR cortex, GABAergic neurons sharing a similar package of up- and downregulated genes as observed in published mouse datasets. These data represent the largest multi-omic characterisation of aged NMR brain to date and findings provide insight into the molecular basis of healthy brain ageing in NMRs. Functional studies are next required to validate our findings and determine the translational potential for developing therapies to combat age-related neurodegenerative diseases.


## Donna M. Wilcock, PhD

Indiana University


# “Hyperhomocysteinemia as a model of spontaneous small vessel disease in misce”

Our group have been studying the hyperhomocysteinemia (HHcy) mouse model of cerebral small vessel disease (cSVD) for a number of years. HHcy is induced by administration of a diet deficient of vitamins B6, B12 and folate (B9), and enriched with methionine. Collectively, this modification drives the accumulation of homocysteine. In C57BL6 mice aged 3 months placed on diet for a 14 week period were found to have multiple cortical and subcortical microbleeds, cognitive impairment, neuroinflammation (observed by microglial activation and increased expression of pro-inflammatory cytokines), and increased expression and activation of matrix metalloproteinases (MMPs) MMP2 and MMP9. When HHcy was induced in APP/PS1 amyloid depositing mice at 6mo of age for 6 months we found a shift in amyloid deposition from parenchymal to vascular in addition to the microbleeds and exacerbated inflammation.

In more recent studies of the HHcy model, we have found that there is reduced cerebral perfusion, determined by MRI-ASL, impaired neurovascular coupling, established by two-photon in vivo imaging, and apparent degeneration of neurovascular astrocytic end-feet. We have also now observed apparent microinfarcts as well as microbleeds. Interestingly, co-administration with atorvastatin with HHcy-inducing diet in C57BL6 mice, we found that there was protection from cognitive impairment and reduced neuroinflammation. Finally, in addition to the brain effects of HHcy induction, we have recently found that there are also retinal changes including microglial engagement with the vasculature, reduced vascular density, and visual deficits.

Overall, the induction of HHcy in C57BL6 mice recreates a number of known vascular changes associated with cSVD and provides a unique model for the study of specific mechanisms underlying cSVD pathologic hallmarks including microbleeds and microinfarcts.


## George Perry, PhD

University of Texas at San Antonio


# “Mitochondria Directed Oxidative Stress in the Human Brain in Alzheimer Disease and Aging”

For nearly four decades, our research has focused on dissecting the cytopathology of Alzheimer’s disease (AD) in human brain with the goal of developing a cure. We have used oxidative stress as a window to view and understand AD. Oxidative damage to sugars, proteins, lipids and nucleic acids increases in neuronal cytoplasm. The same neuronal compartment has increased redox-active iron and copper, which can catalyze oxidative damage, and likely derive from mitochondrial debris (in and outside lysosomes) including cytochromes, mitochondria specific prosthetic groups and mtDNA. Mitochondria show altered axonal transport, size distribution, energetics, fusion/fission, and degradation in AD that correlate with the extent of oxidative damage suggesting they are the origin. Synaptic mitochondria abnormalities correlate with synaptic vesicular changes. Surprisingly, amyloidβ and tau are quantitatively associated with reduced neuronal oxidative damage. Copper sequestration by amyloidβ blocks copper mediated oxidation of lipids and vitamin C indicating amyloidβ can be a protective response rather than the initiator of AD. Instead of being bound to amyloidβ, iron is present as magnetite crystals with super-paramagnetic properties and metallic iron, along with metallic copper. This is the first report of metallic iron and copper in humans. Not just amyloidβ, but also tau, may be protective responses induced in AD to maintain neurons with altered balance for decades. While these studies put oxidative stress at the center of AD, they also highlight a complexity of multifaceted alterations that are homeostatic and requires a deeper level of understanding in humans before an effective cure.


Supported by the Semmes, Lowe, and Kleberg Foundations.


## Adrian Oblak, PhD

Stark Neurosciences Research Institute, Indiana University

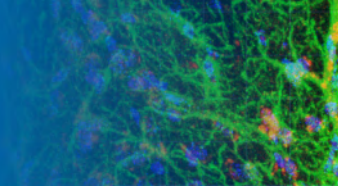

# "Expanding Preclinical Alzheimer Disease Models Beyond Traditional Mouse Strains"

The landscape of preclinical Alzheimer's disease (AD) research is undergoing a critical shift. For decades, the field has predominantly relied on transgenic overexpression models on conventional inbred mouse backgrounds, particularly C57BL/6J, to investigate AD pathogenesis and evaluate candidate therapeutics. While these models have yielded invaluable mechanistic insights, their limited genetic diversity, supraphysiological expression of familial AD genes (e.g., APP, PSEN1), and poor translation to human clinical outcomes have exposed fundamental limitations. There is an urgent need for more representative and scalable models that better capture the complex, polygenic, and late-onset nature of Alzheimer's disease as it occurs in humans.

This session will highlight emerging strategies to diversify and refine the preclinical modeling toolkit for AD. Central to this expansion is the MODEL-AD (Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease) consortium's development of LOAD models. These models utilize knock-in strategies, rather than overexpression, to introduce clinically relevant human risk alleles, such as APOE4, TREM2 variants, and others, on genetically defined and more diverse mouse backgrounds. Unlike traditional models, MODEL-AD LOAD mice display a more progressive and age-related disease course, offering improved translational potential for drug discovery pipelines.

Additionally, we will explore the integration of wild-derived mouse strains and Collaborative Cross (CC) lines into AD research. Wild-derived strains introduce genetic variants absent from classical laboratory strains, broadening the spectrum of biological responses to disease-related stressors. Meanwhile, the CC population, derived from a genetically diverse set of eight founder strains, provides a powerful platform for systems genetics and mapping complex traits relevant to AD phenotypes. These models better mimic the heterogeneity of human AD and allow for the identification of modifier genes and resilience factors not observable in standard inbred models.

By expanding the genetic diversity and construct validity of AD mouse models, these unconventional approaches pave the way for more predictive and mechanistically informative studies. They open new avenues for understanding gene-environment interactions, sex differences, and age-related modifiers of disease, ultimately supporting the development of more effective and personalized therapeutic interventions. This session will discuss ongoing efforts, recent breakthroughs, and future directions in the use of these next-generation preclinical AD models.



# Session 3:

# New Models & Technologies II

## Mathew Blurton-Jones, PhD

University of California, Irvine


# “Examining the interactions between human microglia and AD pathology in vivo with chimeric mouse models”

Microglia are strongly implicated in the development and progression of Alzheimer’s Disease (AD). Yet recent studies have shown limited homology between human and murine AD risk genes and important species-dependent differences in the response of microglia to beta-amyloid pathology. To address these challenges, we developed chimeric mouse models of AD by engrafting human iPSC-derived microglia into xenotolerant transgenic mouse models. By combining this approach with CRISPR gene editing, we can examine the impact of AD risk genes on human microglial function, the development and testing of novel microglial-targeting drugs, and the potential safety and utility of microglia cell therapies. Most recently, we have generated second generation chimeric models that enable complete humanization of the microglial niche and development of both amyloid and tangle pathologies. Using these models we have found that the combination of these two hallmark pathologies induce robust interferon and cytokine responses that are accompanied by adoption of a distinct microglial morphology. Ongoing studies are now using these models to explore the potential effects of microglia that express rare protective genetic polymorphisms.

**Jing Liu, PhD**

Chinese Academy of Science, China

# "Breaking Barriers in Pluripotency: From Guinea Pig Naïve Stem Cells to Panda Conservation and Minimal-Factor Reprogramming in Mice"

Capturing and controlling pluripotency across species remains a frontier in both regenerative medicine and conservation biology. Our work with the guinea pig—a species historically overlooked in stem cell research—established the first epiblast stem cells (gpEpiSCs) from post-implantation embryos. Building on this, we successfully reprogrammed gpEpiSCs into naïve-like pluripotent stem cells (gpNLCs) through a transgene-free, chemical induction protocol, tracked in real time using a pluripotency reporter. These gpNLCs displayed hallmark naïve features, enhanced chromatin accessibility, and trilineage differentiation potential, positioning the guinea pig as a new platform for disease modeling and developmental studies. In parallel, our efforts in species conservation led to the creation of the first giant panda induced pluripotent stem cells (iPSCs) using a non-integrating episomal system alongside a chemically defined culture medium tailored to panda cells. These iPSCs offer new avenues for studying panda biology and advancing reproductive technologies for endangered species. Complementing these studies, we demonstrated in mice that SALL4 alone is sufficient to reprogram fibroblasts into iPSCs, unveiling a streamlined approach to induced pluripotency and revealing novel interactions with key pluripotency factors like OCT4. Together, these cross-species breakthroughs redefine how pluripotency can be engineered—bridging regenerative medicine, species conservation, and the future of personalized cell therapies.

## Amantha Thathiah, PhD

University of Pittsburgh

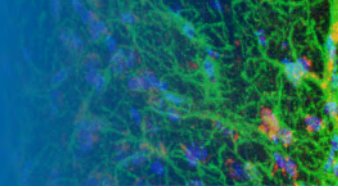

# “From Marmosets to Man: Building a Translational Platform to Advance Alzheimer's Disease Research”

Progress in preclinical Alzheimer’s disease (AD) research has been limited by model systems that fail to faithfully recapitulate human aging and AD neuropathology. The common marmoset (Callithrix jacchus), a New World non-human primate (NHP), exhibits aging trajectories, genetic heterogeneity, and complex social behaviors that closely resemble those of humans, making it a highly translational model for studying age-associated neurodegenerative diseases. Critically, marmoset studies enable the correlation of longitudinal in vitro analyses with in vivo assessments throughout the marmoset lifespan, an approach not feasible in human studies. Here, our objective was to perform a comprehensive ex vivo and in vitro characterization of our marmoset models to maximize the empirical knowledge gained for AD research.

We conducted immunohistochemical analyses of postmortem brains from familial AD and tauopathy marmoset models. In parallel, we employed cellular reprogramming, biochemical, imaging, and RNA sequencing (RNA-seq) approaches to generate and validate newly developed age-conserved marmoset in vitro models.

Ex vivo analyses reveal robust amyloid-β (Aβ), tau, and cellular pathology in AD and tauopathy marmoset brains. Using a well-established human direct reprogramming protocol, we generated age-conserved induced neurons (iNs) from marmoset fibroblasts. Unbiased comparative RNA-seq analyses of marmoset and human iN conversion trajectories identified significant species-specific differences. These findings informed targeted modifications in the reprogramming strategy, resulting in a robust, high-efficiency protocol for marmoset iN generation that improves cell survival and neuronal maturity while preserving AD-relevant protein expression, including amyloid precursor protein (APP)/Aβ and tau.

This integrated ex vivo and in vitro characterization establishes the marmoset as a powerful and translational model for AD research. This approach also provides a foundation for future longitudinal, mechanistic, and therapeutic studies aimed at elucidating novel cellular mechanisms underlying AD pathogenesis and accelerating the identification of disease-modifying therapies.

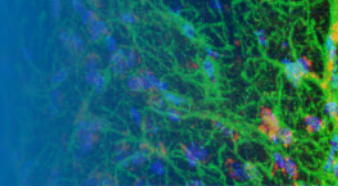



## Christine Charvet, PhD

Auburn University


# “A multi-species big data approach to translating time across the lifespan highlights cats are natural models of brain aging”

Identifying accurate biological age alignments across species is essential for choosing effective models of human aging and age-related disease. Without such alignments, we may miss species that naturally mirror later-life stages of human biology. We are acquiring a large-scale, multi-species dataset to generate age alignments and to identify model systems of aging. We are integrating veterinary health records (including blood work), brain imaging data (MRI), behavioral milestones, and other biomedical indicators. Our dataset includes more than 30,000 observations from over 2,000 individuals spanning species such as cats, chimpanzees, mice, and humans. Our analysis, thus far, has revealed that the pace of development and aging is not linear and varies substantially across species. We also found that not every species lives to the equivalent of a human octogenarian. For example, chimpanzees rarely live beyond their 50s, which roughly equates to humans in their 60s. In contrast, cats, particularly pet cats, reach ages comparable to human octogenarians. Also, aging cats share many biological changes seen in older humans, including brain atrophy. These findings highlight the potential of companion animals, especially cats, as natural models for studying human brain aging, and many opportunities for increased integration across human and veterinary medicine to advance the field of aging.




## Elizabeth Head MA, PhD

University of California, Irvine


# “Aged dogs as a Model for Human Aging and Alzheimer Disease: Results of a Prevention study”

Aged dogs (beagles) naturally develop cognitive decline in cognitive domains such as executive function and memory, while associative learning tasks remain intact. Structural magnetic resonance imaging scans highlight cortical and hippocampal atrophy with increasing age. Studies of neuropathology show that dogs accumulate human type beta-amyloid protein as extracellular diffuse plaques and in association with the vasculature (cerebral amyloid angiopathy). In combination, dogs naturally capture many features of human brain aging and early signs of AD neuropathology. We have completed several treatment studies in aging dogs that will be briefly reviewed. We are currently completing our first 5 year prevention study initiated in early middle age in beagles that captured longitudinal cognitive, neuroimaging and fluid (plasma/CSF) biomarker outcomes.


## William Van Nostrand

The University of Rhode Island


# “Gene editing in rats Produces a cerebral amyloid angiopathy model with distinct pathology and molecular signatures”


Cerebral amyloid angiopathy (CAA) is a common cerebral small vessel disease of the elderly and strongly associated Alzheimer’s disease and related disorders (ADRD). To date, most experimental animal models of CAA are transgenic mice that over express human amyloid ß-protein precursor (AßPP) harboring various mutations. Over the past several years we expanded to using rats as the species platform to develop transgenic models for CAA. However, most transgenic models possess many shortcomings including artificial over expression, insertional effects on the host genome, susceptibility to loss of transgene expression and genetic drift, and, importantly, being ‘sole cellular source’ providers of the transgenic protein. These limitations do not accurately reflect the true pathogenesis of disease. Recent advances in gene-editing in rodents offer the promise of providing a more relevant platform to model the true pathogenesis of CAA in humans. Here, we present a novel gene-edited rat model of CAA designated CRAßDI that involved ‘humanizing’ the Aß domain of the endogenous rat AßPP gene and incorporating the E22Q Dutch and D23N familial CAA mutations in the ‘humanized’ Aß. This new model results in production of human Dutch/Iowa CAA mutant Aß in all relevant cell types and correct anatomical regions where endogenous AßPP is expressed. Gene-edited CRAßDI rats develop capillary CAA and associated pathologies in multiple brain regions, similar to our earlier transgenic rTg-DI rats, but to a lesser degree. However, CRAßDI rats also present with robust CAA in the cerebellum and develop significant amounts of arteriolar CAA type-2, features largely lacking in transgenic rTg-DI rats. Transcriptomic analysis and comparison of expression of specific cell marker genes across numerous cell types revealed that the gene-edited CRAßDI rats present with a milder pro-inflammatory phenotype but with prominent vascular activation in contrast to transgenic rTg-DI rats. Hierarchical agglomerative clustering analysis identified four prominent, but distinct, differentially expressed gene (DEG) clusters in the gene-edited CRAßDI rats and the transgenic rTg-DI rats. Hub gene candidates in each cluster of each model suggests that the regulation patterns among DEGs differ substantially between the two CAA models. This divergence indicates that unlike the rTg-DI transgenic based model, which represents rapidly progressing, severe disease pathology, the CRAßDI model more faithfully reflects the chronic course of pathological CAA development observed in human cases, thereby providing greater opportunities for therapeutic intervention. CRAßDI rats provide a new model of CAA that more accurately reflects the pathophysiological development of disease in humans. This is one model in our suite of new cerebral small vessel disease models in our expanding MODEL-CSVD program.

**Kiho Lee, PhD**

University of Missouri

# "Swine models of Alzheimer's Disease at the National Swine Resource and Research Center"

Alzheimer's disease (AD) is the leading cause of death for people over 65. Although decades of research have identified pathways responsible for AD pathogenesis, no treatment that can reverse trajectory of the disease exists. Proper animal models reflecting phenocopies of AD are critical to deliver effective therapies to the clinic. Conventional animal models such as AD mouse models have assisted identifying key molecules involved in the disease progression; however, due to the differences in size and physiology, it is difficult to translate findings to the clinic. Swine models, on the other hand, offer similar size and physiology to humans and effectively mirror clinical outcomes of new treatments. At the National Swine Resource and Research Center (NSRRC), we have established multiple AD pig models reflecting signs of AD. Using genome editing tools, genes linked to the Amyloid Cascade Hypothesis are altered in these pigs. Specifically, genetically engineered pigs carrying modified APP or PSEN1 have been produced. Another AD pig model mimicking 5xFAD mouse model, which is a leading animal model to study AD pathology, has been developed. Initial phenotyping of the models illustrates that pigs lacking functional PSEN1 carry cognitive deficiencies and abnormal brain physiology as early as six months of age, demonstrating their relevance to study AD. Our ongoing efforts also focus on establishing swine models mimicking signs of sporadic AD. Since APOE4 allele has been identified to have the highest correlation to the progression of sporadic AD, we have designed swine models carrying human pathogenic APOE4 allele in their genome. These swine models are aimed to validate findings from conventional in vitro and animal models of AD and translate successful therapies to the clinic. The mission of NSRRC is to serve as the main bio-depository center for swine models and facilitate use of swine models for biomedical applications. These AD swine models are available to extend our understanding of the disease.

# Session 4:

# Neuroscience, Behavioral Biomarker & Intervention Development

**Kim Green, PhD**

University of California, Irvine

# "Generation of Humanized TREM2 and hTREM2-R47H Mouse Lines Reveals Enhanced Disease Pathogenesis in 5xFAD Mice"

The TREM2 R47H variant is a major genetic risk factor for late-onset Alzheimer's disease (LOAD). However, murine and human TREM2 share only 69% sequence homology, raising questions about whether the R47H variant functions identically in the murine protein. To address this, we generated humanized TREM2 (hTREM2) and hTREM2-R47H knock-in mouse lines, replacing the endogenous murine Trem2 sequence with the human counterpart. These lines were crossed with the 5xFAD model to evaluate the impact of the humanized variant on amyloid-beta (Aβ) pathology.

We compared six genotype groups (WT, WT;hTREM2, WT;hTREM2-R47H, 5xFAD, 5xFAD;hTREM2, and 5xFAD;hTREM2-R47H) at 4 and 12 months of age. Pathogenesis was assessed via immunohistochemistry (IHC) for plaque load, glial response, and neuronal damage (dystrophic neurites). Plasma neurofilament light chain (NfL) was measured as a biomarker of neurodegeneration. Additionally, we utilized CosMx Spatial Molecular Imaging to perform high-plex transcriptomic analysis of glial cell states at single-cell resolution.

Unlike previous models carrying the R47H variant in the murine sequence, 5xFAD;hTREM2-R47H mice exhibited a dramatic, age-progressive increase in plaque load across all brain regions, relative to 5xFAD;hTREM2 and 5xFAD mice. This exacerbated pathology correlated with increased neuronal damage, evidenced by elevated plasma NfL and dense clusters of dystrophic neurites. Characterization of the immune response revealed a profound microglial dysfunction: hTREM2-R47H microglia failed to encapsulate dense-core plaques, remaining in a ramified, "homeostatic-like" state. Spatial transcriptomics confirmed this, showing that hTREM2-R47H microglia failed to downregulate homeostatic genes (e.g., P2ry12, Csf1r, Tgfbr1, Tmem119) or upregulate MHC-related activation genes compared to hTREM2 controls. Notably, while murine-sequence R47H models showed transient effects at 4 months that disappeared by 12 months, the humanized model showed sustained, robust pathology.

Humanizing the TREM2 locus reveals that the R47H variant significantly impairs the microglial transition from a homeostatic to a disease-associated state, leading to uncontrolled plaque growth and neurotoxicity. These findings demonstrate that humanized TREM2 models are a more translationally relevant tool for investigating LOAD risk variants and developing therapeutic interventions.


## Bogdan Bintu, PhD

University of California, San Diego


# “Dissecting single cell Huntington's disease pathology using multimodal spatial transcriptomics"

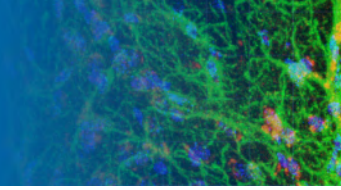

While CAG expansion in the Huntingtin gene (HTT) causes Huntington's Disease (HD), the impact of somatic repeat expansion and intranuclear huntingtin aggregation in the cell types of the HD human cortex is not known. Here, we introduce Multimodal MERFISH, a spatial transcriptomics approach that enables determination of single cell transcriptomes and single cell pathology measurements including huntingtin aggregates, and somatic CAG repeat expansion. In intact sections of human HD cortex, we identify selective vulnerability of both excitatory neurons in layers 5 and 6 as well as inhibitory neurons that are located throughout the cortex. Aggregate load does not predict neuronal vulnerability. Rather, while intranuclear HTT aggregates are most frequent in deep-layer excitatory neurons, they are found in only a small minority of the excitatory or inhibitory neurons that are preferentially lost. In contrast with reports in HD striatum, the frequency and extent of somatic CAG repeat expansion is found to be highest in excitatory neurons, with much reduced levels in vulnerable inhibitory neurons. Vulnerability is found to correlate more closely with large repeat expansions than aggregate burden. However, these two features are related: neurons with HTT nuclear aggregates undergo higher CAG repeat expansion and aggregate burden increases with repeat length, except in neurons with extremely large expansions (>200 CAGs), where HTT RNA becomes transcriptionally downregulated.


## Xiangmin Xu, PhD

University of California, Irvine


# “Modeling Spontaneous Late-Onset Alzheimer’s Disease in the Long-Lived Octodon degus Rodent Model”

Dementia and age-related cognitive decline represent urgent and growing public health challenges in an aging global population. While genetically engineered animal models have yielded important mechanistic insights into Alzheimer’s disease (AD), they inadequately capture the most prevalent form of the disorder, sporadic, late-onset AD. Addressing this gap, our multidisciplinary team has generated strong preliminary evidence establishing the long-lived Chilean rodent Octodon degus as a natural model of spontaneous, late-onset AD. Degus have an extended lifespan of approximately 6–8 years in captivity and naturally develop age-related neuropathological and behavioral features characteristic of AD. Importantly, they also exhibit inter-individual variability resembling the human condition, with only a subset progressing to cognitive impairment while others remain resilient into old age. This natural heterogeneity provides a unique opportunity to investigate mechanisms underlying both disease susceptibility and resistance. In this talk, I will present our ongoing efforts at the UCI Center for Neural Circuit Mapping to establish Octodon degus as a powerful model of human brain aging and late-onset AD using multimodal and multiscale approaches. In a comparative framework alongside mouse models and human brain studies, I will introduce new work mapping local and global neural circuits using genetically modified viral tracing and PET/MRI. I will also present single-cell and spatial multi-omics analyses of aging- and AD-related genomic and epigenomic changes in cognitively characterized young and aged degus. Together, these findings support Octodon degus as a promising and biologically relevant model for uncovering molecular, cellular, and circuit mechanisms of spontaneous late-onset AD, identifying novel therapeutic targets, and revealing resilience factors that protect against cognitive decline in aging brains.




## Stacey Rizzo, PhD

University of Pittsburgh


# “Investigating primate specific mechanisms of cognitive decline in Aging and Alzheimer’s disease: from marmosets to great apes”

Non-human primates (NHPs) share the greatest evolutionary conservation of genes, proteins, behaviors, brain anatomy and function with humans, relative to non-primate species. Importantly, because of their long lifespan, the timeline for close investigation of the behavioral changes that precede aging-related cognitive decline as well as biomarkers of disease is possible in NHPs. As part of our MARMO-AD consortium, we have established a comprehensive testing battery sensitive to detecting age-dependent cognitive decline across the lifespan in our colony of aging marmosets (Callithrix jacchus), and marmosets genetically engineered with mutations in the PSEN1 gene which confers early onset AD in humans. Beginning in adolescence, marmosets are trained using touchscreens through a battery of tests that captures a spectrum of cognitive domains sensitive to aging-related changes in spatial working memory (delayed match to position), behavioral flexibility and reversal learning (delayed non-match to position), recognition memory (trial unique delayed match to sample), attention (serial reaction time task), and episodic-like memory (paired associative learning task). Blood-based biomarkers are evaluated beginning at 6 weeks of age and at 6-month intervals with annual neuroimaging using 18F-PiB-PET to capture disease trajectory across the lifespan in relation to cognitive function. Ongoing studies in our colony have generated baseline and longitudinal cognitive data for more than 100 marmosets with more than 2000 biomarker samples analyzed to date. These laboratory studies allow us an exquisite resolution to study cognitive function prior to disease inception under highly controlled laboratory conditions with well documented health and medical records from birth throughout the lifespan. Expanding beyond this approach, we are now applying our established protocols to analyze biomarkers non-invasively from fecal extracts. Under these conditions we are able to study NHP species in both controlled laboratory environments and their natural free-ranging habitats including in great ape species, which are poised to reveal mechanisms that drive genetics x aging x environment susceptibility and resilience to disease progression and cognitive changes. These comparative evolutionary genomics studies across NHP species will enable the identification of mechanisms that underlie resilience and susceptibility to AD and cognitive decline, including the identification of molecular targets that may provide protection in individuals at risk for AD and dementia.


## Bernard Schreurs, PhD

West Virginia University


# “Feeding rabbits diets high in fat can alter cognition”

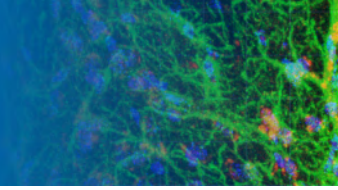

We examined the effects of feeding high fat with or without high sugar on rabbit eyeblink conditioning. Surprisingly, a diet containing fat in the form of soy oil and lard facilitated a rabbit's ability to discriminate between two tones paired with air puff. On the other hand, a diet high in fat in the form of lard and high in sugar retarded the rabbits' ability to acquire a simple trace eyeblink conditioning task especially among male rabbits. These animals showed clear signs of metabolic syndrome including visceral fat, glucose intolerance and high triglycerides. Accompanying the cognitive changes were significant metabolic and lipidomic changes in the hippocampus. Finally, feeding rabbits a low dose of cholesterol over two years which was expected to increase beta amyloid in the brain, did not affect trace eyelid conditioning.


## Frank Longo, MD, PhD

Stanford University


# “Translating a synaptic resilience and tau mechanism from cells to mice to Alzheimer’s patients”


Degeneration and loss of synapses are among the pathophysiological features with the highest correlation with loss of cognitive function in Alzheimer’s and related disorders (ADRDs). The p75 neurotrophin receptor (p75NTR) regulates a network of intracellular signaling elements that regulate fundamental mechanisms of synaptic integrity during development and in disease states. In addition, p75NTR regulates a broad network of intracellular degenerative signaling that has notable overlap with neurodegenerative signaling modules activated in ADRDs. We have developed orally bioavailable, small molecule-modulators of p75NTR that down-regulate its degenerative signaling and upregulated its trophic signaling, resulting in the ability to counteract synaptic degeneration promoted by pathological forms of amyloid and tau in in vitro and mouse models. The lead modulator, LM11A-31, has been applied to multiple ADRD mouse models with monitoring of synapse status and function. It has also been advanced through clinical studies including a phase 2a trial in mild-moderate AD. The trial findings, including proteomic and other biomarker measures, provide an opportunity to compare mouse model and human therapy outcomes.



# Session 5:

# AD Pathological Models


## John Morrison, PhD

University of California, Davis


# “Synaptic Health, Cognitive Aging, and Monkey Models of Alzheimer’s Disease and Related Dementias”

The presentation will briefly review key findings regarding synaptic health in the context of cognitive aging, as well as a more detailed discussion of rhesus monkey models of Alzheimer’s Disease and related dementias (ADRD), particularly a tau-based model that we have developed. We have identified multiple synaptic attributes in prefrontal cortex (PFC) of the rhesus monkey that are highly vulnerable to aging and their loss is strongly correlated with cognitive decline. We have also revealed several reflections of synaptic aging in rhesus monkey hippocampus that lead to age-related cognitive decline, and interestingly, the vulnerable synapses in hippocampus bear little resemblance to the patterns of vulnerability in PFC. Recently, we have developed and characterized both A🚲 oligomer (A🚲O) and tau based rhesus monkey models of AD. The A🚲O based model reveals A🚲O-induced synapse loss similar to that seen in aged monkeys with cognitive decline, with no neuron death. The tau-based model is directed at the degenerative phase of AD and requires the injection of a double human mutant tau construct (AAV1-(P301L/S320F) directly into the entorhinal cortex (ERC). The exogenous human mutant tau coaptates with endogenous monkey tau, leading to extensive tau-based pathology and neurodegeneration across the ERC connectome that is also evident through in vivo imaging and biomarkers in plasma and CSF. We have now analyzed multiple time points following the injection, with extensive degeneration occurring in hippocampus by 3 months that is exacerbated at 6 months. Interestingly, 6 weeks after injection reveals extensive presence of phospho-tau variants in perforant path terminal zones but minimal degeneration, suggesting that tau-based interventions should be administered between 6 weeks and 12 weeks to prevent neuron death. The tau-based model induces a robust neuro-inflammatory response by 3 months that is not apparent at 6 weeks. Recent in vivo behavioral and electrophysiological data demonstrate significant functional decline across the same time frame. Thus, we now have a very comprehensive assessment of the progression of pathology and related functional decrements across a 9 month time frame that will allow for precise testing of tau-based interventions.


## Jeffrey Kordower, PhD

Arizona State University


# "Tau pathology and co-pathologies in Parkinson's disease and nonhuman primate models"

The utility on any animal model, especially nonhuman primate models, is dependent upon how faithfully they mimic the hypotheses that are being tested. For Parkinson's disease (PD), the original definition centered around clinical motor manifestations which was found to be the result of striatal dopamine insufficiency secondary to degeneration of the nigrostriatal system. Following the discovery of mutations in the alpha synuclein gene followed by the presence of aggregated alpha synuclein in idiopathic PD patients, the definition of PD changed to include PD in a class of diseases called synucleinopathies. But this is not correct in all cases with some genetic forms of PD not expressing alpha synuclein at all. More importantly, it has become quite clear that PD, like other neurodegenerative diseases is a disease of co-pathologies.

We and others have demonstrated that phosphorylated tau is present in PD early in the disease process and is expressed in virtually 100% of PD patients over the age of 60. PD subjects over the age of 60 express up of 4 different pathologies in about 25 % of the cases and well over 50% of cases over the age of 70. These data will be discussed.

Our group has created a PD monkey model of copathologies that expresses alpha synuclein, tau, and amyloid with clinical deficits and pathological sequel greater in the copathology groups relative to monkeys receiving a single pathology alone. This will be discussed in the current lecture.

I will also discuss the use of aged monkeys to test specific hypotheses of early nigrostriatal dysfunction.


## Emilio Kropff, PhD

Institute Leloir, Argentina


# “Spatial representations in the hippocampus of Octodon Degus”

Octodon degus is a South American rodent that has attracted increasing interest as a model of aging and sporadic late-onset Alzheimer’s disease (AD). Spatial memory deficits have been reported in this species in association with advanced AD-like pathology or hippocampal lesions, underscoring its potential for investigating how hippocampal network function relates to behavioral performance across disease stages. Despite this promise, little is currently known about neural coding mechanisms in the degu brain.

Here, we characterize neuronal activity and local field potential dynamics in young, healthy animals during (a) spatial navigation in open-field environments and (b) a novel object location task. We show that CA1 place cells exhibit properties comparable to those described in rats and mice, albeit with overall lower levels of spatial information. Although we did not identify object cells—known to be rare in the rat hippocampus—the introduction of an object elicited novelty-driven exploration accompanied by increased CA1 neuronal activity. We also characterize local field potential oscillations across multiple frequency bands, as well as sharp-wave ripple complexes.

Together, these findings point to a shared organizational framework of hippocampal function and establish a foundation for future studies of age- and disease-related hippocampal dysfunction in this species..

## Marina Emborg, MD, PhD

University Wisconsin


# “Tau And Frontotemporal Dementia In Rhesus Macaques”


Frontotemporal dementia (FTD) is the most common dementia in patients under 60 years old. Mutations in Microtubule Associated Protein Tau (MAPT) gene, including the autosomal dominant R406W missense point mutation, have been linked to FTD. Rhesus macaques are an ideal nonhuman primate species to study the onset and development of FTD linked to tau mutations, as they share a >98% sequence homology with humans for the longest tau isoform and, like humans, they express 3R- and 4R- tau isoforms throughout the adult brain. Here we report our 5-year initial phenotypic characterization of rhesus carriers of an exact replica of the human MAPT R406W mutation (n=8, 3 female 5 males; 0-22 years old). Using a battery of behavioral, imaging and blood evaluations we identified a pattern of changes across these rhesus’ lifespan that resemble prodromal signs of FTD, including development of anxious behaviors, significantly decreased volumetric measures in the anterior cingulate, orbitofrontal and prefrontal cortices and increased blood levels of total tau, compared to age- and sex-matched wild type controls. We also detected increased binding of the tau radioligand [F18] RO948 in the anterior cingulate and prefrontal cortices of the eldest carrier. These rhesus macaque carriers provide a unique opportunity to systematically study biomarkers of genetic FTD-tau across the lifespan.

# Session 6:

# Geriatrics and Aging Process Research

**Afonso Silva, PhD**

University of Pittsburgh

# "Development and Characterization of a Marmoset Model of AD Based on Tau-Seeding."

The primary neuropathological hallmarks of Alzheimer's Disease (AD), beta-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated Tau protein, begin accumulating in the brain decades before clinical symptoms appear. This presents a challenge for modeling AD using short-lived animal models like mice. Since age and genetic variation are two of the most significant risk factors for AD, there is a critical need to develop improved animal models that incorporate genetic diversity, aging, and higher-order cognitive processes that more closely resemble humans. The common marmoset, a small non-human primate (NHP), is ideally suited to meet this need. Marmosets display social and cognitive behaviors that are more similar to those of humans. They live 12-13 years and are considered aged at eight years, a time when Aβ plaques and Tau NFTs naturally occur. Developing strategies to accelerate the onset of cognitive decline associated with the presence of AD's pathological hallmarks in marmosets could help establish an NHP model with better translational potential than rodent models. We injected the brains of aging marmosets with Tau to seed NFT formation and spread, speeding up the development of impairments across a range of AD-related sensorimotor, cognitive, and non-cognitive phenotypes linked to disease progression. We conducted comprehensive longitudinal evaluations of functional, behavioral, and clinical biomarkers of AD in these Tau-seeded marmosets. We mapped the spatiotemporal spread of NFTs using longitudinal quantitative PET and MRI imaging measures of Aβ, metabolism, and brain function, aligned with clinical assessments of AD patients. These measures were correlated with time-matched assessments of sensory, motor, cognitive, and non-cognitive phenotypes using a well-established behavioral and cognitive test battery. Additionally, we examined plasma levels of AD-related biomarkers (Aβ, Tau, NfL, GFAP) and monitored transcriptomic changes. Our work enabled the establishment and validation of a marmoset model of late-onset AD based on Tau seeding to accelerate the emergence of AD-related phenotypes. These marmosets are invaluable for translational research, helping to elucidate the pathogenic mechanisms of AD and contributing to the development of new therapies.


## Dirk Keene, MD, PhD

University of Washington


# “Human Neuropathology: Relevance and reference for modeling neurological disease”

Experimental systems/models are essential to understand fundamental biological pathways and mechanisms of brain aging, injury, and disease and to develop diagnostic strategies and therapeutic interventions. However, human neuroanatomy, connectivity, and neuropathology are essential to establish relevance of any observation; if it doesn’t exist in humans, it is probably not relevant to human biology/disease. In order to inform experimental systems/ models, observational studies of the human condition (which most human neuropathology research is by necessity) are essential. Retrospective studies of existing data and materials can be powerful, but prospective longitudinal studies in appropriately controlled representative cohorts that incorporate deep clinical phenotyping are the gold standard. Incorporation of potential biomarker resources including structured structured cognitive, motor, and behavioral endpoints, biometrics, neuroimaging, biofluids and other biospecimens, and molecular profiling compounds the value of these studies. However, the ‘ground truth’ for many human neurobiological processes and pathologies continues to require research of human central nervous system biospecimens/brains. While prospective cohort studies and clinical trials have grown in size and complexity over the past decades, in most cases human neuropathology continues to depend on traditional neuropathological processing and diagnostic approaches; modernization of neuropathological methods and approaches is essential to power discovery in well-characterized human cohorts and to inform experimental models. This includes incorporation of cutting-edge neuroimaging approaches, optimized tissue procurement, processing, and preservation strategies, and application of multimodal, multiomic and quantitative neuropathological analyses that extend knowledge gleaned from every human brain donor, in addition to baseline traditional neuropathological characterization. Accessibility to data and biospecimens in support of novel assessments and powerful analytical strategies maximizes the impact of these unique resources to inform experimental models, diagnostic strategies, novel therapeutics.

## Roberta Marongiu, PhD

Weill Cornell Medicine, Cornell University


# “Menopause as a Biological Trigger in Alzheimer’s Disease: Insights from Non-Canonical Mouse Models of Aging”

Alzheimer’s disease (AD) disproportionately affects women, who comprise nearly two-thirds of cases and exhibit faster progression and poorer response to current therapies. Yet, the biological mechanisms linking female aging processes to neurodegeneration remain unclear, largely because standard preclinical models conflate chronological aging with endocrine aging or rely on surgical ovarian ablation that fails to capture the complexity of natural menopause.

Here, we present an experimental framework that dissociates endocrine aging from chronological aging, using a novel, validated accelerated ovarian failure (AOF) mouse model induced by low-dose vinylcyclohexene diepoxide (VCD). Unlike ovariectomy, the AOF model selectively depletes ovarian follicles while preserving ovarian tissue, recapitulating human perimenopause hormonal fluctuations followed by postmenopausal estrogen decline. This enables mechanistic studies of endocrine aging decoupled from advanced chronological age.

To investigate how endocrine aging interacts with neurodegenerative vulnerability, we applied the AOF model to the J20 transgenic mouse model of AD, and compared behavioral, neuropathological, neuroinflammatory, and transcriptional outcomes in age-matched male, intact female, and AOF female groups. Endocrine aging markedly exacerbated AD phenotypes. AOF females exhibited impaired spatial learning and memory, increased hippocampal amyloid plaque burden, plaque-associated AT8-positive tau pathology, and pronounced microglial and astrocytic activation relative to intact females - at ages when intact females showed only modest pathology.

These results demonstrate that endocrine aging actively accelerates AD vulnerability by reshaping neuroimmune responses and promoting co-pathologies, rather than merely correlating with chronological decline. By decoupling ovarian aging from chronological aging, the AOF model highlights menopause transitions as critical drivers of disease trajectory—often overlooked in conventional aging paradigms.

This work underscores the need for sex- and menopause-specific models in AD research and supports incorporating female endocrine biology into experimental design and therapeutic strategies to address women's heightened vulnerability in late-life neurodegeneration.


## Natalia Chermont, PhD

University of California, San Diego


# “Space Environment-Induced Neural Aging in Human Brain Organoids: Modeling Alzheimer’s Disease and Neurodegeneration”


Human brain organoids derived from pluripotent stem cells offer a versatile platform for modeling neurodevelopment; however, they typically lack the features of aging that are crucial for studying neurodegenerative diseases. Our work leverages space environment-induced neural aging, a phenomenon that accelerates cellular senescence and neurodegenerative phenotypes in organoids, to model Alzheimer’s disease in a compressed timeframe. We investigate how the space environment modulates neuronal maturation, synaptic function, and network activity, revealing latent disease mechanisms that are not observable under standard culture conditions. This approach provides a powerful platform for understanding Alzheimer’s pathology and accelerating translational studies.


## Carol Shively, PhD

Wake Forest University


# "Early Alzheimer's Disease-Like Neuropathology and Functional Decline in Aging Vervet Monkeys"

Age-related neurodegeneration culminating in late-onset Alzheimer's disease (LOAD) begins in middle age, well before cognitive deficits. Most therapies target the disease after significant neurodegeneration when recovery of function is unlikely and currently unachievable with current therapies. Translational models are needed to understand etiology and identify modifiable risk factors and therapeutic targets early in the disease process, prior to loss of function. Here, we outline evidence from vervets (Chlorocebus aethiops sabaeus), an established model of aging, early AD-like neuropathology, and associated phenotypes. Our studies are unique in that they focus on mother-reared, middle-aged to old vervets of known age, that lived throughout life in their family groups in large, complex indoor-outdoor enclosures. This enriched environment supports brain and cognitive development, social interaction, and physical activity, all assessable in our laboratories. Aged vervets develop β-amyloid (Aβ) plaques and paired helical filament (PHF) tau immunoreactivity. Among middle-aged to elderly vervets, cerebrospinal fluid (CSF) Aβ42 and gait speed are inversely related to age and amyloid plaque density. Greater plaque and PHF-tau burden are associated with reduced glucose utilization and brain volumes in several brain regions. These neuropathologic changes are consistent with those observed in early AD. In our ongoing longitudinal study vervets exhibit aging-related declines in cognitive, physical, and social function which are critically interrelated. Those with accelerated physical decline also have accelerated cognitive decline. Likewise, executive function mediates the aging-related decline in social integration. Furthermore, aging is accompanied by reductions in MRI-assessed cortical thickness and gray matter volume, the latter predicting working memory at 1-year follow up. With aging comes increasing incidence of insulin resistance, prediabetes, and sometimes type 2 diabetes; worsening prediabetes predicts worse cognition at 1.5 years follow up. Development of novel fluid and imaging biomarkers provide opportunities for noninvasive assessment of neuropathology and efficacy of novel therapies. Early changes in AD include microtubule dysregulation. Using PET and a novel ligand ([11C]MPC-6827) developed at WFUSM, we have observed higher microtubule instability in older vervets which was associated with lower CSF Aβ42 levels. With another novel ligand ([18F]FC119S), uptake in Aβ-affected regions was negatively associated with CSF Aβ42/40, and positively correlated with CSF pTau181 and pTau181/Aβ42 in the temporal lobe, and CSF NfL in the anterior cingulate gyrus, parietal, and occipital lobes reflecting underlying amyloid accumulation and neurodegeneration. With MRI we quantified spinal CSF flow dynamics and found strong negative correlations with age and positive correlations with CSF Aβ42/40. These observations suggest that diminished CSF flow dynamics may be a valuable imaging biomarker for impaired amyloid clearance, reflecting early-stage AD-like pathology. Thus, aging vervets exhibit a coordinated suite of traits consistent with early AD and provide a powerful, naturally occurring model for LOAD in which relationships between risk factor modification and neuropathogenesis can be determined. We expect future studies to illuminate mechanisms underlying divergent neurocognitive aging trajectories and identify novel therapeutic targets and interventions that increase resilience to aging-associated neurodegenerative disease, particularly LOAD.

**Hong-Wei Dong**

University of California, Los Angeles

# "Development of microscopic imaging and AI-powered computational platform for large-scale characterization of AD-relevant pathology"

Alzheimer's disease (AD) is the leading cause of dementia and remains a major unmet medical challenge. Although amyloid-β deposition and tau aggregation are defining pathological features, AD progression involves complex, spatially organized interactions among neurons, glia, myelin, and neural circuits. A fundamental limitation in the field is the lack of whole-brain, cellular-resolution data describing how these pathological processes emerge, interact, and propagate across the brain over time. Most existing studies rely on bulk molecular analyses or regionally sampled histology, which obscure brain-wide patterns of vulnerability and circuit-level disruption.

Over the past decades, numerous mouse models have been developed to capture distinct aspects of AD pathogenesis, including amyloid-, tau-, APOE-, and glial-driven mechanisms. Despite their widespread use, there has been no systematic effort to acquire and analyze whole-brain microscopic imaging data across disease stages in these models. Such data are essential for linking molecular changes to anatomical degeneration and circuit dysfunction.

To address this urgent need, we are developing an integrated framework that combines whole-brain microscopic imaging with AI-based quantitative analysis and spatial molecular profiling. This approach enables high-resolution mapping of amyloid plaques, tau pathology, neurite degeneration, glial responses, myelin alterations, and connectivity-related changes across the entire brain. By integrating imaging-derived metrics with spatial transcriptomic and proteomic data, we identify region- and circuit-specific pathways associated with selective vulnerability and disease progression. This multiscale, spatially resolved strategy provides new mechanistic insight into AD pathogenesis and offers a powerful foundation for improving preclinical therapeutic evaluation.

**Marcelo P. Coba, PhD**

University of Southern California

# "Apoe genotype and vascular function in unconventional animal models of alzheimer's disease"

Vascular contributions to dementia and Alzheimer's disease (AD) are increasingly recognized. These findings have led to 'neurovascular hypothesis' of AD which holds that cerebrovascular dysfunction contributes to cognitive decline anddementia in AD. Apolipoprotein E4 (APOE4), the major AD susceptibility gene, exerts strong cerebrovascular toxic effects including accelerated blood-brain barrier (BBB) breakdown, and degeneration of pericytes, the BBB-associated cells that maintain BBB integrity. Recent studies have suggested that BBB breakdown is an early biomarker of human cognitive dysfunction, including the early clinical stages of AD. Our preliminary data show that APOE4 compared to APOE3 leads to an early disruption of the BBB molecular composition followed by dysregulation in multiple signaling mechanisms, which precedes synaptic and neuronal dysfunction and behavioral changes in mice. However, current work is based on the study of APOE knock-in variants in mice. Recently, a novel Apoe variant described in Octodon degus has been correlated with brain pathology and hallmarks of AD such as neuroinflammation, hyperphosphorylated tau and amyloid plaque, and therefore, proposing the degu to be an unconventional long-lived animal model of aging and Alzheimer's disease. However, nothing is known about a role of this new variant in vascular pathology in relationship to AD. Here we will present current advances towards the understanding of human and Degu APOE variants in cell-specific vascular function.

# Poster Abstracts

# Poster #1: M. Kumar et al.

## Rescuing a Lost Metabolic Function: AAV9-mGULO Restores Vitamin C Biosynthesis in Mice and Guinea Pigs

**Manish Kumar**, Luyuan Huang, Yusha Li, Lihua Zeng, Xiaoli Zhang, Zhang LV, Jing Guo, Rongping Luo, Haiyun Wang, Li Yi, Duanqing Pei and Jing Liu

South China Institute for Stem Cell Biology and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

The evolutionary loss of L-gulonolactone oxidase (GULO) creates an absolute dietary requirement for vitamin C (VC) and a genetic deficiency without a curative treatment. To reverse this metabolic defect, we engineered an AAV9-based gene therapy (AAV9-mGULO) to restore VC biosynthesis in-vivo. We evaluated efficacy in two stringent mammalian models: CRISPR-generated GULO KO mice and the human-relevant, naturally GULO-deficient guinea pig. A single administration reconstituted physiological VC levels across major organs, including liver, brain, and heart, quantified by LC–MS. Biochemical restoration translated into robust phenotypic benefit: treated guinea pigs showed 100% long-term survival with prevention of scorbutic pathology, while mice maintained healthy weight and metabolic status. Multi-system recovery was further supported by micro-CT imaging demonstrating restored bone mineralization and by neuro-histological analyses indicating preserved neuronal architecture and normalized cerebral epigenetic features. Together, these findings provide proof-of-concept that one-time gene therapy can durably correct a fixed evolutionary metabolic loss, establishing a platform for in vivo pathway restoration in genetic disease.

# Poster #2: H. Bai et al.

## Systems biology of brain aging and neurodegeneration: Peripheral biomarkers and modifiable drivers in a natural Alzheimer's disease model

**Huiru Bai**, Yulong Tang, Yiran Liu, Ruining Zhou, Kerry Obanion, Zhengdong Zhang, Hongbo Liu, Andrei Seluanov, and Vera Gorbunova

University of Rochester

Alzheimer's disease (AD) and related dementias (ADRD) are leading causes of disability and death in aging populations. Despite their increasing public health burden, there are no effective strategies for early diagnosis or prevention. A major barrier is the lack of natural animal models that spontaneously develop hallmark AD pathology. While most models rely on genetic manipulation, the Octodon degus, a long-lived rodent native to Chile, naturally exhibits age-associated features of human AD—including amyloid and tau accumulation, cognitive decline, and neuroinflammation—making it a powerful yet underutilized model for studying the systemic and molecular mechanisms of brain aging in a physiologically relevant context.

Here, I present a comprehensive systems-level characterization of aging in degus integrating behavior, lipid/metabolite profiles, and brain single-cell multi-omics. Across the lifespan (0.5–7.5 years), I generated hippocampal single-nucleus RNA-seq and ATAC-seq datasets, along with matched plasma and brain lipidomic and metabolomic profiles and detailed cognitive/social behavior assays. These data reveal coordinated age-related changes across molecular, cellular, and systemic levels, including immune activation, synaptic dysregulation, and alterations in metabolic and lipid pathways. A key cross-tissue signature emerging from the analysis is the dysregulation of cholesterol metabolism. LDL cholesterol levels increase with age in both brain and plasma and strongly correlate with transcriptional and behavioral readouts of cognitive decline. These findings suggest that LDL-associated metabolic pathways may represent modifiable contributors to neurodegeneration in a natural AD model. It provides novel insight into systemic drivers of brain aging and highlights plasma-based lipid signatures as potential biomarkers of early neurodegeneration. These results support the broader use of natural models to uncover evolutionarily conserved mechanisms of cognitive decline and to identify modifiable metabolic factors relevant to human AD.

# Poster #3: A. Butler et al.

## Plasma Adropin Predicts Decision-Making Performance in Aged Rhesus Macaques Assessed in Home-Cage and Relocation Paradigms

**Andrew A. Butler**, James L. Graham, Lesly C. Ceniceros, Ashlee M. Cruz, Ashley D. Cunningham, Riya Subedi, Anthony P. Brown, Nicolas Dai, Giovanne B. Diniz, Peter J. Havel, John H. Morrison and Erin L. Kinnally

Saint Louis University School of Medicine

Identifying peripheral biomarkers that predict vulnerability to age-related cognitive decline and neurodegenerative conditions is a major priority in aging and Alzheimer's disease research. Adropin is a circulating hepatokine that is also expressed in the brain and other peripheral tissues. High circulating adropin levels in humans are linked to activation of hepatic lipid metabolism, cardiometabolic stress responses, and paradoxically to a reduced risk of age-related cognitive decline. However, the relationship between circulating adropin levels and cognitive aging in nonhuman primate models has not been established. While rhesus macaques do not develop Alzheimer's disease per se, they exhibit age-associated amyloid accumulation, alterations in tau phosphorylation, cerebrovascular dysfunction, and cognitive decline, thereby modeling biological processes that confer vulnerability to neurodegenerative disease in humans. Here, we tested the hypothesis that adropin reflects individual differences in cognitive resilience in aging primates. We tested this hypothesis in a cohort of aged, nondiabetic rhesus macaques (mean age 19.1 years, SD 3.5 years; n = 175) studied using two complementary geriatric phenotyping paradigms. Testing was conducted either during brief relocation to a controlled testing suite or within the home cage. Decision-making performance was evaluated using two-, three-, and four-choice food selection tasks that measure decision latency and choice consistency across increasing choice complexity. Multivariate linear regression modeling was used to predict log-transformed plasma adropin concentrations from rates of behavioral optimization, defined by declines in decision latency and intra-individual variability as task complexity increased, while controlling for age, sex, housing condition, and study cohort. Behavioral optimization measures significantly predicted plasma adropin concentrations in the combined cohort ($R = 0.460$, $p < 0.001$), with contributions from reductions in response variability and decision latency. Notably, this relationship was observed only in animals assessed during relocation ($R = 0.544$, $p < 0.001$) and was absent in animals assessed during home-cage testing. The housing-specific nature of this association is consistent with circulating adropin reflecting cognitive resilience under conditions of novelty or stress, rather than baseline learning or memory capacity. Associations were independent of age and baseline task performance, indicating specificity for adaptive decision-making processes rather than generalized motor slowing. Together, these findings support circulating adropin as a translational biomarker of cognitive vulnerability and highlight the aged rhesus macaque as a powerful model for integrating cardio-metabolic signaling with behavioral phenotyping relevant to human cognitive aging.

# Poster #4: J. Chiu et al.

## Single Cell Profiling of Octodon degus Reveals Gene Regulatory Programs Associated With Alzheimer's Disease-like Phenotypes.

**Jeffrey H. Chiu**, Nathan Zemke, Cuiling He, Bing Yang, Weronika M. Bartosik, Pik Ki Lau, B. Maximiliano Garduño, Micheal Miller, Claudio Urra, Eric Velazquez, Zhiqun Tan, Nicole Berchtold, Patricia Cogram, Chris Glass, Bing Ren, and Xiangmin Xu

Prior research has identified the Chilean rodent Octodon degus (degu) as a promising unconventional model for Alzheimer's disease (AD), as aged, behaviorally deficient individuals exhibit AD-like protein aggregates—including amyloid-beta plaques, hyperphosphorylated tau, and neurofibrillary tangle-like structures. Behavior is assessed through burrowing performance. To elucidate the gene regulatory programs underlying this pathology, we generated single-nucleus, multi-omic profiles of gene expression, chromatin accessibility, DNA methylation, and 3D genome organization from the dorsal hippocampus and prefrontal cortex of 40 behaviorally phenotyped degus (14 young, 26 old). We mapped transcriptional and epigenetic changes associated with aging and behavioral impairment across cell types. Surprisingly, transcriptional changes linked to burrowing deficiency were pronounced in young animals but minimal in the old cohort. Furthermore, differentially expressed genes in young, impaired degus were enriched for known AD-associated genes. We also identified putative AD-associated enhancers and distinct methylation dynamics correlated with cognitive decline. AD- and age-associated putative enhancers were enriched in regions displaying 3D genome restructuring across age and burrowing behavior. Our study reveals transcriptomic, epigenomic, and 3D genome signatures in the degu that reflect human AD pathology, underscoring its role as a powerful model organism for AD research.

# Poster #5: D. Chusyd et al.

## From the Savanna to Senescence: Insights into Neurodegeneration in Elephant Brains

**Daniella E. Chusyd**, Madison Hillegas, Melissa K. Edler, Patrick R. Hof, and Chet C. Sherwood

Indiana University

Elephants share several life history traits with humans, including comparable lifespans and complex cognitive skills, such as strong long-term memory, advanced problem-solving abilities, and elements of theory of mind. Matriarchs lead until death, and older elephants maintain centrality and play critical roles in decision-making and knowledge transmission. While observational evidence suggests cognitive resilience with age, whether elephants develop neurodegenerative diseases remains unclear. To begin to address this question, we examined the anterior cingulate cortex (ACC) of one female African savanna (46 years) and two female Asian elephants (62 and 71 years). Brain sections were Nissl-stained and immunohistochemically labeled for tau protein (AT8) and a marker of microglia (IBA1). Neuron, microglia, and tau pathology densities were obtained using stereological methods. Tau-positive neuropil threads and pretangles were sparsely observed in all three elephants, though pretangles were extremely infrequent in the youngest individual (46 years). Neurofibrillary tangles (NFTs) were observed in the two oldest elephants (62 and 71 years), although the tau burden (percent of total tau-positive neurons relative to total neurons) was well below one percent (~.10) of neurons. The occurrence of tau pathologies in the older elephants involved both pretangles and NFTs, but did not demonstrate a predominance of NFTs. Notably, total tau burden remained significantly lower than what is typically reported in elderly human brains. Overall neuron density increased with age in the sample, consistent with age-related shrinkage of dendritic and other neuropil components. IBA1 was predominantly expressed in intermediate microglia across all ages, suggesting limited age-related changes in microglia activation for this pilot sample. Ongoing analyses include quantification of Aβ40 and Aβ42 plaque area and expansion of the sample size across ages. These preliminary findings suggest changes in the ACC, including tau pathology, which is consistent with both normal aging and possible early neurodegeneration, although at levels that are substantially lower than reported in humans. These data are the first to suggest elephants may develop some age-related neuropathology but also resilience, an intriguing finding given the importance of cognitive function in older elephants for social cohesion and survival. Future work will expand sample size to assess prevalence and ecological relevance of neurodegenerative changes in aging elephants.

# Poster #6: D. Cribbs et al.

## Development of a Rapid Cerebral Amyloid Angiopathy Model to Investigate the Adverse Cerebrovascular Responses to Anti-Abeta Immunotherapy

**David H. Cribbs**, Christian Crouzet, Jihua Liu, and Bernard Choi

University of California, Irvine

The initial preclinical studies exploring increases in vascular Aβ and microhemorrhages induced by anti-Aβ immunotherapy used large cohorts of very old mice (20 to 25 months of age) with substantial amyloid deposition and required 2 months of passive immunotherapy to achieve significant microhemorrhage accumulation. Thus, developing new models that better facilitate the investigation of adverse cerebrovascular responses classified as Amyloid Related Imaging Abnormalities (ARIA), ARIA-E edema, and ARIA-H microhemorrhages in response to passive anti-Aβ immunotherapy within a reasonable time frame is highly desirable. In our initial study, 8-10-month-old 5XFAD.WSB.EiJ female mice received a single IP injection of 3D6.IgG2a anti-Aβ antibody (7.0 mg/kg) and were sacrificed 36 hours later. Control mice received IgG2a(k) isotype control (7.0 mg/kg, BioXCell). Retro-orbital (RO) injection of Lectin-Dylight-649 was used to label cerebral blood vessels, and RO injection of Evans blue and anti-fibrinogen/fibrin immunostaining were used to assess loss of blood-brain barrier (BBB) integrity. Amyloid plaques and cerebral amyloid angiopathy (CAA) were labeled with Amylo-glo RTD, and H&E staining was used to detect vasculitis/angitis. Anti-IBA1 and anti-GFAP immunostaining were used to monitor gliosis. Anti-Mac2 (Galectin-3) was used as a marker of peripheral cell infiltrates (monocyte/macrophages) into the mouse CNS. To investigate complement activation in response to 3D6.IgG2a dosing, we used antibodies against C1q, C3b/iC3b/C3c, C5b-9. In our second study, we focused on the temporal sequence of adverse events following a single dose of 3D6.IgG2a by using earlier time points (12, 24, 36 hours). In the 5XFAD mice on a WSB/EiJ background, there was a progressive increase (F1, F2, & F3 generations) in CAA in the cortex and the meninges. Remarkably, we observed striking strain differences with 5XFAD.C57B/6J mice being resistant to 3D6.IgG2a at all timepoints, while 5XFAD.WSB.EiJ brains showed modest surface lesions at 12 hours, prominent hemorrhages by 24 hours, and distress signs in the mice by 27-36 hours. Considerably more Evans blue and fibrin leakage was observed in the 5XFAD.WSB.EiJ mice than in the 5XFAD.C57B/6J mice at 12 hours and 24 hours post 3D6.IgG2a administration. In the 5XFAD.WSB.EiJ mice, anti-Mac2 peripheral cell infiltration was observed at 24 and 36 hours, and there was a progressive increase in complement deposition and activation, which was not observed in 5XFAD.C57B/6J mice. In this study, we first crossed 5XFAD mice onto the WSB/EiJ wild-derived inbred strain to leverage its unique vascular phenotypes when human APP is overexpressed. Secondly, we chose the mouse 3D6 monoclonal anti-Aβ antibody because its humanized version, bapineuzumab, has previously been shown to reduce Aβ plaque pathology in patients, and to induce ARIA-E and ARIA-H. Finally, we selected the Fc heavy chain IgG2a isotype for our 3D6 antibody to take advantage of the robust complement fixation and strong proinflammatory activating FcgR-mediated responses associated with the IgG2a isotype. The 5XFAD mouse model on the WSB.EiJ background allows significantly younger mice and smaller cohorts to be used to investigate adverse cerebrovascular responses to anti-Aβ immunotherapy. The serious adverse responses to 3D6.IgG2a in the female 5XFAD.WSB mice appear quite similar to the rare serious AEs and even deaths that have occurred in human patients receiving amyloid immunotherapy. Thus, we believe that the novel preferential CAA deposition and the loss of vascular integrity phenotypes observed in APP transgenic mice on the WSB/EiJ background may represent a valuable mouse model for studying the adverse cerebrovascular responses to antibodies targeting CNS amyloid.

# Poster #7: A. Gillan et al.

## Constructing a High-Resolution 3D MRI-Based Brain Atlas of Octodon degus for Aging and Alzheimer's Disease Research

**Arjan Gillan**, Andy Thai, Christopher Liang, Yujia Li, Patricia Cogram, Andre Obenaus, Jogeshwar Mukherjee, Gultekin Gulsen, Gopi Meenakshisundaram, B. Maximiliano Garduño, and Xiangmin Xu

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Alzheimer's disease (AD) is the most common form of dementia, yet effective treatments remain limited, and no definitive cure exists. Although mice are the most widely used animal model in neuroscience research, they do not naturally develop the spectrum of pathologies characteristic of human AD, limiting their translational relevance. The Octodon degus, a long-lived, diurnal rodent that can spontaneously develop human AD-like neuropathology's, offers a promising natural model for studies of aging, neurodegeneration, and Alzheimer's disease. However, the utilization of degus in neuroscience research has been constrained by the shortcomings of existing degu brain atlases. These preliminary degu atlases lack reliable stereotaxic coordinates, suffer from low spatial resolution due to large inter-slice intervals, provide limited multi-planar (coronal, sagittal, and horizontal) representations, and offer incomplete anatomical delineation and labeling of brain regions and subregions. Together, these limitations hinder experimental precision and reproducibility in degu brain studies.

Here we present our progress in the construction of a high-resolution 3D atlas of the degu brain. Brains were obtained from wild-caught, outbred Chilean degus (N=4), spanning adult and advanced age cohorts (2 and 7 years old, respectively). Animals were transcardially perfused, and intact heads were post-fixed in paraformaldehyde (PFA) prior to imaging to preserve anatomical integrity. High-field magnetic resonance imaging (MRI) was performed at the University of Calgary using a 9.4T MRI system achieving an isotropic voxel resolution of 50 μm. Following image acquisition, skull stripping was performed, and the brain structures were isolated from young and aged degus from MRI scans via ITK-SNAP software. To achieve detailed anatomical parcellation, the degu MRI datasets were registered onto the established rat Waxholm atlas, generating a high-resolution, annotated atlas adapted for the degu brain. The quantitative analysis of age-associated volumetric changes was assessed for brain regions of interest including hippocampal and neocortical subregions. An additional group of young and aged animals (N=12; 0.5 and 4.5 years old, respectively) from our UCI degu colony underwent in-vivo micro-computed tomography (μCT) imaging to characterize age-related skull morphology and complement our MRI-based atlas.

Future work will further enhance our atlas by integrating light-sheet or serial two-photon tomography of the degu brain with tissue clearing and immunolabeling, enabling incorporation of cell-type–specific molecular information. This multimodal framework will produce the most comprehensive and anatomically precise degu brain atlas to date, facilitating wider adoption of Octodon degus as a critical model for neuroscience, aging, and Alzheimer's disease research.

# Poster #8: C. Glavis-Bloom et al.

## The common marmoset as a translational model for cognitive aging

Casey R. Vanderlip, Shelby R. Dunn, Payton A. Asch, John H. Reynolds, and **Courtney Glavis-Bloom**

Salk Institute for Biological Studies

Aging is the predominant risk factor for cognitive decline and neurodegenerative diseases such as Alzheimer's disease, but cognitive aging in humans is highly variable; some individuals experience widespread decline, while others remain cognitively stable for decades. This variability exists not just across individuals, but also across cognitive domains, with those dependent on the prefrontal cortex and hippocampus especially vulnerable and among the earliest and most severely impacted in Alzheimer's disease (AD). Translationally relevant models are crucial for understanding the mechanisms that drive divergent cognitive aging outcomes and differentiate healthy aging from pathological decline. The common marmoset (Callithrix jacchus) has emerged as an advantageous non-human primate model for this work due to shared behavioral, neuroanatomical, and age-related neuropathological features with humans. Critically, their short lifespan enables a longitudinal approach to studying aging as a process that unfolds over extended durations of time, and that is highly variable amongst individuals. Despite their growing popularity as a model, robust cognitive phenotyping of marmosets, particularly as a function of age, across multiple cognitive domains, and longitudinally, is lacking. To address these major limitations for the development and evaluation of the marmoset as a model of aging, we developed MamoCog, a comprehensive touchscreen-based neuropsychological test battery for marmosets that mirrors diagnostic tests in humans. We administered MarmoCog twice per year for six years to a large cohort of marmosets ranging in age from young adult to geriatric. Our results show that marmosets exhibit marked domain-specific and individual variability in cognitive aging; some animals decline across multiple domains, others in just one, and some show no decline at all. When decline occurs, it is most severe in domains dependent on the prefrontal cortex and hippocampus. These patterns closely mirror human cognitive aging. Concurrent longitudinal collection of biosamples enables us to directly link cognitive aging to underlying biology. Together, these approaches establish the marmoset as a powerful model for identifying the age-related biological changes that drive individual differences in vulnerability to neurodegenerative disease, and for bridging the gap between normative aging and disease-related trajectories.

# Poster #9: G. Gomez et al.

## Repeated Closed Head Injuries Alter Brain Bleed Patterns Elicited by a Single Injury in Juvenile Male Mice

**Gustavo A. Gomez**, Akanksha Lakkapragada, Brandon Vo, Paul Territo, and Andre Obenaus

University of California, Riverside

Mild Traumatic Brain Injuries (mTBI) are known to lead to chronic physiological defects and are prognosticated to contribute to the development of Alzheimer's Disease and Related Dementias (ADRD) symptomology, with repeated mTBIs exacerbating these effects. We investigated the occurrence of intracerebral bleeding between mice subjected to a single closed head injury (sCHI) or repeated CHI (rCHI). Male and female juvenile C57BL/6J mice underwent either sham treatment (anesthesia only), sCHI, or rCHI. We delivered the first CHI to the left somatosensory cortex on postnatal day 17. rCHI involved a second hit to the ipsilateral prefrontal cortex 3, 5, or 7D (days) later. Brain volumes and bleeding were evaluated ex vivo by MRI (T2-weighted imaging, Susceptibility Weighted Imaging). rCHI groups demonstrated increased weight and decreased righting and exploration time, immediately following injury. Whole brain volume was lowest in 3D rCHI mice and highest in the 7D rCHI cohort in males, with no changes observed in females. In mice that underwent CHI, 72% exhibited bleeding on MRI, with more bleeding seen in females (95%F vs 56.6%M). Bleeding volume standardized by cerebrum volumes was not statistically significant across injury groups, but the 5D rCHI group had the highest mean. Intriguingly, bleed distribution was shifted posteriorly in all rCHI groups relative to sCHI, particularly in males. Moreover, all groups exhibited more bleeding ipsilateral to CHI's. The data suggest that rCHI results in a posteriorly shifted, expanded bleed distribution relative to sCHI, which may accelerate the transition to neurodegeneration and blunt long-term recovery.

# Poster #10: S. Govindarajan et al.

## High-resolution behavioral phenotyping of cognitive aging in Octodon degus using motion sequencing

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Age-related neurodegenerative disorders such as Alzheimer's disease (AD) are marked by progressive cognitive decline, yet subtle behavioral alterations often precede overt impairment by months or years. Conventional rodent behavioral assays frequently lack the temporal resolution and sensitivity required to detect these early changes and are susceptible to experimenter bias. Here, we investigate age-associated shifts in exploratory behavior in Octodon degus, a long-lived, diurnal rodent that naturally develops AD-like neuropathology without genetic manipulation. We applied Motion Sequencing (MoSeq), an unsupervised machine-learning framework for sub-second behavioral analysis, to quantify spontaneous behavior across the adult lifespan of degus, from early adulthood (~10 months) to advanced age (>4.5 years). Using depth-camera recordings, MoSeq decomposed continuous behavior into discrete, sub-second behavioral "syllables" reflecting posture dynamics, movement transitions, and latent neural state organization. To ground these high-resolution behavioral features in ethological relevance, we complemented MoSeq analyses with burrowing assays, a validated measure of cognitive and functional integrity in degus. Across age timepoints, we observed systematic remodeling of behavioral composition and syllable usage, revealing age-dependent changes in both behavioral structure and organization that are not readily captured by traditional assays. Together, these analyses provide an unbiased framework for identifying early, ethologically meaningful behavioral signatures of cognitive aging in Octodon degus, and highlight the utility of machine-learning-based behavioral phenotyping for aging and Alzheimer's disease research.

# Poster #11: L. Harvey et al.

## Lifespan Development and Colony Management of Octodon degus for Aging Research

**Layla Mariela Harvey,** Satya Govindarajan, Yuta Sato, Tiago Osinalde, Robert Deacon, Patricia Cogram, Carolyn Bauer, B. Maximiliano Garduño, and Xiangmin Xu

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The Octodon degus is increasingly recognized as a valuable yet underutilized animal model for aging and dementia research. These long-lived, diurnal Chilean rodents naturally develop a range of age-progressive conditions relevant to human disease, including diabetes, atherosclerosis, and Alzheimer's disease. Despite their strong translational potential, systematic examination of degu development, maturation, and colony management practices remains limited, creating barriers to broader adoption of this model in biomedical research. Here, as one of the few research groups in the United States maintaining a long-term degu colony, we present a comprehensive developmental and husbandry characterization spanning the full lifespan of degus, from newborns (postnatal day 0) to aged animals (up to 4.5 years). We quantified growth and maturation trajectories using longitudinal measures of body weight, body length, tail proportions, tarsus-to-metatarsus length, and tooth pigmentation; these are biological markers that change predictably with age and provide reliable benchmarks for developmental staging. In addition to developmental metrics, we detail species-specific colony management guidelines, including cage configuration, environmental enrichment strategies, handling and acclimation methods, and breeding practices optimized for animal welfare and experimental reproducibility. These protocols were developed through sustained colony management experience and iterative refinement and are designed to be readily implemented by laboratories seeking to establish or expand degu research programs. Together, our developmental data and colony management recommendations provide foundational reference standards for Octodon degus research and support the degu as a practical model organism in neuroscience and aging studies.

# Poster #12: W. Hopkins et al.

## The Michale E Keeling Center for Comparative Medicine and Research: A Resource for Preclinical Studies on Alzheimer's Disease and Related Dementias

**William D Hopkins**

MD Anderson Cancer Center

The Michale E Keeling Center for Comparative Medicine and Research (KCCMR) is part of MD Anderson Cancer Center and houses 5 different nonhuman primate species including chimpanzees, baboons, rhesus monkeys, squirrel monkeys and owl monkeys. Each of these species offer specific advantages for modeling different aspects of Alzheimer's disease pathology including aggregations of the protein amyloid-beta (Aβ) into extracellular plaques, tau-associated neurofibrillary tangles (NFT), and cerebral amyloid angiopathy (CAA), a condition in which Aβ build up occurs in the brain's blood vessels. Here, I present an overview of nonhuman primate resources, brain and biological materials and research services provided by the KCCMR to support research on aging. In addition, I present recent results at the KCCMR examining species and age effects on (1) brain aging and atrophy and (2) biomarkers of AD including pTau-217, total tau, Aβ40, Aβ42, GFAP and NfL in chimpanzees, rhesus monkeys and baboons.

# Poster #13: B. Hrvoj Mihic et al.

## The effects of age and Alzheimer's disease-like pathology on synapses in the cerebral cortex and hippocampus of chimpanzees

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Chimpanzees (Pan troglodytes) are among our closest living relatives and can reach advanced ages (up to ~70 years in captivity), yet they do not exhibit the full spectrum of age-related neuropathologies observed in humans, such as Alzheimer's disease (AD). AD-associated pathology, namely amyloid-beta protein (Aβ) plaques, tau-associated neurofibrillary tangles (NFT), and vascular amyloid accumulation (cerebral amyloid angiopathy, CAA) has been reported in the cerebral cortex of aged chimpanzees, without the accompanying severe cognitive decline and neuronal loss seen in humans. At the same time, the effects of such pathological markers on the structure of chimpanzee brains are not well understood; therefore, we evaluated the impacts of age- and AD-related pathology, including Aβ plaques, NFT, and CAA, on synaptic densities in the chimpanzee brain. Using electron microscopy, we quantified the density of asymmetric (excitatory) and symmetric (inhibitory) synapses in the dorsolateral prefrontal cortex, middle temporal gyrus, entorhinal cortex, and CA1 subfield of the hippocampus in 50 chimpanzees, ranging in age from 16 to 61 years. We found a significant age-related decrease in overall synaptic density in the hippocampus of chimpanzees, which was most pronounced for asymmetric subtypes, while other cortical areas showed no change with age. In addition, symmetrical synapse densities were significantly decreased in prefrontal and entorhinal cortex of chimpanzees with moderate to severe CAA compared to controls, but Aβ plaques and NFT had no effect on synaptic densities regardless of region. These findings suggest that the effects of aging and the response to AD-associated markers differs in chimpanzees compared to humans, affecting hippocampus more than cortical areas and a specific subset of synapses more than others, yet sparing the areas vulnerable to pathologies in humans. This work was supported by the National Institutes of Health (AG067419, AG087945, NS092988).

# Poster #14: V. Ajith et al.

## Cytoarchitectural Changes in the Aging Temporal Cortex and Ventral Hippocampus of the Canine

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Age-related dementias comprise a heterogeneous group of neurodegenerative disorders characterized by progressive cognitive decline, neuroinflammation, and neuronal loss. Across these conditions, convergent neuropathological and cellular abnormalities emerge during disease progression. In this study, we examined the effects of aging on distinct neuronal subpopulations within the temporal cortex and ventral hippocampus of young (1–5 years) and aged (9–11 years) canines, including beagles and golden retrievers. Canines represent a valuable natural model of aging-associated cognitive decline and related dementias. Unlike murine models, they spontaneously develop cognitive impairment and Alzheimer's disease (AD)-like neuropathological features with age. We focused on neuronal populations expressing parvalbumin (PV), somatostatin (SST), and calbindin (CB), markers of interneuron subtypes that exhibit selective vulnerability in aging and dementia. In addition, we examined neurons expressing Purkinje cell protein 4 (PCP4), a calmodulin-binding protein implicated in neuronal excitability and synaptic plasticity. Beyond its role in calmodulin-dependent signaling, PCP4 serves as a reliable marker of the hippocampal CA2 subregion in several mammalian species. Here we report a distinct PCP4 staining pattern spanning the CA2 and CA1 regions of the canine ventral hippocampus, suggesting species-specific cytoarchitectural organization. Given the hippocampus's central role in learning and memory and the temporal cortex's involvement in age-related neurodegenerative processes, both regions were systematically assessed. Together, our findings establish a detailed cytoarchitectural profile of the aging canine brain and provide critical context for understanding how aging differentially impacts specific neuronal populations in a natural model of aging and dementia.

# Poster #15: Y. Li et al.

## Hippocampal Neurogenesis Across Development and Aging in the Long-Lived Octodon degus

**Yujia Li,** Yuta Sato, Layla Harvey, Carolyn Bauer, B. Maximiliano Garduño, and Xiangmin Xu

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Octodon degus, a diurnal rodent endemic to Chile, is increasingly recognized as a valuable natural model for studying brain development, aging, and dementia-related processes. Unlike traditional laboratory rodents, degus are born precocial (fully furred, with eyes open and coordinated locomotion) and exhibit an extended lifespan (~5–8 years, compared to ~2 years for mice/rats), providing a unique opportunity to examine neurodevelopmental and aging trajectories across an expanded temporal window. In this study, we characterized hippocampal neurogenesis across six defined age groups spanning development to advanced age: postnatal day 0 (P0), 2–3 months, 5–6 months, 1 year, 2 years, and 5 years. Using immunohistochemical labeling of proliferative and neuronal progenitor markers, including Ki67, doublecortin (DCX), and proliferating cell nuclear antigen (PCNA), we quantified neurogenic activity in hippocampal sections. Analyses focused on subregions of the dentate gyrus including the subgranular zone, granule cell layer, molecular layer, and polymorphic layer, as well as the CA1 region. Neurogenic signals were quantified using normalized mean fluorescence intensity and thresholded particle analysis implemented using Fiji, an open-source platform for biological image analysis. Our results revealed a gradual, age-dependent decline in hippocampal neurogenic signatures across the degu lifespan, while also identifying inter-individual variability, with some animals maintaining detectable neurogenic activity into adulthood. These findings establish baseline trajectories of hippocampal neurogenesis in Octodon degus and underscore their value as a longitudinal model for investigating mechanisms of brain development and aging. Future integration of behavioral, molecular, and genomic profiling will be critical for elucidating how neurogenic dynamics relate to cognitive function and vulnerability to age-associated neurodegenerative disease.

# Poster #16: P. Marvar et al.

## Longitudinal Genomic Analysis of the Brain Renin–Angiotensin System in a Novel Mouse Model of Alzheimer's Disease (AD)

Amy Dunn, Catherine Kaczorowoski, Hui Lu, Lara Pramanik and **Paul Marvar**

The George Washington University

Clinical and rodent studies suggest that the brain renin-angiotensin system (bRAS) may play a role in Alzheimer's disease (AD) pathology and cognitive decline. This study utilized recently developed novel transgenic AD-BXD mouse strains, designed to enhance understanding of genetic diversity, in susceptibility and resiliency factors, in AD. B6-5XFAD mice were crossed with 28 BXD strains to generate a population of AD-BXDs (Neuner et al, 2019;). Bulk RNA sequencing (RNAseq) data from the hippocampus of male and female mice at 6 and 14 months of age were evaluated for bRAS-related protein gene expression changes (GEO accession numbers: GSE101144, GSE119215, and GSE119408). Comparisons between AD gene carriers (AD-BXD, n = 135) vs noncarrier littermates (Ntg-BXD, n = 157) assessed differential expression of bRAS-related genes; Agtr1b, AP-A, Rnpep, Ace, Agtr1a, Agtr2, Ren, Agt, AP-N, Ace2, Atp6ap2, Agtrap, Adam17, MasR, Lnpep, and Nr3c2. Single-nucleus RNA sequencing data from the Religious Orders Study and Memory and Aging Project (ROS/MAP; PMID: 37774677; n = 427) was also used. Parallel comparison of bRAS-related genes were analyzed in amyloid+ and amyloid- populations from the human ROS/MAP data base.

Expression of the primary receptor subtypes of the bRAS, Agtr1 and Agtr2, were unchanged, however a significant main effect of genotype was observed in the expression of , the mineralocorticoid receptor (Nr3c2), Mas receptor (MasR), pro-renin receptor (Atp6ap2), and the angiotensin type IV receptor (Lnpep) were significantly downregulated in AD-BXD mice compared to Ntg-BXD mice, suggesting a potential moderation of function of the bRAS in AD mice. A significant main effect of sex was observed in the expression of Adam17, MasR, Lnpep, and Nr3c2.. Interaction analysis revealed a significant genotype × age interaction for the expression of Agtrap, Adam17, and MasR, indicating potential age-specific roles in AD pathophysiology. In human cortical tissue, expression of MasR and Atp6ap2 was also significantly decreased in individuals with amyloid+ status (MasR: -0.02 logFC, adj-p = 0.03; Atp6ap2: -0.03 logFC, adj-p = 0.005).

Our findings reveal significant changes gene expression of bRAS related receptors and regulatory proteins in a mouse model exhibiting genetic, transcriptomic, and phenotypic diversity. This study provides valuable insights into the regulatory mechanisms of the bRAS in AD pathology and may provide novel therapeutic targets for preventing or delaying the onset and progression of AD.

# Poster #17: M. Mejias Ortega et al.

## Neurobehavioral Recovery and Local Pathology Modulation through Microbiome-Based L-DOPA Therapy in APPNL-G-F-KI Mice

**Marina Mejias-Ortega**, Siok-Lam Lim, Joan Vu, Naoki Hida, Heng-Wei Hsu, Rachel Kim, Gregory De Carvalho, Piyush Padhi, Vellareddy Anantharam, Gregory Phillips, Lulu Chen, Anumantha G. Kanthasamy, and Masashi Kitazawa

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Alzheimer's disease (AD) is the most common cause of dementia, and no effective treatments exist to alleviate the progression and clinical symptoms. Monoamine neurotransmitter systems, including norepinephrine (NE) and dopamine (DA), are increasingly recognized to play a crucial role in AD. This study evaluates therapeutic efficacy of oral administration of our novel genetically engineered L-DOPA bacterial live-therapeutic (LDBL). This strategy is designed to maintain stable therapeutic levels of plasma L-DOPA, hence increases brain DA and NE to rescue clinical symptoms. To evaluate its therapeutic efficacy, we administered LDBL treatment every 12 hours for 2 weeks to 12-month-old APPNL-G-F-KI and strain-matched wild-type mice. We then assessed their memory function and depressive-like behavior using contextual fear conditioning and forced swim tests, respectively. We found that LDBL-treated APP-KI mice performed significantly better than vehicle-treated mice. These positive behavioral outcomes were also supported by restoration of firing frequency at single neuronal cell levels in the hippocampus of the treated mice. Histopathological analysis revealed that Aβ pathology was mostly unchanged. However, plaque-proximal dystrophic neurites were markedly reduced, indicating localized neuroprotective effects. Synaptic analyses showed increased Homer1/Bassoon in CA3 and cortical regions, reflecting enhanced excitatory connectivity. Interestingly, glial alterations were spatially restricted to amyloid plaque–proximal regions in LDBL-treated mice. Although the overall parenchymal areas positive for glial markers (Iba1, Clec7a, Tmem119, CD68, GFAP, C3) remained unchanged, detailed analyses revealed enhanced microglial activation and phagocytic engagement around plaques, accompanied by a selective reduction of $C3^{+}$ neurotoxic astrocytes in these local regions. These findings provide a better understanding of the immunological mechanisms underlying AD and highlight the critical contribution of LDBL to activate immune response modulation in the brain. Moreover, these results open the door to further refinement and enhancement of our proposed microbiome-based live biologic therapy to alleviate neuropsychological deficits in AD.

# Poster #18: T. Melgarejo et al.

## Untargeted Plasma Metabolomics in Canine Cognitive Dysfunction: The Naturally Occurring Alzheimer's Disease Analog in Dogs

**Tonatiuh Melgarejo**, Scarlett Harrison, Yan Chang, Miriam Munoz, Maya Kim, Youna Choi, Joyce G Riveroll-Gonzalez, Barbara Natterson-Horowitz, and Annika Linde

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Canine Cognitive Dysfunction (CCD) is an increasingly prevalent, naturally occurring neurodegenerative condition in aging dogs that shares core clinical, neuropathological, and molecular features with human Alzheimer's disease (AD). As such, CCD represents a compelling unconventional model for studying age-related cognitive decline under real-world environmental conditions. Metabolomic profiling offers a powerful approach to identify systemic biochemical alterations associated with neurodegeneration and to discover candidate biomarkers with diagnostic and therapeutic relevance. Despite its strong translational potential, plasma-based metabolomic characterization of dogs with CCD has not previously been reported. In this case–control study, untargeted plasma metabolomics was performed in ten client-owned geriatric dogs, including five with severe CCD and five age-matched, clinically healthy controls. Ultra-performance liquid chromatography–mass spectrometry (UPLC-MS) coupled with multivariate and univariate statistical analyses was used to identify metabolic features that differed significantly between groups. Fifteen metabolites spanning seven distinct chemical classes were significantly altered in dogs with CCD relative to controls. These included glycerophospholipids, steroid derivatives, indole compounds, and metabolites linked to mitochondrial function. Among the most notable findings were elevated levels of lysophosphatidic acid (LPA 20:2/0:0), suggesting enhanced neuroinflammatory signaling, and reduced levels of ubiquinone-2, consistent with impaired oxidative stress regulation and mitochondrial dysfunction. Cholesterol demonstrated the highest fold change and variable importance scores, further reinforcing its established role in AD-related neurodegenerative processes. Hierarchical clustering and pathway enrichment analyses revealed distinct metabolic signatures in CCD that parallel pathways implicated in human AD. This study provides the first untargeted plasma metabolomic profile of dogs with CCD and demonstrates that naturally occurring cognitive decline in companion dogs is associated with systemic metabolic disturbances closely aligned with AD pathophysiology. Importantly, samples were collected from senescent, community-dwelling dogs rather than laboratory-housed animals, enhancing the ecological validity and translational relevance of the findings. These results support the utility of CCD as an unconventional yet biologically informative model of AD and identify plasma-based metabolic candidates that merit further investigation as biomarkers of neurodegeneration. Longitudinal studies integrating metabolomics with neuroimaging, histopathological validation, and behavioral phenotyping will be critical to confirm these associations and advance biomarker discovery and therapeutic development across species.

# Poster #19: M. Mulholland et al.

## High-Throughput Assessments of Cognitive Aging in Nonhuman Primates

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One bottleneck for more rapid development and utilization of nonhuman primates in aging and Alzheimer's Disease related research is the lack of high-throughput methods for assessing cognitive function in relatively large samples of animals within and between species. Manual testing apparati can be cumbersome, inefficient, and have significant limitations in the range and scope of tasks that can be administered to the animals. We have developed automated cognitive testing systems (ACTS) for socially living nonhuman primates to address this need. Individual animals are identified via radio frequency identification tags controlling individualized programming and data collection within their social groups. This prevents the need to separate or singly house individuals for testing which can often be stressful to the animal and introduce a potential source of measurement error. So far, we have programmed and tested 14 tasks covering multiple cognitive domains including learning, memory, pattern recognition, inhibitory control, and cognitive flexibility. The same system configurations and tasks can be used for different nonhuman primate species thereby harmonizing and standardizing the methods used to assess cognitive functions between them. To date, we have implemented ACTS with five species of nonhuman primates (chimpanzees-Pan troglodytes, olive baboons-Papio anubis, rhesus monkeys-Macaca mulatta, and squirrel monkeys-Saimiri boliviensis and S. sciureus). We have found age-related differences in recognition and discrimination learning, and cognitive flexibility for multiple species. For example, geriatric rhesus monkeys perform worse on learning tasks (recognition and discrimination learning) compared to younger rhesus monkeys ($p<0.05$). System usage and training data, and preliminary age-related differences in task performance across multiple species will be presented, along with information on the hardware and software and future applications.

# Poster #20: S. Omotoso et al.

## Statistical Complexity Reveals Internal Learning Dynamics of Deep Neural Networks in Alzheimer's and MCI MRI Classification

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The diagnosis of Alzheimer's disease, MCI and dementia presents a critical challenge, as these neurodegenerative conditions often involve subtle brain changes that conventional imaging methods fail to detect. Traditional metrics such as loss and entropy capture error and uncertainty but don´t uncover the deeper, intricate patterns within MRI data [1]. These limitations restrict early detection and accurate diagnosis, necessitating advanced computational techniques. This study introduces a novel metric that identifies subtle brain patterns, enhancing the understanding of dementia. This metric is called statistical complexity [2]. Using DenseNet-121 and EfficientNet-B1 models, the dataset was partitioned into ten subsets ranging from 10% to 100% in 10% increments to examine how statistical complexity evolves with increasing data availability. Synaptic weights were extracted from each model and transformed into probability distributions, from which entropy and disequilibrium were computed. Statistical complexity was then obtained as the product of entropy and disequilibrium, following the definition of LMC complexity (https://www.sciencedirect.com/science/article/pii/0375960195008675). Results showed that statistical complexity increases with dataset size. Smaller datasets exhibited an irregular (zigzag) pattern in training loss and statistical complexity, indicating overfitting. Larger datasets demonstrated smoother patterns, suggesting better model learning. Using the full dataset, a layer-by-layer analysis revealed distinct architectural signatures. DenseNet-121 exhibited increasing complexity in deeper layers—particularly in denseblock3, norm5, and transition3—indicating progressive refinement of high-level neuroanatomical features, while early layers such as conv0 and denseblock2 showed reduced complexity. In contrast, EfficientNet-B1 displayed fluctuating complexity in early layers and consistent declines in mid-layers, stabilizing only at the final layer, suggesting weaker hierarchical feature organization compared to DenseNet-121. These findings confirm that statistical complexity is a reliable metric for assessing model performance in Alzheimer's disease classification and may provide more nuanced insights into model training dynamics. This approach has the potential to significantly improve early diagnosis and model reliability in clinical settings.

# Poster #21: T. Osinalde et al.

## Functional Impact of Naturally Occurring ApoE213 Variants in a Rodent Model of Sporadic Alzheimer's Disease

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Alzheimer's disease (AD) is a multifactorial disorder where genetic predisposition, behavioral decline, peripheral biomarkers, and neuropathological changes converge. Traditional rodent models capture isolated aspects of AD but often fail to reproduce the natural trajectory of the disease. The Octodon degus offers a unique natural model of sporadic AD, displaying features that parallel the human condition, including a relatively long lifespan, diurnal habits, and naturally occurring genetic variability in Apolipoprotein E (ApoE) (Tan et al., 2022; Hurley et al., 2018; Mugnaini et al., 2022). In humans, apolipoprotein E (ApoE) represents the strongest genetic risk factor for AD, with the APOE2, APOE3, and APOE4 isoforms conferring differential risk largely through their effects on lipid metabolism. The discovery of naturally occurring ApoE variants in O. degus suggests that comparable ApoE-dependent mechanisms may shape disease vulnerability in this species.

Here, we examine whether ApoE variation at position 213 influences cellular lipid homeostasis in degus. Guided by structural predictions indicating altered lipid interactions, we focused on two prevalent variants, E and K, which appear to parallel wild-type–like and risk-associated ApoE states, respectively. Using primary fibroblasts derived from genotyped animals, we assessed lipid droplet dynamics as an integrated readout of cellular lipid handling. Cells carrying the ApoE213K variant exhibited increased lipid droplet number and size relative to ApoE213E cells, consistent with a lipid storage phenotype associated with disease risk. Strikingly, these alterations mirror emerging evidence linking human APOE4 to lipid droplet dysfunction in Alzheimer's disease, supporting the notion that ApoE-driven lipid dysregulation represents a conserved pathogenic mechanism across species. In parallel, we are exploring peripheral biomarkers, including plasma pTau217, in relation to brain pathology and behavior to enable minimally invasive stratification of disease progression in degus. Ongoing mechanistic studies targeting autophagy and ferroptosis aim to further elucidate the pathways underlying ApoE-dependent lipid alterations.

Together, this work establishes Octodon degus as a powerful natural model to investigate how ApoE variation shapes lipid biology and contributes to Alzheimer's disease risk.

# Poster #22: U. Raychaudhuri et al.

## Effects of T3D-959 on a tauopathy mouse model

**Urmimala Raychaudhuri**, Candice Tang, Harmanjeet Singh, Melika Seyedmohammadlou, Soo Jung Park, Nate Addonizio, Mishika Agarwal, Nimrah Ashfaq, Krutik Patel, Matthew F Rose, and Albert R La Spada

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Elevated levels of p-tau (phosphorylated tau) is directly correlated with neurodegeneration and neuropathogenesis in Alzheimer's disease (AD). The presence of ApoE allele is a significant genetic risk factor for the progression of AD. PPAR-δ, a nuclear receptor highly expressed in CNS neurons, regulates metabolic processes that helps boost mitochondrial function and improve quality protein control; processes that deteriorate as neurodegeneration progresses. This makes PPAR-δ an appealing candidate for neurodegenerative diseases such as Alzheimer's. Here we assess the effect of PPAR-delta agonist, T3D, on a mouse model of tauopathyP301S/E4 against a saline control group.

T3D was administered intraperitoneally at 50mg/kg/day, 3 days a week from~4 to ~11 month of age. Neurological testing was performed every alternate month. Behavior studies such as Object Recognition Memory test (ORM), Object Location Memory (OLM), and Y maze studies were conducted at 7, 9 and 11 months. p-tau staining was performed to compare phosphorylated tau staining in Treated vs control mice.

The weight of T3D-959 treated mice appear to deteriorate less compared to saline treated mice. Not much difference was seen in the overall neurological exam scores. In behavioral studies, T3D-959 treated mice subjected to OLM performed the long-term memory task significantly better compared to saline treated mice. Significant superior performance of the T3D-959 treated mice was observed at 11months of age ($p=0.02$, $n=5$ per group, two-tailed t-test; error bars = s.e.m.), indicative of better long-term hippocampal memory function upon treatment with T3D-959. There was no significant difference in the ORM and Y-maze test. p-tau staining(n=1) of the hippocampus appears to show a correlation with discrimination index (DI) of behavior (OLM) studies with relatively less p-tau staining in T3D treated mice which had high positive DI.

OLM testing evaluates dorsal hippocampus long term memory function and is transcription based. Y-maze is non-transcription based and studies short-term memory function and spatial recognition. Several relevant brain regions, including the entorhinal cortex and ventromedial prefrontal cortex, are required for ORM. Significantly higher discrimination index (DI) scores were observed with OLM testing at 11 months of age in the T3D-959 treatment group compared to saline, which demonstrates that T3D rescues hippocampal long term memory function better than saline. This is a potentially important finding that indicates that T3D-959 can impact the hippocampus to preserve long term memory function.

# Poster #23: A. Samawi et al.

## Comparative Hippocampal Circuit Mapping Reveals Enhanced Contralateral Connectivity in Octodon degus

**Alexandra Samawi**, B. Maximiliano Garduño, Hai Zhang, Gocylen Gast, Megan Jeide, Youssef Elnaggar, Adam Yoo, Andy Thai, and Xiangmin Xu

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The hippocampus plays a central role in learning, memory, and the integration of sensory and spatial information. Characterizing hippocampal connectivity is essential for understanding the circuit organization that underlies both normal cognitive function and neurological disease. Although laboratory mice have been extensively used for neural circuit mapping and have yielded foundational insights into hippocampal organization, comparatively little circuit-level information is available for Octodon degus, a non-murine rodent species with distinct biological and behavioral characteristics. Degus are long-lived, diurnal, and highly social animals with extended aging trajectories that more closely parallel key aspects of human neurobiology, making them a promising yet underexplored model for translational neuroscience research. Here, we employed monosynaptic rabies viral tracing to systematically map local and long-range presynaptic inputs to hippocampal CA1 of degus (male and female animals, ~8 months of age). This approach enabled comprehensive, brain-wide identification of direct synaptic inputs to CA1 neurons. We observed that degu CA1 neurons received inputs from multiple hippocampal and extrahippocampal regions, including ipsilateral and contralateral CA1, CA2, and CA3 as well as the MS-DB, subiculum, and entorhinal cortex, indicating a diverse and distributed input organization. To assess species-specific circuit organization, we compared these results with our existing CA1 input mapping data obtained from age-matched laboratory mice. This comparative analysis revealed striking differences in hippocampal connectivity patterns between species. Notably, degu CA1 neurons exhibited predominantly strong contralateral hippocampal inputs, with the connectivity strength index (CSI) of contralateral CA1 and CA3 measured at 24.67 ± 8.81 and 188.36 ± 106.12, respectively. In contrast, ipsilateral hippocampal inputs to degu CA1 were comparatively weaker (CSI values for ipsilateral CA1 and CA3: 35.96 ± 10.69 and 130.30 ± 23.6), deviating from the typical hippocampal organization described in mice. This degu-specific circuit feature contrasts sharply with mouse hippocampal circuitry, in which CA1 neurons receive predominantly ipsilateral hippocampal inputs and exhibit only limited contralateral connectivity (mouse CSI values for ipsilateral CA1 and CA3: 5.774 ± 1.266 and 2.506 ± 0.986; CSI values for contralateral CA1 and CA3: 0.266 ± 0.150 and 0.777 ± 0.346). The relative enhancement of contralateral hippocampal inputs in degus suggests fundamental differences in interhemispheric hippocampal communication and information integration across species. Together, these findings identify a previously unrecognized organizational feature of hippocampal circuitry in Octodon degus and establish a circuit-level framework for understanding hippocampal function in this species. By revealing species-specific patterns of CA1 connectivity, our work lays important groundwork for future studies investigating how hippocampal circuits in degus support cognition, aging, and vulnerability to neurological disease.

# Poster #24: D. Sastre et al.

## Naked mole rat responses to proteotoxic stress

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The naked mole rat (NMR), the longest-lived rodent (37 years), is an emerging model for resilience to neuronal proteotoxic stress. Analyses of aged NMR brains have revealed that they do not develop Alzheimer's disease (AD)-like pathology 3,4 despite living long enough to allow for the progressive accumulation of proteotoxic damage that leads to neurodegeneration. The absence of AD-like pathology is remarkable given the NMR's long lifespan and the high prevalence of neurodegeneration-predisposing factors, including high levels of oxidative stress, tau phosphorylation and amyloid-β (Aβ). The proteasome is responsible for the clearance of aged, damaged and misfolded proteins and is implicated in neurodegenerative diseases. NMR cells present high proteasomal activity, but the underlying mechanisms are still not fully understood. We hypothesized that NMR cells modulate unique cellular pathways to promote proteotoxic stress resilience and high proteasome activity. To test this hypothesis, we sought to characterize the responses of NMR cells to proteotoxic stress induced by pharmacological proteasome inhibition (bortezomib, BZ). We treated immortalized skin-derived fibroblasts from NMR and mouse, as control, with varying concentrations of BZ for 24h (1 nM - 50 nM). NMR cells showed higher resilience to the toxic effects of the treatment, showing higher viability at higher concentrations. We also tested the effect of BZ on autophagy pathways using a fluorescently-tagged LC3A probe. In flow cytometry, NMR cells upregulated the LC3A probe signal in a concentration-dependent manner. In fluorescence microscopy, NMR cells presented a more diffuse LC3A signal while mouse cells presented the expected LC3 puncta. Differences in species-specific sequences were not sufficient to explain the pattern. To further understand the global responses to proteasome inhibition, we performed whole transcriptomic analysis of cells undergoing proteasome inhibition for 24h (50 nM). Cell pellets from three independent biological replicates containing three technical replicates (n = 9 per species) each were collected, and total RNA was processed for short-read sequencing (Illumina platform). BZ-treated NMR cells downregulated a similar number of genes compared to mouse cells (1,548 vs 1,650) but upregulated a significantly lower number of genes (1,096 vs 2,906), suggesting a more targeted transcriptional response in the NMR. Pathway enrichment analysis revealed "Metabolic pathways" as the top downregulated cellular pathway in the BZ-treated group in both species. In contrast, BZ-treated NMR cells' top two upregulated pathways were "Protein processing in the endoplasmic reticulum" and "Proteasome" while BZ-treated mouse cells upregulated "Lysosome" and "Sphingolipid metabolism". Since our experimental model focused on the inhibition of the proteasome, the differential enrichment of proteasome subunit genes only in the NMR species indicates a more robust and specific response in this species to combat proteotoxic stress at the proteasome level. This preliminary transcriptomic analysis will be used to guide the selection of hit genes identified in a whole-genome CRISPR screen in the NMR species for validation (ongoing work). Dissection of the key components underlying NMR's resistance to toxic protein aggregation could illuminate novel pathways to prevent or reverse this process in human diseases.

# Poster #25: H. Scholtzova et al.

## Squirrel Monkeys as a Translational Model of Sporadic Alzheimer's Disease Pathology.

Akash Patel, Suleiman Khan, Muhammad Soliman, Noor Salaymeh, Bharti Nehete, Qiao Zhang, Charles Kingsley, Jody Swain, Yongzhao Shao, Jelle Veraart, Youssef Zaim-Wadghiri, Pramod Nehete, William D Hopkins, Michele M Mulholland, Thomas Wisniewski, and **Henrieta Scholtzova**

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Cerebral amyloid angiopathy (CAA) is characterized by the cerebrovascular deposition of amyloid-β in cortical and leptomeningeal arteries, arterioles, and capillaries. CAA often co-occurs with Alzheimer's disease (AD), contributing to AD pathogenesis and cognitive decline. The squirrel monkey (SQM), a New World non-human primate species, has been highlighted for its importance in studying Alzheimer's disease (AD) and AD related dementias (ADRD) research due to its sporadic AD-related pathology with a unique propensity for developing extensive age-associated CAA. Our initial published studies demonstrated that SQMs are a suitable choice for evaluating the efficacy and safety of our innovative concept of AD immunotherapy using TLR9 agonist, CpG ODN. Moreover, we have demonstrated the effectiveness of multi-gradient echo (MGE) MRI in generating T2*-w anatomical brain maps, used in tandem with quantitative R2* (1/T2*) mapping to discern age-related regional differences in SQM brains. Here, we aimed to characterize trajectories of biofluid biomarkers, neuroimaging correlates, and behavioral measures across the SQM lifespan. Plasma and CSF biomarkers of AD core pathology (Aβ), neurodegeneration (NfL, GFAP, Ng), neuroinflammation (e.g., YKL-40, TREM2, S100B), and cerebrovascular dysfunction were analyzed cross-sectionally using SIMOA and Luminex immunoassays. A touchscreen-based Automated Cognitive Testing System (ACTS) was implemented within SQM cohorts to assess behavioral performance. SQMs underwent T2-w TSE/FLAIR, T2*-w MGE, and multi-shell diffusion-weighted (DWI) imaging. Coronal brain sections were examined to evaluate histopathological features of MRI abnormalities. Segmented regression analyses estimated changepoints in plasma/CSF biomarker levels ranging from 9.9 to 19.1 years of SQM age. Significant age-associated decreases in plasma/CSF Aβ40, Aβ42, and Aβ42/40 were observed after the estimated changepoints. Plasma/CSF NfL and GFAP, and plasma Ng levels increased significantly with age following their respective changepoints. Plasma YKL-40 levels increased in an age-dependent manner after the changepoint, while plasma TREM2 levels continuously increased throughout the SQM lifespan. Assessment of fluid biomarkers reflecting cerebrovascular dysfunction across disease continuum are underway. Multiparametric neuroimaging identified spontaneous amyloid-related imaging abnormalities (ARIA) in geriatric SQMs, including vasogenic edema (ARIA-E) and cerebral microhemorrhage (ARIA-H). DWI enabled more sensitive brain microstructural assessment. Histological assessment of brain tissue corresponding to MRI abnormalities revealed extravascular fibrinogen deposits indicating BBB dysfunction, reactive gliosis, disruption of myelin integrity, and microhemorrhages. Moreover, in the ACTS Transfer Index (TI) Task, geriatric SQMs performed significantly worse than young SQMs during the learning phase, while geriatric SQMs performed better on the reversal trials. Overall, geriatric SQMs had significantly higher TI values compared to young SQMs. In the Conceptual Set Shifting Task, geriatric SQMs had worse learning latencies, overall and on both intra- and extra-dimensional shifts, compared to young. Our continuous efforts aim to integrate fluid biomarkers and neuroimaging data with cognitive measures, further advancing this model for translational research on CAA/AD and innovative therapeutic interventions.

# Poster #26: N. Tichy et al.

## Investigating Microglial Lipid Dysregulation Using Zebrafish and Human-like Xenotransplantation Models

**Nathalie Tichy** and Francesca Peri

University of Zurich, Switzerland

Microglia have become a major focus in Alzheimer's disease research due to their role in clearing synapses and neuronal debris, a process that requires not only uptake of neuronal material but also its efficient degradation, recycling, and sorting. Understanding these processes is critical, as many Alzheimer's disease risk genes encode proteins involved in microglial cargo degradation, trafficking, and lipid handling. Consistent with this, disease-associated microglia exhibit an accumulation of lipid inclusions, which can impair cellular function and further disrupt homeostatic microglial responses. However, how microglial lipid handling pathways shape the phagocytic processing of neuronal cargo in vivo remains poorly understood.

The zebrafish has emerged as a powerful experimental system to uncover key regulators and mechanisms of neuron–microglia interactions in vivo. The development of methods to induce targeted neuronal cell death has led to the identification of the gastrosome, a recently discovered single vesicular compartment in the phagocytic pathway with distinct molecular and structural features, as revealed by correlative light and electron microscopy (CLEM). We have found that the gastrosome is conserved in human iPSC-derived microglia, where it expands in response to increased neuronal cell death. Notably, in phagocytic microglia lacking the cholesterol transporter NPC1, the gastrosome enlarges due to the accumulation of cholesterol and gangliosides, driving microglia toward an amoeboid, disease-associated morphology.

Several studies on neurodegeneration have shown that disturbances in microglial lipid metabolism are not only by-products of pathology but active drivers of disease. Genetic and functional studies implicate several ATP-binding cassette (ABC) transporters, including ABCA1, ABCA7, ABCG1 and ABCG4, in cholesterol efflux, amyloid-beta handling and Alzheimer's disease risk. Building on these findings, we performed a CRISPR–Cas9 knockout screen in zebrafish and identified ABCA1 and ABCG1, whose loss similarly leads to lipid accumulation and gastrosome enlargement. Together, these results identify lipid transporters as key regulators of gastrosome function and highlight the central role of lipid trafficking in microglial phagocytosis.

To dissect the contribution of these transporters and identify rate-limiting steps in lipid handling that promote maladaptive microglial responses, we combined quantitative imaging with genetic and pharmacological perturbations in zebrafish microglia and HuZIBRA, a new scalable human–zebrafish platform in which human iPSC-derived microglia-like cells are transplanted into the developing zebrafish brain. This model complements established murine models and enables probing of acute, cell-autonomous responses of transplanted human-like microglia to apoptotic and metabolic stress.

# Poster #27: Z. Treadwell et al.

## Effects of Calcineurin Inhibition in a Canine Model of Human Aging and Alzheimer disease

**Treadwell, Z**., Noche, J., Sordo, L., Gross T., Radhakrishnan, H., Stark, C., Norris, C., and Head, E.

University of California, Irvine

Aging beagles naturally develop spontaneous, age-related increases in Alzheimer's disease (AD)—associated amyloid-β (Aβ) pathology that coincide with cognitive decline. Beagles possess several advantages for translational AD research, including larger brain size, greater cognitive complexity, and longer lifespan, making them well suited for neuroimaging, plasma and cerebrospinal fluid (CSF) collection, multi-domain cognitive testing, and long-term pharmacological intervention studies. Furthermore, the aging beagle has demonstrated strong predictive validity in prior anti-Aβ therapeutic studies.

Our present study utilizes the aged beagle to examine whether the protein phosphatase calcineurin (CN) is a key mechanism related to AD pathophysiology. CN signaling is hyperactivated in early stages of cognitive decline in AD and in preclinical models, including dogs. In humans, CN inhibition by tacrolimus treatment (to prevent organ transplant rejection) is associated with a significantly lower rate of dementia. We have completed a longitudinal prevention study in cognitively intact, middle-aged (5–8-year-old) beagles treated for five years with calcineurin (CN) pathway inhibitors or placebo. Dogs received tacrolimus (0.075 mg/kg/day, oral; n=15), Q134R, a novel inhibitor of the CN-dependent transcription factor NFAT (8mg/day, oral; n=14), or placebo (n=14). All dogs also received behavioral enrichment. Longitudinal outcomes included repeated assessments of learning, executive function, and spatial and object recognition memory, serial MRI measures of brain structure and plasma and CSF biomarkers of AD pathology (including Aβ, neurofilament light chain, and GFAP).

Results from our study to date show that 1) tacrolimus treatment protected against age associated microstructural changes by MRI; 2) CN inhibition overall was associated with a maintenance of cognitive function; 3) Behavioral enrichment leads to an increase in hippocampal volume by MRI. We will also show preliminary results from immunohistochemical and fluorescent staining for Aβ in the brains of treated animals.

Overall, our study in the beagle preclinical model may be predictive of outcomes for a clinical trial of tacrolimus in future.

# Poster #28: A. Vásquez et al.

## ApoE variants in Sei Whale (Balaenoptera borealis): From the Perspective of Cetaceans and 'Alzheimer's like' Pathology

**Amanda A. Vasquez,** Pablo Villalobos, Tiago Osinalde, Maria Jose Perez, Elie Poulin, and Patricia Cogram

IEB, Faculty of Science, University of Chile

Alzheimer's disease is a neurodegenerative condition whose study has been limited by the scarcity of natural models that replicate its spontaneous development. Natural models of "Alzheimer's-like" pathologies have the potential to expand our understanding of the biological processes underlying disease development and their interaction with environmental factors, contributing with translational knowledge to the study of Alzheimer's, as well as to provide new experimental study models that more accurately reflect the characteristics of the disease. Recent evidence of Aβ plaques and Tau tangles in cetaceans suggests the presence of an "Alzheimer's-like" pathology in this group, whose research interest is further strengthened by their longevity, prolonged postmenopausal periods, and mechanisms of protection against oxidative damage; important factors underlying the pathology. ApoE, the main genetic risk factor for sporadic Alzheimer's disease, has not yet been structurally characterized in cetaceans. Following the mass stranding of sei whales (Balaenoptera borealis) that occurred in Chile (2015), two ApoE variant sites (S22R and S112R) were identified for the first time in structurally relevant regions, as observed in their AlphaFold-predicted structures. These variants may influence neurodegenerative processes in a manner analogous to pathogenic ApoE variants described in humans and other mammals. Their impact is proposed to be evaluated through computational and experimental studies, including the generation of transgenic lines using CRISPR.

# Poster #29: C. He et al.

## Integrated Gene Expression & Chromatin Accessibility Profiling Reveals Molecular Insights into PS19 Mouse Model

**Cuiling He,** Nathan R. Zemke, Jeffrey Chiu, Bing Yang, Weronika M. Bartosik, Kristie Wong, Eric Velazquez, Zhiqun Tan, Christopher K. Glass, Xiangmin Xu and Bing Ren

University of California, San Diego

Tauopathies, pathologically defined by the deposition of neurofibrillary tangles, are implicated in various neurodegenerative disorders, including Alzheimer's disease (AD). While transcriptomic studies of AD-related tau pathology have revealed molecular characteristics, the mechanisms driving these features remain poorly understood. In this study, we investigated gene expression and chromatin accessibility in the entorhinal cortex, dorsal hippocampus, and prefrontal cortex of the P301S tau mouse model (PS19), which recapitulates key phenotypes of AD-related tau pathology. We profiled PS19 transgenic mice (TG) and wild-type (WT) mice at the age of 4 months and 10 months, representing the early stage and advanced stage of AD. Using 10x Multiome technology to simultaneously profile single nucleus gene expression (snRNA-seq) and chromatin accessibility (snATAC-seq), we characterized the gene expression and gene regulatory landscape of AD-related tau pathology in this model. From the single nucleus gene expression profiles, we recovered 934,211 high quality nuclei and identified 47 cell types across brain regions. We Identified 816,287 candidate cis-regulatory elements across 3 brain regions in our snATAC-seq dataset. We also observed region-specific neuronal loss and microglia cell expansion in TG mice. Tau pathology in our mouse model induces robust transcriptional changes in microglia, specifically, microglia in TG mice exhibit upregulated inflammatory gene expression and downregulated homeostatic signature genes. These changes are accompanied by coordinated chromatin accessibility changes. We identified distinct activated microglial states that emerge in response to tau pathology and are shaped by genotype, age, sex, and brain region. We inferred trajectory dynamics using RNA velocity, revealing a unidirectional transition from homeostatic to activated microglial states along the tauopathy progression axis. We mapped transcription factor (TF) regulatory networks, highlighting state-specific TF motif accessibility and expression for each microglial state. In conclusion, our study provides a comprehensive multiomic atlas of the PS19 mouse brain across genotype, age, sex, and region, revealing how tau pathology and aging differentially shape cellular identity and regulatory programs in a region- and cell type–specific manner. We identify microglia as primary responders to disease, and characterize the TF networks and chromatin landscapes that underpin these transitions. The progressive microglial state shift reveals a trajectory that may serve as a key biomarker of early tau pathology.

# Poster #30: C. Lisgaras et al.

## The cholinergic system exerts opposing effects on memory at different stages of disease progression in Alzheimer's and Down syndrome model systems

**Christos Panagiotis Lisgaras** and Helen E. Scharfman

NYU Neuroscience Institute, New York University Grossman School of Medicine
The Nathan S. Kline Institute for Psychiatric Research, New York State Office of Mental Health,

The long-standing cholinergic hypothesis traditionally posits that cholinergic signaling is uniformly deficient in Alzheimer's disease (AD) and Down syndrome (DS). We tested the hypothesis that this deficiency occurs primarily late in disease, while early stages involve excessive cholinergic signaling, with distinct implications for memory.

Tg2576 (AD model; n=38), Ts65Dn (DS model; n=14) and wild-type (WT; n=17) mice at young (3-4months) and old (>14months) ages received treatments to reduce cholinergic signaling (medial septum chemogenetic inhibition or muscarinic antagonist scopolamine) or enhance it (acetylcholinesterase inhibitor donepezil). Memory assessments used novel object recognition.

Anticholinergic manipulations robustly restored memory in young Tg2576, Ts65Dn mice but impaired age-matched WT performance. Conversely, donepezil improved memory of old Tg2576, Ts65Dn and WT, but not young Tg2576 and Ts65Dn animals.

These findings refine and challenge the cholinergic hypothesis, revealing for the first time a functional shift from cholinergic hyperactivity driving early cognitive impairment to late-stage degeneration requiring enhancement. This dynamic shift offers critical insights for stage-specific therapeutic interventions in AD and DS and underscores the value of translational animal models for understanding disease progression.

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# Acknowledgments

Welcome to the UAMAA 2026 Conference, *"Unconventional Animal Models of Alzheimer's Disease and Aging,"* hosted at the University of California, Irvine. Now in its second international edition, UAMAA 2026 brings together a diverse group of researchers from across academia and industry to advance innovative approaches to understanding Alzheimer's disease and related dementias.

We are sincerely grateful to the UCI School of Medicine for their continued support of this meeting and to institutional leadership for fostering an environment that encourages interdisciplinary collaboration and scientific exchange.

We thank the conference co-organizers—Afonso Silva, Stacey J. Rizzo, Patricia Cogram, Bing Ren, and Xiangmin Xu—for their scientific vision, leadership, and dedication in shaping the program.

Behind the scenes, we are grateful to the many UCI administrative and operational teams whose expertise made this conference possible. We especially acknowledge the Department of Anatomy & Neurobiology team—Doug Schroettinger, Arnold Ortiz, and Lesley Dowd—for their continued support and guidance. We also thank Crystal Camarena, Special Projects & Events Manager in the Office of the Vice Chancellor, and Ivan, Educational Technology Specialist, for their assistance with event planning and technical support.

Our appreciation extends to Justin, Arnold, and Margaret in Travel & Accounting for their guidance and support throughout the financial and reimbursement processes. We also thank the Sonesta Irvine team—Gayle, Annie, and Marissa—for their professionalism and hospitality in supporting conference accommodations.

We are grateful to our corporate sponsors, including Complete Genomics, Tissue Vision, and Quanterix, as well as MARMO-AD and the Universidad de Chile, for their generous support of this meeting and commitment to advancing Alzheimer's disease research.

To our speakers and poster presenters, thank you for sharing your work, ideas, and insights. Your contributions are at the heart of this meeting and are what make UAMAA a vibrant and impactful forum.

Finally, we recognize the CNCM team—Michele Wu and Ginny Wu for their hands-on leadership across operations, and Jabez Domingo for managing critical logistical and financial elements. We also extend our sincere thanks to the CNCM staff, students, and volunteers for their dedication and tireless efforts before and during the conference.

We are honored to host you at UAMAA 2026 and look forward to the continued growth of this community in the years ahead.

Jane Alshami

Jane Alshami
Conference Coordinator & CNCM Administrative Assistant
UC Irvine Center for Neural Circuit Mapping

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