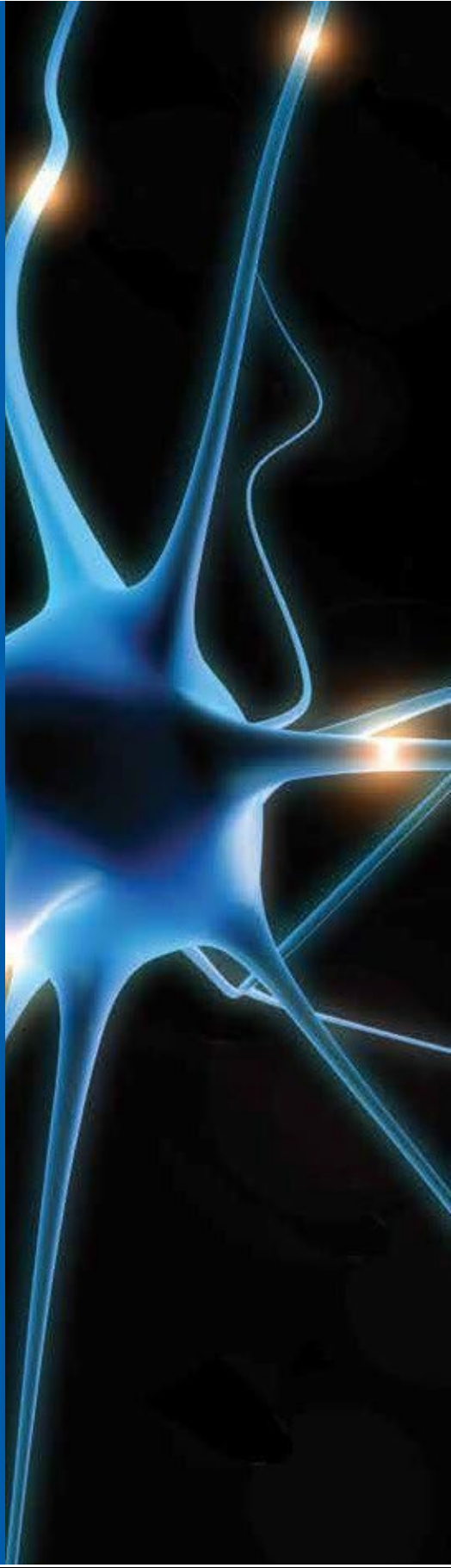
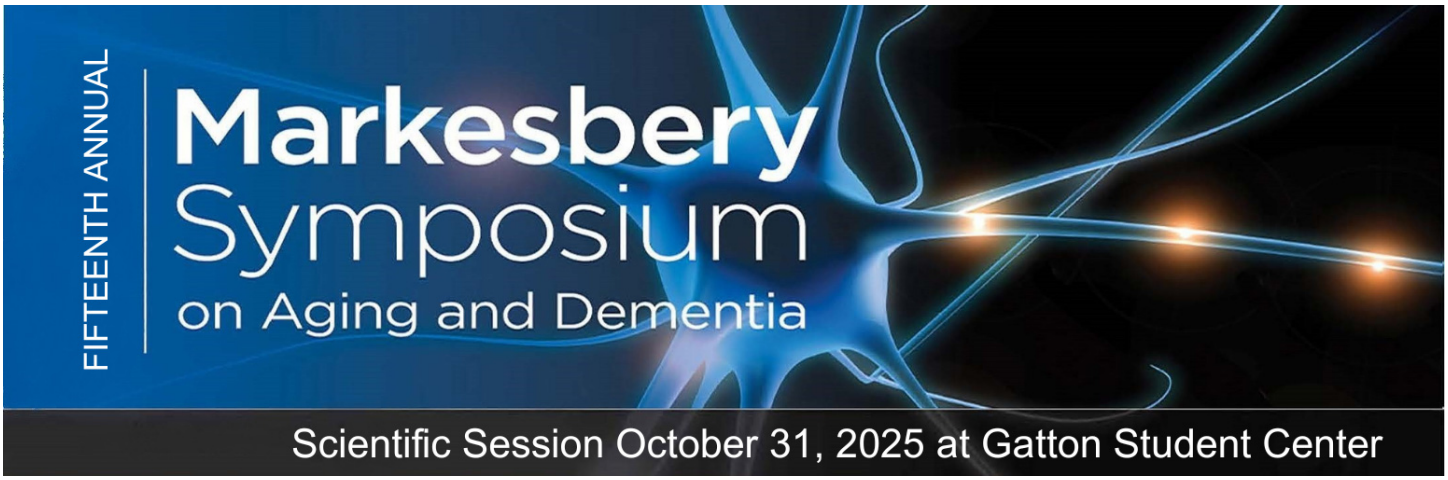
FIFTEENTH ANNUAL

Markesbery Symposium on Aging and Dementia

Scientific Session
October 31, 2025
10:00am - 3:00pm



Sanders-Brown Center on Aging



On behalf of the Sanders-Brown Center on Aging, our philanthropy council, and the symposium planning committee, I am pleased to welcome you to the 15th annual "Markesbery Symposium on Aging and Dementia."

The symposium is named in honor and memory of the late William R. Markesbery, MD, founding director of the Sanders-Brown Center on Aging and Alzheimer's Disease Research Center at the University of Kentucky. Dr. Markesbery's legacy of groundbreaking research at the Center on Aging has formed the bedrock for our quest to understand and treat Alzheimer's disease and to improve the quality of life of the elderly. We have no doubt that Dr. Bill Markesbery's work will live on for generations to come as we continue the work he started here four decades ago.

In the scientific session today you will have the opportunity to hear clinicians and researchers from the University of Kentucky and other institutions share current findings, trends, and latest updates on dementia and aging disorders particularly as related to Alzheimer's disease.

We are honored that so many of you have chosen to join us in seeking to expand our knowledge and friendships. I hope the symposium will be both scientifically rewarding and enjoyable.

Sincerely,

Linda J. Van Eldik, Ph.D.
Director, Sanders-Brown Center on Aging & Alzheimer's Disease Research Center

Symposium Planning Committee:

Linda Van Eldik, PhD	Josh M. Morganti, PhD	Beverly Baesler	April Stauffer
Steve Estus, PhD	Elizabeth Rhodus, PhD	Laura Clewett	Beth Wells
Anika Hartz, PhD	Frederick Schmitt, PhD	Derrick Hord	Charlotte Wood
Daniel Lee, PhD		Hillary Smith	

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2025 Markesbery Symposium, Scientific Session

Friday, October 31, 2025

9:00am	**Display posters before 10am** Trainees have 20-minute breakfast meetings with each speaker in meeting rooms adjacent to Harris Ballroom.	330D & 330E
9:50am	**Registration**	Harris Ballroom
10:00am	**Symposium Welcome** Linda Van Eldik, PhD, Director, Sanders-Brown Center on Aging & University of Kentucky ADRC	
10:10am	***Precision Health Strategies for Alzheimer's Disease and Related Dementias: From Systems Biology to Biomarkers and Therapeutic Targets*** Andrew Saykin, PsyD, Director, Center for Neuroimaging and Indiana Alzheimer's Disease Research Center; Professor, Departments of Radiology, Psychiatry, Neurology, and Medical & Molecular Genetics, Indiana University School of Medicine	
11:10am	**Creating Harmony While Living with Dementia** Elizabeth Rhodus, PhD, Assistant Professor, Sanders-Brown Center on Aging and Department of Behavioral Science, University of Kentucky	
11:30am	**Lunch** Boxed lunches	
12:15pm	**Poster Session #1**	
12:50pm	**Poster Session #2**	
1:25pm	***The Amyloid Cascade Hypothesis; Arguments For and Against, With Public Health Implications*** Peter Nelson, MD/PhD, Professor and Vice Chair for Basic Science Research, Pathology and Laboratory Medicine; Director, Neuropathology Core, University of Kentucky ADRC	
1:45pm	***Hippocampal Breakdown at the Crossroads of Proteinopathy and Inflammation in Aging*** Julie Schneider, MD, Professor, Departments of Pathology and Neurological Sciences; Director, Alzheimer's Disease Research Center, Rush University	
2:45pm	**Poster Award Presentations**	

KEYNOTE SPEAKER

"Precision Health Strategies for Alzheimer's Disease and Related Dementias: From Systems Biology to Biomarkers and Therapeutic Targets"

Andrew Saykin, PsyD
Director, Center for Neuroimaging and Indiana Alzheimer's Disease Research Center; Professor, Departments of Radiology, Psychiatry, Neurology, and Medical & Molecular Genetics, Indiana University School of Medicine

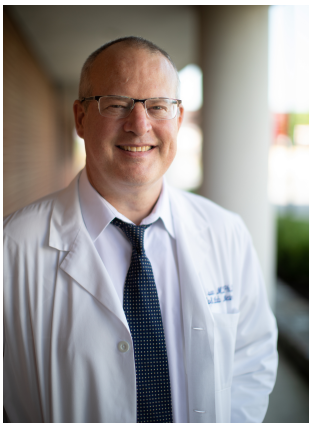
Andrew Saykin, PsyD, is Director of the Indiana Alzheimer's Disease Research Center at Indiana University. He is also the Raymond C. Beeler Professor of Radiology and Professor of Medical and Molecular Genetics, Neurology and Psychiatry. In addition, he leads the Genetics Core of the Alzheimer's Disease Neuroimaging Initiative. Dr. Saykin's research focuses on precision medicine for early Alzheimer's disease detection and for identification of disease mechanisms that may lead to potential therapeutic targets. Dr. Saykin uses integrative analysis strategies to study the relationship among clinical phenotypes, genetic susceptibility, and molecular signatures in Alzheimer's disease and other complex diseases. He participates in multiple training programs where he is committed to fostering the next generation of translational researchers. He is founding Editor-in-Chief of Brain Imaging and Behavior and has an extensive publication record.

KEYNOTE SPEAKER

"Hippocampal Breakdown at the Crossroads of Proteinopathy and Inflammation in Aging"

Julie Schneider, MD, Professor, Departments of Pathology and Neurological Sciences; Director, Alzheimer's Disease Research Center, Rush University

Julie Schneider, MD, is Director at the Rush Alzheimer's Disease Research Center at Rush University in Chicago where she is the Deborah R. and Edgar D. Jannotta Presidential Professor of Pathology and Neurological Sciences. She completed her Neurology residency at the University of Chicago and Neuropathology fellowship at Emory University. Dr. Schneider leads clinicopathologic work for multiple studies including the Rush Religious Orders Study and Memory and Aging Project. Dr. Schneider's research explores the relationship between neuropathology and age-related cognitive decline, with particular emphasis on risk factor discovery, biomarker development, and prevention/treatment strategies. Her research expertise includes Alzheimer's disease, Limbic-predominant Age-related TDP-43 Encephalopathy (LATE), Vascular and Mixed Dementias. She is a member of the National Advisory Council on Aging and has an extensive record of publications.



"The Amyloid Cascade Hypothesis: Arguments For and Against, With Public Health Implications"

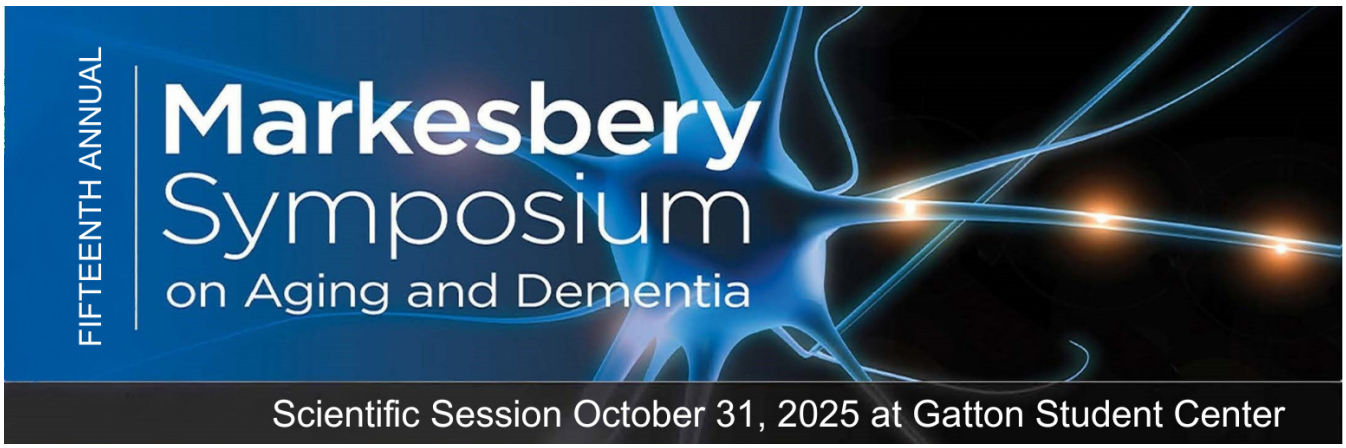
Peter T. Nelson, MD, PhD
Professor and Vice Chair for Basic Science Research, Pathology and Laboratory Medicine; Director,Neuropathology Core, University of Kentucky ADRC

Peter Nelson received his medical degree and a doctorate in philosophy in Neurobiology, from the University of Chicago Pritzker School of Medicine. He then completed anatomic pathology residency, neuropathology clinical fellowship, and post-doctoral fellowship at the University of Pennsylvania Medical Center, Philadelphia. Nelson is board certified by the American Board of Pathology in Anatomic Pathology and Neuropathology. He leads the Neuropathology Core of the University of Kentucky Alzheimer's Disease Research Center. Nelson's areas of interest include neuropathology, microRNAs (miRNAs), Alzheimer's disease, Limbic-predominant age-related TDP-43 encephalopathy (LATE), hippocampal sclerosis of aging (HS-Aging), dementia with Lewy bodies, and other neurodegenerative diseases.

"Creating Harmony While Living With Dementia"

Elizabeth Rhodus, PhD
Assistant Professor, Sanders-Brown Center on Aging and Department of Behavioral Science, University of Kentucky

Elizabeth Rhodus received her PhD in Gerontology from the College of Public Health at the University of Kentucky and experimental training as a post-doctoral scholar at University of Kentucky's Alzheimer's Disease Research Center. Rhodus is an Assistant Professor at the UK Sanders-Brown Center on Aging, Department of Behavioral Science, and the Center for Health, Engagement, and Transformation. Since 2020, she has authored 17 peer-reviewed articles, presented at numerous national and international conferences, and currently has a 5-year NIH/NIA K23 career development award. Dr. Rhodus' work creates opportunities for increased knowledge for functional aging in community-dwelling older adults with cognitive impairment with a goal to translate rigorous science into medically at-risk communities.



Please take an opportunity to review the posters from our emerging scientists that are located in the Harris Ballroom.

Poster Abstracts

Page Number	Poster	Last Name	First Name	Category
9	1	Aguzzoli Heberle	Bernardo	Graduate Student
10	2	Allen	Valerie	Undergraduate Student
11	3	Amin	Kishan	High School Student
12	4	Ashley	Clair	Graduate Student
13	5	Aung	Khine Zin	Postdoctoral Scholar
14	6	Banik	Avijit	Staff
15	7	Bailey	Caleb	Postdoctoral Scholar
16	8	Barber	Justin	Staff
17	9	Buzinova	Valeria	Graduate Student
18	10	Byer	Blake	Undergraduate Student
19	11	Bytyki	Leke	Staff
20	12	Clark	Maria	Staff
21	13	Constantino	Nicholas	Graduate Student
22	14	Crawford	Stirling	Staff
23	15	D'Elia	Noelia	Postdoctoral Fellow
24	16	Dimas	Sophia	Graduate Student
25	17	Doyle	Patricia	Graduate Student
26	18	Drinkard	Esther	Postbaccalaureate Student
27	19	Fariduddin	Osswaah	Staff
28	20	Fox	Grant	Graduate Student
29	21	Gant	Chris	Staff
30	22	Gazula	Meghana	Staff
31	23	Gholamrezaeinejad	Fatemeh	Graduate Student
32	24	Gordon	Lacey	Staff
33	25	Hall	Megan	Staff
34	26	Green	McKenna	Undergraduate Student
35	27	Islam	Jahid	Postdoctoral Scholar
36	28	Holland	Will	Medical Student
37	29	Irmen	Riley	Graduate Student
38	30	Hamid	Omar	Undergraduate Student
39	31	Jinawong	Kewarin	Postdoctoral Scholar
40	32	Karki	Bikram	Graduate Student
41	33	Lu	Ting-Hsuan	Postdoctoral Scholar
42	34	Lin	Ruei-Lung	Staff
43	35	Lundt	Samuel	Postdoctoral Fellow
44	36	MacLean	Steven	Graduate Student
45	37	Lysaker	Colton	Postdoctoral Scholar
46	38	Moallem	Elika	Graduate Student
47	39	Muzyk	Hana	Graduate Student
48	40	Moore	Lauren	Undergraduate Student

Page Number	Poster	Last Name	First Name	Category
49	41	Ning	Xiaotong	Graduate Student
50	42	Neltner	Allison	Undergraduate Student
51	43	Nolt	Georgia	Graduate Student
52	44	Onishchenko	Dmytro	Graduate Student
53	45	Palacio	Sara	Graduate Student
54	46	Oviedo	Jason	Undergraduate Student
55	47	Pallerla	Akhil	Graduate Student
56	48	Pandey	Rajita	Graduate Student
57	49	Patterson	Brady	Graduate Student
58	50	Presley	Parker	Undergraduate Student
59	51	Phe	Panhavuth	Medical Student
60	52	Roberts	Taylor	Undergraduate Student
61	53	Rocha-Rangel	Patricia	Staff
62	54	Rock	Miriam	Staff
63	55	Rogers	Colin	Staff
64	56	Sabra	Hady	Graduate Student
65	57	Sales	Johnathan	Staff
66	58	Sharpe	Julianne	Undergraduate Student
67	59	Shahidehpour	Ryan	Postdoctoral Fellow
68	60	Sims	Sophiya	Graduate Student
69	61	Speaks	Hannah	Graduate Student
70	62	Spiller	Emily	Undergraduate Student
71	63	Stephens	Isaiah	Graduate Student
72	64	Sumithrarachchi	Manekya	Graduate Student
73	65	Turner	Sierra	Graduate Student
74	66	Vincent	Jonathan	Graduate Student
75	67	Weiss	Blaine	Graduate Student
76	68	Witucki	Addison	Undergraduate Student
77	69	Wolff	Nancy	Staff
78	70	Wright	Nicholas	Staff
79	71	Xu	Xizhi	Graduate Student
80	72	Zuluaga-Osorio	Sofia	Graduate Student
81	73	Yanev	Pavel	Postdoctoral Scholar
82	74	Shepard	Savannah	Undergraduate Student
83	75	Oyarzún-González	Ximena	Postdoctoral Scholar

Poster Number 1

RNA isoform changes in human Alzheimer's disease brains using deep long-read RNA sequencing in 115 subjects

Bernardo Aguzzoli Heberle[1,2], J. Anthony Brandon[1], Lacey A. Gordon[1], Madeline L Page[1], Mark E. Wadsworth[1], Yuriko Katsumata[1,3], Sonja Scholz[4], Edward J. Fox[5], Anantharaman Shantaraman[5], Sidra Aslam[6], Geidy Serrano[6], Thomas G. Beach[6], Peter T. Nelson[1], Dave W. Fardo[1,3], Nicholas T. Seyfried[5], Mark T. W. Ebbert[1,2,7]

[1]Sanders-Brown Center on Aging, University of Kentucky; [2]Dept of Neuroscience, UK College of Medicine; [3]Dept of Biostatistics, UK College of Public Health; [4]National Institute of Neurological Disorders and Stroke, Bethesda, MD; [5]Dept of Neurology, Emory University School of Medicine, Atlanta, GA; [6]Banner Sun Health Research Institute, Sun City, AZ; [7]Division of Biomedical Informatics, Internal Medicine, UK College of Medicine.

Graduate Student

Background: Alzheimer's disease (AD) risk genes average 14 annotated RNA isoforms, with each gene encoding an average of five different proteins. Previous AD RNA sequencing (RNA-seq) studies overlooked isoforms due to limitations of short-read sequencing. Long-read RNA-seq enables more accurate isoform quantification and discovery. We therefore applied deep long-read RNA-seq in human frontal cortex brain tissue to (1) catalogue new isoforms and genes, (2) test AD associated changes in isoform expression and usage, and (3) map DNA variants associated with changes in isoform expression patterns. An interactive web portal is provided to facilitate data-driven hypothesis generation and study designs.

Methods: We sequenced 115 frontal cortex postmortem aged human brain samples (29 AD males, 26 AD females, 30 control males, 30 control females) using one R10.4.1 Oxford Nanopore PromethION flow cell per sample (~70 million mapped reads/sample). To our knowledge this is the largest human brain long-read RNA-seq cohort sequenced to date. Analysis tools included pychopper, minimap2, bambu, EdgeR, and MatrixEQTL.

Results: We uncovered 3,177 new high confidence isoforms with counts per million (CPM) > 0.5 and unique reads > 10 in at least 24 samples. Out of these 3,177 new isoforms, 2,788 came from known genes and 389 came from unannotated loci (new genes). We identified 322 differentially expressed isoforms (FDR < 0.05 & $|\log_2$ fold change$|$ > 0.38) and 644 usage shifted isoforms (FDR < 0.05) between cases and controls. Over 100 differentially expressed/used RNA isoforms arose from loci without a significant gene-level differential expression signal. Quantitative trait loci (QTL) mapping yielded 329 isoform expression QTLs (FDR < 0.05) from over 100 genes that lacked a gene-level QTL signal, highlighting isoform specific regulation.

Conclusions: We identified thousands of new high-confidence isoforms, demonstrating that significant gaps remain in our understanding of isoform diversity in the human brain. We found differential isoform expression/usage patterns and QTLs that are hidden when collapsing isoforms into a single gene measurement. These results highlight the importance of isoform level analysis using long-read RNA-seq and open new avenues for the development of therapeutics and biomarkers in AD and other brain-related disorders.

Poster Number 2

Treatment of glycosaminoglycan-interacting small molecule reduces cytoplasmic accumulation of TDP-43 in hippocampal and cortical regions in TDP-43 G348C transgenic mouse model

Valerie M Allen[1,2], Johnathan Sales[1,2], Lee Dix[1,2], Myung-Hee Kim[3], Paul Gregor[3], Maj-Linda B. Selenica[1,2]

[1]Department of Molecular and Cellular Biochemistry, UK College of Medicine; [2]Sanders-Brown Center on Aging, University of Kentucky; [3]Gismo Therapeutics, Lexington, KY

Undergraduate Student

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the cytoplasmic accumulation of transactive response DNA-binding protein 43 (TDP-43). Heparan sulfate glycosaminoglycans (HS-GAGs) are a novel therapeutic target in neurons for enabling the endocytosis of TDP-43 aggregates. GTC-3295, a glycosaminoglycan-interacting small molecule developed by Gismo Therapeutics, aims to treat ALS by potentially inhibiting TDP-43 binding to HS-GAGs, therefore, reducing the spread of TDP-43 proteinopathy.
Methods: Animal model: The G348C mouse model develops cytoplasmic aggregates of TDP-43 in the spinal cord, hippocampus, and cortex, and presents impaired motor function, spatial learning, and memory. We performed po?? administration of two different and performed drug dose responses. Mice were grouped based on drug dosages and genotype: Cohort 1 was administrated with GTC-3295 compound: group 1=non-Tg vehicle (n=14, 7M, 7F), group 2=G348C vehicle (n=14, 7M, 7F), group 3= G348C [3mg/kg], group 4=G348C [10mg/kg] (n=14, 7M, 7F), group5=G348C [30mg/kg] (n=14, 7M, 7F). Cohort 2 received the following treatment: group 1=non-Tg vehicle (n=14, 7M, 7F), group 2= G348C vehicle (n=14, 7M, 7F), group 3=G348C GTC-3062 [10mg/kg] (n=14, 7M, 7F), group 4=G348C GTC-3332 [10mg/kg] (n=14, 7M, 7F).
Immunohistochemistry (IHC): Polyclonal human (Protein Tech, 1:50,000) antibody was used to analyze the expression of total TDP-43. Biotinylated NeuN (Millipore Sigma, 1:30,000) was used to measure neuronal loss. Polyclonal chicken (Encor Biotech, 1:2,000) antibody was used to analyze the reduction of neurofilament light chain levels. Behavior: Motor coordination and learning were tested using the rotarod behavior assay. Anxiety and motor coordination were measured using the spontaneous open field assay. The outputs of the Y-maze assay provided insights into spatial learning and memory.
Results: Our analysis revealed a significant decrease in total TDP-43 accumulation in the cortex and hippocampus for G348C TDP-43 mice groups treated with GTC-3925 at [3mg/kg] and [10mg/kg] when compared to the G348C TDP-43 vehicle group. The GTC-3062-treated group showed a significant decrease in the medial cortex and hippocampus, while the GTC-3332-treated group had a significant decrease in the anterior and medial cortices. We observed no changes in the behavior battery test performed.
Conclusion: This study revealed that GTC-3295, GTC-3332, and GTC-3062 effectively reduced cortical and hippocampal TDP-43 aggregation in the G348C ALS mouse model with no effects on cognitive and motor behaviors.
Acknowledgments: This study was supported by DOD-ALSRP Therapeutic Idea Award/Gismo Therapeutic: W81XWH2210379.

Poster Number 3

Cell type–specific expression and subcellular localization of C/EBPβ in primary astrocytes and microglia

Kishan Amin[1,2], Paresh Prajapati[2], and Wang-Xia Wang[2,3]

[1]Paul Laurence Dunbar High School, Lexington, KY; [2]Sanders-Brown Center on Aging, [3]Pathology and Laboratory Medicine, College of Medicine, University of Kentucky, Lexington, KY

High school student

Background: Research has indicated that neuroinflammation is a key component of the pathophysiology of Alzheimer's Disease. One prominent protein in AD pathology is CCAAT-Enhancer Binding Proteins β (C/EBPβ), which regulates pro-inflammatory genes. However, it is not known whether a pattern is shown in terms of which brain cells C/EBPβ expresses in, as well as where inside the cell its isoforms express in.

Methods: Two types of cells were used: astrocytes and microglia. The methodology for this experiment was split into 2 main parts. The first was Immunocytochemistry, where the proteins inside the cells were fixed, then cells were permeabilized and incubated with primary C/EBPβ antibodies. The second was Fluorescent Detection, where fluorophore attached secondary antibodies were then bound to primary antibody in the cells, were excited with light, showing the relative position of the C/EBPβ.

Results: The results showed that in microglia, C/EBPβ was most prevalent in the nucleus, and in astrocytes, C/EBPβ was most prevalent in the cytoplasm. The average quantity of cells expressing C/EBPβ was slightly higher than in the microglia.

Conclusion: These results indicate that C/EBPβ exhibits cell type–specific subcellular localization, suggesting distinct regulatory functions in microglia and astrocytes during cellular activity or inflammatory responses. Future work should explore how to mitigate the effects of C/EBPβ or to rid excess from the cell location entirely, in an effort to mitigate the symptoms of Alzheimer’s Disease.

Acknowledgments: This project is supported by National Institute on Aging (R01AG082142).

Poster Number 4

Microglial metabolic reprogramming links lactate to Alzheimer's disease

Clair C. Ashley[1], Nicholas J. Constantino[3], Evan M. Neary[1], J. Andy Snipes[1], Lance A. Johnson[1,2], Shannon L. Macauley[1,2]

[1]Department of Physiology, College of Medicine, University of Kentucky, Lexington, KY; [2]Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY; [3]Department of Neuroscience, College of Medicine, University of Kentucky, Lexington, KY

Graduate Student

Background: Alterations in metabolism may drive early pathology in Alzheimer's Disease (AD). Metabolic changes involving glycolysis and its end product, lactate, occur in pre-symptomatic AD, prior to late-stage reductions in glucose metabolism. Microglia, the brain's innate immune cells, become reactive in response to amyloid-beta (Aβ) and shift metabolism from favoring oxidative phosphorylation to glycolysis. The drivers and consequences of these early metabolic adaptations remain unclear. Therefore, this project aims to characterize brain lactate metabolism relative to amyloid pathology using the APPswe/PSEN1dE9 (APP/PS1) mouse model and test whether blocking lactate metabolism alters pathology, brain metabolism, and neuroinflammation.

Methods: Interstitial fluid (ISF) and brain lactate levels were measured in APP/PS1 and WT mice using in vivo microdialysis and metabolomics. Transcriptomics data was analyzed to determine cellular expression of lactate production (*Ldha*) and consumption (*Ldhb*) transcripts. Immunohistochemistry quantified Aβ load, lactate metabolism, and microglial subtypes. Mice were injected with Stiripentol, an LDH inhibitor, to examine the effects of blocking lactate metabolism on amyloid pathology and reactive glia.

Results: Brain and ISF lactate increased with Aβ pathology, while ISF glucose decreased, suggesting a glycolytic shift occurs with amyloid plaques. Specifically, LDHA was elevated peri-plaque, suggesting increased lactate production. Contrary to dogma, this is driven by peri-plaque microglia, not astrocytes. Microglia highly express both *Ldha* and *Ldhb*, with *Ldha* enriched in disease-associated microglia surrounding plaques. Pharmacological inhibition of lactate metabolism reduced ISF Aβ, ISF lactate, and reactive plaque-associated microglia.

Conclusion: Our findings suggest that glycolytic reprogramming in reactive microglia occurs in response to Aβ and that targeting lactate metabolism could be a viable therapeutic strategy in AD.

Acknowledgments: NIA R01 AG068330 (PI: Macauley); NIA R01AG093847 AG068330 (PI: Macauley); NIA K01 AG050719 (PI: Macauley); BrightFocus Grant (PI: Macauley); CNS Metabolism COBRE P20 GM148326 (PI: Macauley); CART grant (PI: Macauley)

Poster Number 5

Filling the genetic gaps in neurodegenerative disorders: A multi-allelic variant perspective

Khine Zin Aung[1,2], Inori Tsuchiya[1,2], Xian Wu[1,2], Erin L. Abner[2,3], Peter T. Nelson[2,4], David W. Fardo[1,2], Yuriko Katsumata[1,2]

[1]Department of Biostatistics, University of Kentucky, Lexington, KY, USA
[2]Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA
[3]Department of Epidemiology and Environmental Health, Lexington, KY, USA [4]Department of Pathology, University of Kentucky, Lexington, KY, USA

Postdoctoral Scholar

Background: Genome-wide association studies (GWAS) often overlook multiallelic variants because most standard methods are designed for biallelic loci, leaving an underexplored area of genetic risk in neurodegeneration. To address this, we are developing a software tool to analyze multiallelic variants using score-based algorithms within a generalized linear model framework. Our approach jointly encodes all alternative alleles, enabling both global and per-allele tests while adjusting for covariates. Applied to neurodegenerative disease outcomes, this method will reveal multiallelic associations that conventional biallelic-only pipelines overlook.
Methods: We have conducted a simulation study using 1000 Genomes Project Phase 3 genotypes from five ancestry groups (European, African, Admixed American, East Asian, South Asian). We simulated null continuous and binary phenotypes within each group to evaluate type I error. Score-based global tests were performed separately in each group, followed by an inverse-variance-weighted approach to combine score statistics across groups as a meta-analysis. We will next apply our score-based multiallelic variant analyses to neuropathology (NP) datasets from the National Alzheimer's Coordinating Center (NACC), the Alzheimer's Disease Neuroimaging Initiative (ADNI), and the Religious Orders Study and Memory and Aging Project (ROSMAP), all of which are linked to the Alzheimer's Disease Sequencing Project (ADSP) whole genome sequencing (WGS) data. All analyses will adjust sex, age at death, principal components.
Results and Conclusion: The simulations demonstrated well-calibrated type I error for both continuous and binary outcomes; Q-Q plots of meta-analytic p-values showed no evidence of inflation or deflation. Our framework accommodates both bi- and multiallelic loci, enabling to handle loci that appear biallelic due to missing alleles, and provides both global (variant-level) and allele-specific tests with meta-analysis options for multi-cohort integration. Leveraging this score-based test in neurodegenerative disease cohorts will recover multiallelic signals overlooked by biallelic pipelines, thereby advancing genetic discovery in neurodegenerative disease and facilitating downstream variant-to-function and biomarker discovery. The details will be shown at the time of presentation. **Acknowledgments:** This study is supported by UK-ADRC Developmental Project Program-P30AG072946 and P01AG078116, Levis D. and Margot D. McCullers Fund for Research and Education on Alzheimer's Disease and Related Dementia 2024.

Poster Number 6

Glycolytic transporters in epileptic brain capillaries: Impact on brain energy metabolism

Avijit Banik[1], Manekya D. Sumithrarachchi[1], Makenna N. Pelfrey[1], Elizabeth N. Clark[1], Rebecca R. Smith[2], Anika M.S. Hartz[2,3], Björn Bauer[1,2]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky; [2]Sanders-Brown Center on Aging, University of Kentucky; [3]Department of Pharmacology and Nutritional Sciences, College of Medicine, University of Kentucky

Staff

Background: Metabolic homeostasis in the brain is plastic and shifts in disease, including epilepsy. Four major processes in the brain are responsible for metabolic homeostasis and conduct energy transfer: glycolysis, oxidative phosphorylation, glutamine metabolism, and fatty acid oxidation. Of those, glycolysis is the primary process that generates metabolic energy for the brain. At the molecular level, the solute carrier transporters glucose transporter 1 (GLUT1) and monocarboxylate transporter 1 (MCT1) facilitate glucose and lactate transport, respectively, across the brain capillary endothelium. In epilepsy, however, the blood-brain barrier is dysregulated, which affects glucose transport and downstream brain metabolism. The details of how blood-brain barrier GLUT1 and MCT1, and ultimately brain metabolic homeostasis, are altered in epilepsy are unknown. Therefore, in the present study, we conducted first experiments aimed at understanding GLUT1 and MCT1 expression levels in brain capillaries of rats with chronic epilepsy (CE).
Methods: We induced seizures in 8-9-week-old female Wistar rats using the lithium-pilocarpine protocol. Six months after seizure induction, animals exhibiting spontaneous recurrent seizures (CE) were identified with piezo/video monitoring. At 17 months of age, CE rats and age-matched controls (CTRL) were euthanized, and brain capillaries were isolated for GLUT1 and MCT1 immunostaining. We visualized immunostained GLUT1 and MCT1 with confocal microscopy and used the Nikon NIS Elements tool to quantitate GLUT1 and MCT1 fluorescent intensity in brain capillary membranes.
Results: Confocal images of immunostained brain capillaries showed a distinct expression pattern for both GLUT1 and MCT1 along the luminal and abluminal capillary membranes. Quantitation of fluorescence intensity revealed a statistically significant ($p<0.0001$) two-fold increase in GLUT1 levels in brain capillaries from CE rats (1,679 ± 70 afu) compared to capillaries from CTRL rats (757 ± 40 afu). For MCT1, we did not find a difference in fluorescence intensity between the two groups.
Conclusion: Our data suggest increased GLUT1 expression in brain capillaries from CE rats compared with CTRL rats. This may reflect a compensatory adaptation to meet the energy demands in epilepsy, supporting a metabolic shift toward glycolysis and lactate shuttling during seizures. In future studies, we will examine the role of glycolytic enzymes in brain capillaries to elucidate the mechanisms underlying this metabolic shift in epilepsy.
Funding: This research was supported by NIH R01NS079507 (BB) and NIH R01AG075583 (AMSH).

Poster Number 7

Early loss of astrocyte p38α MAPK reduces hippocampal neuroinflammation and alters mitochondrial function in female mice during non-pathological aging

Caleb S. Bailey[1], John C. Gant[1,2], Hilaree N. Frazier[1,3], Josh M. Morganti[1,3], Meggie J. Coleman[1], Verda A. Davis[1], Hemendra J. Vekaria[4], Patrick G. Sullivan[3], Christopher M. Norris[1,2], Linda J. Van Eldik[1,3], and David J. Braun[1,3]

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[2]Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, KY
[3]Department of Neuroscience, University of Kentucky, Lexington, KY
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Postdoctoral Scholar

Background: The p38 mitogen-activated protein kinase has a well-characterized role in modulation of inflammatory processes throughout the body. In the central nervous system, p38 is primarily studied within neurons and microglia, most commonly in the context of neurological insult. The present study was designed to determine its function in astrocytes during non-pathological aging.

Methods: We generated a conditional knockout model in which a tamoxifen-inducible *Aldh1l1* promoter drives Cre recombinase expression in mice with exon 1 of the p38α gene flanked by loxP sites. Knockout of astrocyte p38α was achieved via tamoxifen administration in young sexually mature mice at 3-4 months old. Animals were subsequently aged to 21-24 months prior to performing electrophysiological, immunohistochemical, and biochemical analyses.

Results: We found that early loss of astrocyte p38α was associated with a reduction in hippocampal neuroinflammation and concomitant enhancement of synaptic strength in aged female mice. In subsequent experiments in younger animals, the knockout reduced peripheral GFAP levels and increased non-synaptic mitochondrial uncoupling.

Conclusions: These findings indicate that astrocyte p38α has wide-ranging effects on brain metabolism, inflammation, and synaptic function during the course of normal aging, including release of GFAP from the central nervous system to the periphery. Follow-up studies exploring the role of astrocyte p38α in various age-associated neuropathological contexts are warranted.

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Poster Number 8

Tau PET Standardized Uptake Value Ratio associates with visuoconstructional and visual memory in older adults with elevated brain amyloid

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Staff

Background: The complex figure copy and delayed recall is widely used to assess visuospatial, visual memory, and executive abilities in ADRD. Lesion and neuroimaging studies indicate that the spatial operations of these tasks are largely processed in the right brain hemisphere. However, studies of nuclear imaging of tau burden—a marker of neurodegeneration—and visuoconstructional tasks are few. The present study examined complex figure performance in relation to right relative to left regional tau ratios.
Methods: Data from the UK Sanders-Brown ADRC longitudinal cohort were used in the analyses. Inclusion criteria were having tau PET and a UDS visit within 3 years of tau PET with process scoring data available for the complex figure. Cerebellar tau was used as the reference for Standardized Uptake Value Ratio (SUVr). For each region, the right SUVr was divided by the left. Figure copy and delayed recall and story delayed recall scores were converted to z-scores adjusted for age, sex, and education using national norming equations. Raw figure process scores were examined as well.
Results: Of 28 participants with tau PET, all of whom had elevated brain amyloid, 9 had tau PET scans >3y prior to the UDS visit. Results were unchanged if analyses were performed with or without the 9, so all 28 were used. A negative correlation trend between figure copy and occipital tau ratio ($r = -0.31$, $p = 0.08$) was found. Figure delayed recall had a modestly negative correlation with tau temporal ratio ($r = -0.39$, $p = 0.05$). Planning was not correlated with frontal or any regional tau ratios. Story delayed recall had a modest positive correlation with parietal tau ratio ($r = 0.38$, $p = 0.05$).
Conclusion: The results suggest that greater tau burden in the right hemisphere (relative to the left) is related to slight impairments in complex figure copy and recall. Limitations of the study include a small and highly selected sample and lengthy time between PET and testing in ~30% of cases. Future studies will need to assess these associations in a larger sample.
Acknowledgments: P30AG072946

Poster Number 9

Sleep fragmentation in wild-type & PS19 mice

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Graduate Student

Background: In AD, tau forms toxic intracellular tangles, known as neurofibrillary tangles (NFTs). Cognitive and functional decline begins approximately when NFTs develop. Although amyloid-β (Aβ) has long been believed to drive tau pathology, the mechanism is unsettled. Sleep fragmentation (SF) and circadian rhythm disruption are evident in AD. SF studies, including those conducted by our lab, have demonstrated that fragmented sleep in various AD mouse models results in an increase in Aβ pathology and disrupts circadian rhythms. The objective of this study was to determine whether SF similarly affects tau levels in a well known model of tau deposition, the PS19 mouse.

Methods: The study comprised 16 PS19 mice and 16 wild-type (WT) mice, half male and half female, in each group. To record a baseline sleep-wake activity, all 32 mice were placed in Piezo cages for a week. Following this, half of the mice remained in the piezo cages, which constituted the control group with unrestricted sleep (US), while the other half were moved to cages that contained a bar that swept across the bottom of the cage and under the mice, thereby fragmenting the mice's sleep. The sweep-bar cages were also set up with a system to record activity. After four weeks, the mice were removed from the cages, and their brain tissue collected at a single time point, in the late afternoon. Following tissue collection, immunoassays were used to measure the levels of total tau and hyperphosphorylated tau in the neocortex and hippocampus.

Results: SF resulted in a loss of sleep during the light phase, and an increase in dark phase sleep, with no net loss of total sleep. SF also caused an increase in intradaily variability, a decrease in activity amplitude, and a shift in acrophase. Changes in the amounts of total and phosphorylated tau were relatively modest in both brain regions, in all fractions analyzed. Soluble rodent Aβ was actually decreased.

Conclusion: Tau levels may be more resistant to SF compared to Aβ.

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Poster Number 10

Automated quantification of field potential recordings in mouse hippocampal slices using a derivative-based approach

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Undergraduate Student

Background: Input/output (I/O) curve analysis of field potential recordings in ex vivo hippocampal slice electrophysiology provides critical insights into synaptic function. Still, it is traditionally quantified manually, a process prone to variability and inefficiency.

Methods: We developed an automated pipeline in MATLAB and Python to analyze field potentials across 11 stimulus intensities (25–600 µA) in the CA1 and dentate gyrus of mouse hippocampal slices. A derivative-based approach identified physiological landmarks, with slope peaks corresponding to fiber volley extrema, the peak of the EPSP, and the population spike amplitude. EPSP slope was extracted from the upper third of the EPSP to capture AMPA receptor–mediated synaptic function best.

Results: This approach enables automated quantification of fiber volley amplitude, EPSP slope, EPSP maximum amplitude, and population spike threshold (EPSP slope at the first spike). The pipeline generates standard output plots, including presynaptic excitability (fiber volley amplitude vs. stimulus intensity), postsynaptic response curves (EPSP slope vs. stimulus intensity), and basal synaptic strength (EPSP slope vs. fiber volley amplitude), and summary bar graphs. Automated results showed ~76% concordance with hand-calculated datasets, supporting the method's accuracy.

Conclusion: Our automated pipeline provides a robust and objective framework for quantifying hippocampal synaptic function, reducing user bias and time burden while enabling standardized electrophysiological analyses across experimental cohorts.

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Poster Number 11

Dim light at night disrupts circadian rhythms and exacerbates Alzheimer's-related pathology in hAPPSAA mice

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Staff

Background: Disruption of circadian rhythms has been increasingly linked to Alzheimer's disease (AD) progression, with mounting evidence that alterations of light–dark cycles contribute to sleep fragmentation and heightened AD risk.

Methods: A cohort of 40 mice both male and female hAPP-SAA KI and hAPP-WT KI mice (12–13 mo) were housed for 8 weeks in either standard 12:12 h light–dark (LD) or a 12:12 h light–dim light at night (dLAN) cycle (5–10 lux at night) cycles. After 8 weeks, the mice were euthanized and brains were collected for immunohistochemistry (IHC), ELISA, and multiplex cytokine analysis in neocortex and hippocampus.

Results: dLAN reduced circadian rhythm amplitude and stability while increasing fragmentation in both genotypes within two weeks. In hAPP-SAA KI mice, dLAN modestly increased hippocampal plaque burden and soluble neocortical Aβ. Astrocyte reactivity was elevated by genotype but not altered by nighttime light exposure. In contrast, microglial markers (CD45+, MHCII) were increased with dLAN with CD45+ area elevated in hippocampus, and MHCII+ cell counts greater in the cortex and hippocampus of hAPP-SAA KI mice. There were also distinct spatial responses between the microglia markers suggesting that dLAN primes microglia toward an antigen-presenting phenotype (MHCII) in the presence of Aβ. Yet, the microglia/macrophage priming was not associated with amplified cytokine or chemokine levels.

Conclusion: These findings demonstrate that low-level light at night is sufficient to perturb circadian organization and selectively amplifies amyloid deposition and immune activation most notably in the hippocampus, in a predisposed AD background. Nighttime light exposure may thus represent a modifiable environmental factor influencing progression of AD-related pathology.

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Poster Number 12

Grit, Resilience, and Subjective Cognitive Decline: Insights from Black American Adults

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Staff

Background: Research shows that an early indicator of cognitive impairment is subjective cognitive decline (SCD). Yet, the associations of psychosocial coping mechanisms like grit and resilience with SCD, particularly in Black Americans, remain understudied. Previous research shows that grit and resilience are key coping mechanisms in Black individuals. Grit reflects perseverance toward long-term goals, while resilience represents the ability to positively adapt and recover from adversity. Both grit and resilience have been found to increase throughout one's lifespan and are often shaped by unique cultural and social experiences. This study examined sex differences in the impact of grit and resilience on SCD.

Methods: Two hundred forty-two cognitively normal (Mean age = 44.3, SD = 8.6; 147 female) participants were recruited from CloudResearch for the study. The participants completed standardized measures assessing SCD, grit, resilience, and health and demographic characteristics. We performed linear regression analyses and reported standardized beta coefficients to describe the estimated independent effect of the predictor variables.

Results: show that greater levels of grit are associated with higher SCD scores, with high scores indicating worse SCD. However, the relationship between grit and SCD is stronger in Black men ($\beta = 0.704$, $p = <0.001$) than in women ($\beta = 0.528$, $p = <0.001$). In contrast, higher resilience is significantly associated with lower SCD scores in Black women ($\beta = -0.186$, $p = <0.002$) but not in men ($\beta = -0.081$, $p=<0.326$).

Conclusions: Our findings suggest that grit may have a worse impact on SCD in men as a coping mechanism, while resilience appears protective against SCD in Black women. These results highlight potential gender differences in how psychological traits influence the experience of cognitive health among Black Americans. Also, our study emphasizes the need to consider and further explore gender-specific factors when addressing cognitive health in diverse populations.

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Poster Number 13

Dichotomous sleep phenotypes in Alzheimer's disease and aging: Sleep loss occurs with early amyloid-beta pathology but increased REM vulnerability occurs with age

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Graduate Student

Background: Alzheimer's disease (AD) pathology, particularly amyloid-beta (Aβ) deposition, is associated with sleep disturbances, but how these changes relate to total Aβ burden and aging remains unclear.

Methods: Aβ plaque staining was done using the HJ3.4 antibody, and quantification was done using Halo quantitative image analysis. Sleep architecture was examined in 6- and 18-month female APP/PS1 and wildtype (WT) mice using EEG/EMG recordings. A sleep deprivation (SD) challenge assessed the effects of age and Aβ on rebound sleep.

Results: At 6 months, <8% cortical Aβ deposition coincided with a 43% and 61% reduction in NREM and REM sleep, specifically in the dark period. Aβ deposition reduced sleep drive and NREM slow-wave sleep quality (delta power) by 6 months, but no further NREM loss occurred despite a 2.5X increase of cortical Aβ deposition at 18 months. Aging independently decreased REM sleep at 18 months in WT mice, with a 40% reduction from 6 months. Following SD, young WT mice exhibited robust rebound with NREM sleep increasing by 60% three hours post-SD. At 6 months, APP/PS1 and WT mice showed similar rebound, indicating early Aβ pathology does not impair sleep recovery. By 18 months, both genotypes exhibited diminished sleep rebound, indicating aging, not Aβ pathology, drives a vulnerability to sleep loss.

Conclusion: Aβ pathology causes NREM and REM sleep loss, but this phenotype does not progress with further pathology. With aging, REM sleep is reduced but NREM sleep remains intact. Sleep drive and sleep quality are reduced with the emergence of Aβ pathology, and high frequency EEG activity increases at the expense of low frequency EEG. Aged mice lose the ability to sleep rebound, suggesting an age dependent vulnerability to sleep loss.

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Poster Number 14

Depressive symptoms moderate the relationship between sleep and memory in older Black Americans

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Staff

Background: Slow wave sleep (SWS) has been linked to better visual-spatial working memory (VSWM)—a sensitive early marker of cognitive decline. Depressive symptoms have been shown to modulate memory performance, but their interactive effects on the relationship between SWS and VSWM remain underexplored in Black American populations disproportionately impacted by sleep disturbances. This study investigated the interaction between objectively measured SWS and depressive symptoms on VSWM among older Black Americans.

Methods: As part of a larger observational study examining longitudinal benefits of sleep in older Black Americans, participants (N=59; mean age 52.76) completed three consecutive nights of at-home sleep monitoring using the Sleep Profiler, a validated wearable device. VSWM performance was assessed using standardized memory tasks, while depression was assessed using the Geriatric Depression Scale. The analysis was conducted using Hayes' PROCESS macro for SPSS, which examined whether depression moderated the relationship between SWS and VSWM, while controlling for age, gender and marital status.

Results: SWS (B=0.665, p=0.006) and depressive symptoms (B=-2.177, p=0.008) had significant independent effects on VSWM. The moderation analysis revealed a significant interaction (B=-0.1106, p= 0.007) between SWS and depressive symptoms. Further examination of the conditional effects revealed a positive association between SWS and VSWM at low depressive symptom levels (t=2.8847, p=0.0057) and a negative association at higher depressive symptom levels (t=-2.7760, p=0.0076).

Conclusions: These findings suggest that while SWS supports VSWM at low levels of depressive symptoms, the benefit diminishes under high depressive symptoms. Thus, emphasizing the need to investigate sleep–mood interactions when assessing the benefits of sleep among aging Black Americans.

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Poster Number 15

Immunological profiling of human peripheral nerve cells during development and aging

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Postdoctoral Fellow

Background: The goal of this study is to define basic cellular and noncellular constituents of adult peripheral nerves using intact human nerve tissues from donors across a range of ages.

Methods: We detected Schwann cell (SC)-specific markers, such as S100β, NGFR, Sox10 and myelin protein zero (MPZ), together with axonal, extracellular matrix (collagen, fibronectin, laminin) and fibroblast markers to assess the SC's relationship to myelin, axons, other cell types, and the acellular environment by using a combination of fluorescent and chromogenic immunostaining methods, myelin-selective fluorophores, and standard histological stains.

Results: Whereas S100β and Sox10 were sufficient to reveal the SC phenotype in the absence of other stains, discriminating myelinating and non-myelinating SCs in mature and immature nerves required co-immunodetection of NGFR along with axonal and myelin markers. Surprisingly, our analysis of NGFR stained samples uncovered the existence of three different novel populations of NGFR positive nonglial cells in the stroma and perivascular areas of the endo-, peri-, and epineurium from all fetal, pediatric, and adult nerve biospecimens analyzed.

Conclusion: We provide a generic immunochemical roadmap to reveal the complex arrangement of both cellular and acellular elements in human nerve tissues to ascertain their changes during development, maturation, and aging.

Acknowledgments: NEUSTAR funding from the Dept. of Neurosurgery; Biospecimens Core Facility from the Markey Cancer Center; Ann Hanley Neuroscience Fund.

Poster Number 16

Microglial HIF1α is necessary to restrict demyelination and maladaptive neuroinflammatory responses in a mouse model of white matter degeneration

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Graduate Student

Background: White matter (WM) degeneration, though commonly affiliated with Multiple Sclerosis (MS), is also a feature of several neurodegenerative conditions, suggesting convergent mechanisms. Previous studies across different WM degenerative conditions demonstrate a commonality- reactive microglial subsets responsive to WM pathology, differentially enriched for expression of HIF1α, a master regulator of cellular glycolytic metabolism. HIF1α has been demonstrated to be instrumental in myeloid responses to inflammatory challenges *in vitro* and *in vivo* and plays a significant role in driving a disease responsive phenotype within mouse models of amyloidosis. The degree to which HIF1α drives microglial disease responses to WM pathology, however, remains a critical gap in knowledge.
Methods: We generated microglial-specific conditional knockouts of HIF1α via Tmem119CreERT2^{+} Hif1$\alpha^{fl/fl}$ ('cKO') and their wildtype littermates: Tmem119CreERT2^{-} Hif1$\alpha^{fl/fl}$ ('WT'). Following recombination, mice were subjected to cuprizone-mediated demyelination for 5 weeks (demyelination paradigm), or cuprizone-mediated demyelination followed by 2 weeks of normal chow (remyelination paradigm) with endpoints of histopathology, single-cell RNA sequencing, and spatial transcriptomics. A parallel approach was taken using immortalized murine microglia (BV2 cells), in which cells were pre-treated pharmacological inhibitor of HIF1α transcriptional activity (PX-478) prior to a type I interferon challenge. Endpoints included bulk RNA sequencing, Seahorse functional analysis, and metabolomic analysis.
Results: Our findings demonstrate that compared to WT, cKO mice exhibited enhanced deficits demonstrated by MBP and Olig2 staining and increased microglial reactivity (CD68, Iba1, Clec7a, MHCII, Stat1). Myelin deficits persisted in the remyelination paradigm. scRNAseq revealed exacerbated disease-reactive subtypes of microglia in cKO mice, relative to WT. Using a novel 480 gene panel in our Xenium spatial transcriptomic workflow, we demonstrated the spatial accumulation of several subsets of microglia demonstrating varying heterogeneity across anatomical locales. Specifically, we observed significant accumulation of disease-reactive microglial subsets in response to cuprizone, while cKO mice demonstrated a dramatic expansion of an interferon-responsive population, concurrent with histological findings. In vitro, we observed significant increases in interferon-responsive transcripts in PX-478 pre-treated wells, as well as potentially maladaptive bioenergetic and metabolic disturbances.
Conclusions: Our findings are the first to demonstrate that HIF1α is a necessary restraint of microglial over activation in response to cuprizone-mediated demyelination, and loss of this transcription factor drives exacerbated outcomes during both demyelination as well as remyelination. These findings may point toward targeting glycolytic intermediates in microglia as a potential therapeutic to combat against WM degeneration.
Acknowledgement: R01AG070830

Poster Number 17

Decoding the human PBMC isonome: Establishing an isoform-level framework with single-cell long-read transcriptomics

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Graduate Student

Background: Peripheral blood mononuclear cells (PBMCs) are major mediators of systemic inflammation, with changes in their abundance and gene/protein expression linked to neurodegenerative disease via dysregulated immune signaling. With clinical neural samples rarely accessible, PBMCs offer a peripheral window into immune roles in neurological disorders and a potential biomarker source. The isoform transcriptomic landscape, in PBMCs remains largely unexplored due to the limitations of short-read sequencing—the conventional approach.

Methods: We adapted PIPseq, a benchtop single-cell approach, for use with Oxford Nanopore long-read sequencing. To evaluate its utility in characterizing isoform expression and isoform-driven immune mechanisms, we performed the first broad-scale long-read scRNA-seq profiling of human PBMCs (492M reads; two technical replicates). A custom barcode recovery pipeline enhanced read yield before pseudobulk isoform discovery with Bambu. Cell identities were assigned with canonical cell-type markers.

Results: We discovered 166 novel isoforms, including from unannotated genes. Cell-type-specific isoform signatures resolved major PBMC populations (T cell, B cell, Natural Killer, Monocyte-derived, and Megakaryocytes) and T cell subtypes (memory, CD4+, CD8+, transition). While canonical isoforms localized to expected cell types, alternative protein-coding isoforms of immune marker genes were enriched in unexpected clusters, suggesting previously unrecognized regulatory roles.

Conclusion: This exploratory study demonstrates the value of long-read scRNA-seq for isoform characterization and discovery in PBMCs. Isoform-level studies reveal hidden diversity in immune populations, highlighting how transcriptional regulation differs according to cell identity. This establishes a foundation for isoform-level studies to investigate complex systemic immune responses relevant to neurodegeneration.

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Poster Number 18

Niacin-mediated HCA2 activation reduces neuroinflammatory chemokine profiles in aged APP/PS1 knock-in mice following closed-head injury

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Postbaccalaureate Student

Background: Traumatic brain injury (TBI) is a major risk factor for dementia, with incidence doubling every decade after age 65. Yet, no FDA-approved therapies exist to curb post-injury neuroinflammation in individuals at elevated risk for Alzheimer's disease (AD). β-Hydroxybutyrate, an endogenous HCA2 agonist, has low affinity for the receptor (EC_{50} ~1 mM), limiting its utility for mechanistic studies.

Methods: To directly examine HCA2 signaling, we administered niacin, a potent, brain-penetrant HCA2 agonist (EC_{50} ~0.1 μM), to aged APP/PS1 knock-in (KI) and wild-type (WT) mice subjected to closed-head injury (CHI). Starting 3 days post-injury, mice received control chow or diets supplemented with 0.06%, 0.2%, or 0.6% niacin for 28 days. Endpoints included cortical cytokine/chemokine levels (IL-1β, IL-6, IL-10, IL-33, TNF-α, CCL2, CCL3, CXCL1, CXCL2, CXCL10), amyloid burden, nesting behavior, and bodyweight.

Results: Principal component analysis (PCA) revealed two major components: PC1 (36% variance) distinguished KI from WT mice, driven by elevated CXCL10, CXCL2, CCL2, CCL3, and TNF-α, and PC2 (20% variance) reflected a shift toward anti-inflammatory profiles (↑IL-10/IL-6, ↓IL-1β/IL-33) with niacin. Female KI mice showed significant PC2 increases at 0.06% ($p=0.0266$) and peaked at 0.2% ($p=0.0038$), independent of injury status (main effect $F=11.77$, $p=0.0024$). No significant PC2 effects were seen in males or WT mice. Neither amyloid burden nor nesting behavior was altered by treatment. High-dose niacin (0.6%) selectively promoted weight gain in KI mice, modulated by sex and unrelated to injury.

Conclusion: Niacin-mediated HCA2 activation attenuates pro-inflammatory chemokines and enhances anti-inflammatory cytokines in a sex- and dose-dependent manner in an AD-relevant TBI model, without affecting amyloid pathology or behavior. These findings support HCA2 as a viable target for post-TBI immunomodulation and highlight niacin's potential for preclinical therapeutic development.

Poster Number 19

The impact of sleep on the association between everyday discrimination and memory in Black adults

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Staff

Background: Slow wave sleep (SWS), a key stage for memory consolidation, declines with age and is disrupted by psychosocial stressors such as discrimination. Black Americans disproportionately experience everyday discrimination—unjust treatment based on race, limiting opportunities— which has been associated with risk of impaired visuospatial memory, an early indicator of cognitive decline. The present study examines whether SWS moderates the association between visuospatial memory and discrimination among aging Black Americans.

Methods: As part of an ongoing study, participants (N=59, M_{age}=52.76) completed three nights of at-home objective sleep monitoring using a wearable device and measures assessing demographic and social characteristics and the experience of discrimination. Visuospatial memory was measured using the Benson Complex Figure Task. PROCESS Macro (Model 1) was used to test the moderating role of SWS on the association between discrimination and visuospatial memory, while adjusting for age, sex, and marital status.

Results: SWS significantly moderated the relationship between discrimination and visuospatial memory (B=-0.0093, p=0.047). At lower levels of discrimination, SWS had a positive association with visuospatial memory (B=0.13, p=0.089). However, at higher levels of discrimination, the association was negative (B=-0.089, p=0.32). No significant main effects were found for age, sex, or marital status.

Conclusion: Findings suggest that while SWS may be beneficial for cognitive health, the benefit is eroded by the presence of discrimination in aging Black Americans. Our study highlights how the combined effects of psychological and biological factors can provide crucial insight into cognitive aging among populations at high-risk of developing cognitive decline.

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Poster Number 20

Beyond proteinopathies: Direct RNA sequencing uncovers epi-transcriptomic alterations in Alzheimer's disease

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Graduate Student

Background: Alzheimer's disease, the most common cause of dementia, accounts for 60–80% of cases and is defined by progressive memory loss and cognitive decline. Despite decades of work, diagnosis remains definitive only post-mortem, where amyloid-beta plaques, tau tangles, and neuronal atrophy mark late-stage pathology. These proteinopathies illuminate what happens after neurons fail but provide little insight into the early molecular events that precede decline. Emerging evidence points to RNA modifications—particularly pseudouridine (Ψ)—as regulators of neuronal stability, yet conventional short-read sequencing cannot detect Ψ reliably, leaving this layer of regulation largely unexplored in Alzheimer's disease.
Methods: To address this gap, we applied Oxford Nanopore Technologies' direct RNA sequencing to dorsolateral prefrontal cortex tissue. This approach reads native, full-length transcripts with RNA modifications preserved, enabling isoform-specific mapping of Ψ across the transcriptome.
Results: Preliminary analyses revealed distinct Ψ sites within protein-coding regions of genes linked to neurological function and Alzheimer's disease. These modifications may alter RNA stability, splicing, and translation in ways that influence neuronal vulnerability and protein expression.
Conclusion: Direct RNA sequencing uncovers an epitranscriptomic dimension of Alzheimer's disease biology that extends beyond protein aggregates. By capturing RNA modifications within native transcripts, this technology provides a direct window into regulatory changes, with potential to identify biomarkers that anticipate disease onset and clarify mechanisms that drive progression. In shifting attention from late-stage aggregates to early RNA regulation, it positions RNA as both a lens for understanding Alzheimer's disease and a potential target for therapeutic intervention.
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Poster Number 21

Vascular and astrocytic markers associated with vascular and glial pathology are influenced bylipopolysaccharide insult and the normal progression of pathology in the 5XFAD mouse

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Background: Two very important hallmarks of Alzheimer's disease are cerebral small vessel disease and astrogliosis. While both are independent systems, the astrocyte/vessel interaction is a complex process involving signaling in the blood and astrocytes. One protein common amongst both systems is cystatin C, a ubiquitous protease inhibitor implicated in stress, injury and nondegenerative disease. Changes in CysC might be implicated in the endfoot/vascular interaction complex. Another complex involved in endfoot/vascular interaction is the Dystrophin associated complex. Aquaporin4 is a protein that resides in this perivascular complex and is involved with lymphatic clearance. It is unclear if these factors influencing endfoot/vascular function and interaction are stable during aging of the 5XFAD mouse model or during systemic infection initiated through lipopolysaccharide (LPS) injection.

Methods: Here we examine the potential changes in expression using immunofluorescence microscopy at different aged of wild-type and 5XFAD mice, and at different time points before, during and several weeks after LPS injections.

Results: Result suggest that these proteins are dynamic with increased or decreased in different domains with CysC increasing during aging in 5XFAD in astrocytes and vessels. AQP4 is more complicated and may be redistributed to different domains of the astrocyte away from the endfeet.

Conclusions: These results suggest that 2 important regulators of endfoot/vascular interaction are altered in a model of AD and during bacterial infection induced by LPS, potentially leading to loss of function.
Acknowledgements: Supported by grants RF1AG027297, P01AG078116

Poster Number 22

PTDP-43 pathology induces astrocytosis, endfeet disruption, and vascular remodeling driving neurovascular uncoupling and neuronal loss

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Staff

Background: TDP-43 proteinopathy, a hallmark of Alzheimer's disease (AD), Frontotemporal Dementia (FTD), and Limbic-Predominant Age-Related TDP-43 Encephalopathy (LATE), is increasingly recognized as a driver of endothelial dysfunction. Previous studies from our lab showed that human TDP-43 overexpression disrupts blood–brain barrier (BBB) and impairs neurovascular unit integrity. This study expands on those findings by examining how TDP-43 pathology impacts astrocytic endfeet integrity, vascular remodeling, glial activation, BBB permeability, neuronal activity, and neurovascular coupling in the TAR6/6 transgenic mouse model.
Methods: Animal model: TAR6 and TAR 6/6 mouse models express wild-type human TDP-43. The het TAR6 mice exhibit moderate expression of hTDP-43 and display mild pathology without neuronal loss. In contrast, the TAR6/6 mice express 1.2-fold hTDP-43 with extensive TDP-43 cytoplasmic inclusions, phosphorylated aggregates, motor neuron degeneration, and reduced lifespan. Mice were divided into four groups based on age and genotype. IHC: Total TDP-43 was analyzed using a polyclonal rabbit antibody (Proteintech, 1:50k). Neurodegeneration with biotinylated NeuN (EDM Millipore, 1:30k). Astrocytic activation using GFAP (Dako, 1:3k) and S100B (Abcam, 1:30k). Vascular basement membrane structure with Collagen IV (Abcam, 1:1k), and astrocytic endfeet integrity with AQP4 (MyBioSource, 1:1k). Immunofluorescence (IF): Double labeling with GFAP (Abcam, 1:1k) and dystrophin-DP71 (Abcam, 1:1k) was performed to visualize astrocytic endfeet coverage and perivascular localization. Multiphoton: Mice were injected with the calcium flux indicator AAV9-GCaMP8f into the barrel cortex, followed by 2-P imaging 3–4 weeks later, as previously described (Sompol et al., *JNI*, 2023).
Results: Astrocytes displayed hypertrophy and increased branching, confirming reactivity. GFAP analysis revealed reduced endfeet coverage along thinned vessels, while Collagen IV staining showed basement membrane irregularities with vessel tortuosity and fragmentation. NeuN staining indicated neuronal loss in cortical and hippocampal regions. Multiphoton imaging showed neuronal hyperactivity and network hyperexcitability in TAR6/6 mice, accompanied by reduced vasodilatory responses.
Conclusion: These findings suggest that TDP-43 pathology drives astrocytic and vascular remodeling that compromises neurovascular integrity that supports the idea of TDP-43–induced neurovascular uncoupling in TDP-43 proteinopathies.
Acknowledgments: MLBS SBCoA start-up funds; NIH/NIGMS COBRE grant P20GM148326-01; NIH/NIA ADRC Development Grant P30AG072946-03.

Poster Number 23

Impacting Inflammation through Mechanistic Target of Rapamycin (imTOR)

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Graduate Student

Background: Inflammatory diseases, partially regulated by T cells, control the length of one's healthspan. When used at low doses or intermittently, the rapamycin analog everolimus selectively inhibits mTOR complex 1 in T cells while improving multiple age-related inflammatory conditions and metabolic dysfunction, as shown in animal studies. However, the effect of everolimus in humans remains unclear. *In vitro,* everolimus modulates T cell inflammation by altering cytokine profiles and lowering multiple upstream regulators, including ROS, mitochondrial OXPHOS, glycolysis, and lysosomal mass, while upregulating CISH, an emerging regulator of T cell inflammation. We will employ a clinical trial design to test the hypothesis that low-dose/intermittent everolimus reduces the risk of inflammation-related health problems by modulating T cells in obese, insulin-resistant subjects.

Methods: We will analyze T cells from 84 subjects aged 55-80 years before and after intervention with placebo, 0.5 mg/day, or 5 mg once weekly everolimus. We will also analyze T cells from sixteen 18-30-year-olds as a comparator "healthy" group. Following the isolation of peripheral blood mononuclear cells (PBMCs), the CD4+ T cells were obtained through negative selection. The cells were then resuspended in RPMI-1640 at a concentration of 1 × 10^6 cells/mL and stimulated with human CD3/CD28 antibody-coated beads, either with or without 0.01 μM everolimus. Supernatants were harvested at 40 hours and stored at -80°C. The cells were fixed for confocal microscopy analysis of autophagy and lysosomal markers. Cytokines were quantified by Luminex using a Milliplex human Th17 25-plex kit in 384-well plates. The data were analyzed in GraphPad Prism 10.2.2.

Results: Most cytokines, except for IL-12, decreased or showed a downward trend with in vitro everolimus treatment. Analysis of cells from the clinical trial is ongoing to determine concordance between in vitro and in vivo treatment.

Conclusion: Our data suggest that everolimus may decrease chronic systemic inflammation, and thus may improve healthspan in people with excess weight and insulin resistance

Acknowledgment: NIH award: 1R01AG079525-01

Poster Number 24

From extraction to discovery: high molecular weight DNA isolation enables comprehensive structural variant analysis

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Staff

Background: The sequencing of DNA through short-read technologies opened the door for long molecule technologies that allow for the sequencing and visualization of complex genomic regions, structural variants, and proper genomic assembly that short-read technologies had failed to provide. Optical genome mapping technologies, such as the Bionano Saphyr, use high- resolution microscopy and microfluidics to perform cytogenic analysis at a more detailed level than older techniques allowing for long-range genomic structural analyses and the identification of large structural variants. The Saphyr requires high molecular weight DNA, typically defined as ≥50 kbp, which is extremely difficult to extract from aged human prefrontal brain tissue due to high levels of ferritin, myelin, and other cellular debris that must be removed from the sample for proper staining and labeling in the Saphyr. We developed a method to mitigate and remove the effects of these debris and contaminants through the development of precise cellular and nuclear lysis buffers for DNA extraction.

Methods: Frozen post-mortem brain tissue was first homogenized using custom laboratory-prepared lysis buffers to reduce ferritin, myelin, and other debris that interfere with long DNA extraction. Following homogenization, nuclei were isolated and incorporated into the workflow of the Bionano Prep Animal Tissue DNA Isolation Soft Tissue Protocol.

Results: Our tailored DNA extraction protocol produces clean, homogenized gDNA of ≥150 kbp and an average concentration of 100 ng/μl from approximately 60 mg of post-mortem aged human prefrontal cortex tissue.

Conclusion: The production and proper labeling of gDNA allowed for visualization of structural variants and copy number variants in disease-related genes including MAPT, CR1, and C9orf72. C9orf72 mosaicism can be visualized by the individually labeled DNA molecules that show the vast difference between the number of repeat expansions between molecules, with high levels of repeat expansions being indicative of amyotrophic lateral sclerosis.

Acknowledgments: Alzheimer's Association: 2019-AARG-644082, Bright Focus Foundation: A2020161S, NIH/NIA: RO1AG068331, NIH/NIGMS: GMI138636

Poster Number 25

Effect of demographic variables on trajectory of cognitive decline

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Staff

Background: The Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium created harmonized composite scores for three cognitive domains: memory (MEM), executive function (EXF), and language (LAN). The objective of this study is to evaluate the effects of sex, age, APOE-ε4 carrier status, and education on these scores.

Methods: Using data from the National Alzheimer's Coordinating Center (NACC), we identified participants who had at least one visit prior to their Alzheimer's dementia (AD) diagnosis. We modelled cognitive measures covering the three domains. Time to AD was defined as time from a visit to the first AD diagnosis in years. We fit two change-point models to the data using the R nlive package: piecewise linear mixed models with (1) abrupt change, and (2) smooth polynomial transition. Models included covariates for sex, age at visit, APOE-ε4 status (carrier, non-carrier), and education.

Results: Data from 1,604 participants were analyzed. The mean age was 77.6 years; the mean education was 15.7 years, and the majority of participants were women (53.4%) and APOE-ε4 carriers (56.4%). Significance of covariates varied by cognitive domain and model. Of note, MEM, EXF, and LAN scores at time of diagnosis were higher for those with more education in both models (model 1: $P<0.001$, <0.001, <0.001; model 2: $P<0.001$, <0.001, <0.001, for MEM, EXF, LAN, respectively). Additionally, sex significantly affected the changepoint for MEM scores in both models (model 1: $P<0.001$; model 2: $P<0.001$), and the rate of change after the changepoint in the smooth polynomial EXF model ($P<0.001$) and both LAN models (model 1: $P=0.01$; model 2: $P<0.001$).

Conclusion: This study aimed to evaluate the effects of sex, age, APOE-ε4 carrier status, and education on the harmonized cognitive measures. Effects of each variable vary by cognitive domain and model; however, education plays a prominent role across all domain and model combinations.

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Poster Number 26

Operant rule-change tasks for early and longitudinal evaluation of cognitive deficits in female 5XFAD mice

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Undergraduate Student

Background: Traditional maze-based assays of mouse learning and memory are difficult to reproduce, challenging to interpret, insensitive to subtle changes, and have low translational value. Operant behavior-based assays, in contrast, perform significantly better in each of these areas. We therefore designed a battery of traditional and operant-based behavioral testing to assess changes in behavioral performance across age in a cohort of wildtype (WT) and 5xFAD mice.

Methods: 11 WT and 11 5xFAD female mice performed a behavioral battery over the course of 12+ months beginning at 4 months old, including Barnes Maze, novel spatial recognition, and frailty assessment, alongside operant-based spatial discrimination and reversal, demand analysis, delayed non-match to position, and extradimensional set shifting tasks.

Results: 5xFAD mice were impaired in the Barnes Maze test of hippocampal learning and memory by 4 months which is in contrast to the operant spatial discrimination task. In the delayed non-match to sample task of working memory, there was no difference between WT and 5xFAD mice. The operant demand analysis revealed that 5xFAD mice have a higher motivation for a caloric reinforcer; regardless, 5xFAD displayed impaired performance relative to WT in the cortical-dependent reversal phase of the spatial discrimination task, particularly in the presence of a cue-light distractor. Finally, WT mice had reversal phase deficits at ~12 versus ~5 months of age.

Conclusions: The use of operant conditioning based behavioral assays represents a promising avenue to glean deeper and more translational behavioral endpoints in mouse studies. By quantifying and controlling for the salience of the task motivator, and using flexible rule-change tasks to uncover different aspects of learning and memory, operant-based assays represent an alternative to the more widely-used maze-based assays.

Acknowledgments: This work was supported by the University of Kentucky Neuroscience Priority Research Area Pilot Grant (DJB, JSB) and National Institute on Aging training grant T32AG078110 (CSB). Non-operant behavioral endpoints were performed in the Sanders-Brown Center on Aging Mouse Behavior Facility.

Poster Number 27

Modeling lab-grown micro-brain for *in vitro* assessment of microRNA therapeutics targeting neurodegenerative diseases

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Postdoctoral Scholar

Background: The substantial dependence on rodent models in neurodegenerative disease (NDD) research has contributed to translation challenges stemming from species-specific biological difference. Drug delivery to central nervous system (CNS) remains particularly difficult because restrictive nature of the blood-brain barrier (BBB). Although many CNS drugs show promise in rodent models, they often fail in clinical trials. To address this gap, developing human-derived cellular models is essential for accelerating the identification and validation of more effective therapeutic candidates. However, traditional 2D cell cultures lack extracellular matrix architecture and intercellular communication necessary to mimic *in vivo* physiology. Therefore, there is a critical need for advanced *in vitro* models that more accurately replicate the structural and functional characteristics of the human BBB and brain. MicroRNAs (miRNAs) have emerged as promising therapeutic agents for brain disorders. Our previous work demonstrated that miR-223 modulates neuroinflammation, and its augmentation via lipid nanoparticles (LNPs) in mouse brains led to altered inflammatory markers, highlighting its translational potential. However, LNP-mediated delivery of miR-223 faces similar BBB-related challenges, and *in vivo* testing in mouse models remains labor-intensive, costly, and variable. In this project, we aim to construct a human cell-derived micro-brain model utilizing a transwell system that integrates human brain endothelial cells (hCMEC/D3) with astrocytes, pericytes, neurons, and microglia. The BBB model will feature a sandwich culture of hCMEC/D3, astrocytes, and pericytes, while iPSC-derived brain organoid will serve as the micro-cerebral unit. This system will be used to evaluate the effects of miR-223 augmentation in a physiologically relevant human *in vitro* model.
Methods: hCMEC/D3 cells was seeded in 24 well transwell inserts and cultured up to 100% confluency to form the tight junction. Then BBB permeability and leakage were assessed using fluorescently labeled 3 kDa dextran. We will introduce human astrocytes, and pericytes into the system as to form the sandwich BBB. Embryonic bodies were developed from iPSC in 24-well microwell plate and later will be differentiated into astrocytes, neurons, and microglia using differentiation media which will serve as the micro-cerebral unit.
Results: Preliminary data demonstrated that the model effectively blocked dextran diffusion across the transwell barrier, confirming BBB integrity. Tight junction formation in the BBB model was also confirmed by the presence of zonula occludens-1 (ZO-1), a marker of tight junction formation. The model also successfully supported the viability and maintenance of iPSC embryonic bodies.
Conclusion: Collectively, these data indicated that our micro-brain model recapitulated the major characteristics of functional human brain tissue and can be utilized for diverse *in vitro* studies including miRNA treatment to improve clinical translation.
Acknowledgments: Dr. Wang's startup funding from Sanders-Brown Center on Aging.

Poster Number 28

Astrocytic genetic associations with blood-oxygen-level dependent (BOLD) brain responses and working memory performance

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Medical Student

Background: Pathological changes in Alzheimer's disease (AD) and related dementias (ADRD) can begin decades before symptoms, but early detection is limited by subtle, variable molecular changes. Because 60–80% of AD risk is heritable, we investigated single nucleotide polymorphisms (SNPs) in five astrocyte-related genes and one NMDA gene for associations with behavioral performance and BOLD fMRI responses during a working memory task in UK-ADRC participants.
Methods: Along with memory performance and BOLD fMRI, we studied 1,889 SNPs in five astrocyte-related genes (*SLC1A2*, *NFATC3*, *GFAP*, *APOE*, and *S100B*) and one NMDA subunit receptor gene (*GRIN2B*) and genetic data from 21 cognitively intact older adults (mean age = 76.24). Multiple linear regressions were carried out to examine genetic associations with behavioral measures (reaction times, accuracy, correct responses, hits, misses, no responses, and false alarms) and BOLD signals, controlling for age, sex, and education.
Results: We found significant SNP-fMRI associations per brain region, right insula (an integration hub of cognition, affect, and body function) had the most associations (100 SNPs) and the left fusiform (processing visual objects) with 93 SNPs. The left fusiform had R^2 ranging from 0.34-0.65 (e.g. with APOE), and the right insula had R^2 ranging from 0.37-0.64. After Bonferroni correction ($p < 0.05/1889$), two GRIN2B SNPs were significantly associated with accuracy ($R^2 = 0.91$), hit rate ($R^2 = 0.83$), and miss rate ($R^2 = 0.89$). No SNPs were significantly associated with fMRI measures.
Conclusion: These pilot findings suggest that genetic contributions to astrocyte-mediated processes may play a role in early AD/ADRD pathology, highlighting the value of integrating genetics, fMRI, and behavioral measures to investigate the causes of dementia.

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Poster Number 29

Excitatory/inhibitory imbalance underlies tau-dependent sleep loss, but is rescued by targeting GABA.

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Graduate Student

Background: Over 50% of Alzheimer's disease (AD) patients report sleep disturbances. Tau pathology and sleep are bidirectionally related, yet mechanisms remain unclear. We show that tau pathology reduces NREM/REM sleep by reducing beta power (13-30 Hz), linked to cortical synchrony and GABAergic inhibition. This study examines how tau disrupts sleep via excitatory/inhibitory (E/I) imbalance and whether GABAergic positive allosteric modulators (PAMs) can restore sleep, E/I balance, and mitigate tau pathology.

Methods: EEG/EMG electrodes were implanted in 3-, 6-, and 9-month P301S and wildtype (WT) mice. Sleep stages (wake/NREM/REM) and power spectra were analyzed. Transcriptomics and immunostaining assessed E/I gene expression and neuron populations in 9-month cortex. Wide field optical imaging (WFOI) assessed glutamatergic calcium dynamics during rest, evoked response, and pharmacological manipulation. Stable isotope resolved metabolomics (SIRM) quantified glutamate and GABA relative to tau pathology. 9-month P301S mice received vehicle (ZT0, 3 days) followed by 3-day GABA PAM treatment. EEG was analyzed and cortical tissue used for transcriptomics.

Results: Tau pathology decreased NREM/REM and beta power by 6 months, driven by altered E/I gene expression, neuron populations, and GABA/glutamate levels. Glutamatergic neurons in P301S cortex showed heightened calcium dynamics to stimulation and pharmacological inhibition. GABA PAMs increased NREM/REM, restored beta power, and lowered theta:beta and theta:gamma ratios, markers of cognition, in P301S mice. Postmortem analyses suggest reduced neuroinflammation and increased inhibitory gene expression, highlighting the role of GABAegric neurons in tauopathy.

Conclusions: Tau pathology disrupts sleep and cortical beta power, suggesting altered inhibition. Transcriptomics, metabolomics, and fluorescent imaging confirm tau-dependent E/I imbalance. Acute GABA PAM treatment increased sleep, restored beta activity, and shifted EEG power suggesting improved cognition. These results support E/I imbalance as an underlying mechanism in tau-dependent sleep loss.

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Poster Number 30

Effects of APOE genotype, age, sex, and diet on lipid accumulation in an Alzheimer's disease mouse model

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Undergraduate Student

Background: Alzheimer's disease is the most common form of dementia, characterized by amyloid beta plaques and neurofibrillary tangles, but also by the presence of understudied "adipose saccules" in glial cells such as microglia and astrocytes. Adipose saccules likely represent lipid droplets, which are bona fide organelles that serve roles in mediating lipotoxicity, autophagy, and membrane homeostasis. A protein known as apolipoprotein E (APOE) is a lipid droplet-associated protein that plays a role in sequestering lipids.

Methods: The goal of this experiment was to image the distribution of lipid droplets across the brain in glial cells based on factors including the mouse's genotype, sex, age, diet, and presence of amyloidosis. Mouse brains were cryosectioned into 30-micron coronal sections and processed for immunohistochemistry staining for microglia (IBA1), astrocytes (GFAP), lipid droplets (Plin2), and amyloid beta plaques (Amylo-Glo). Mouse brains were imaged with the Nikon AXR confocal microscope, and HALO software was used for regional annotation and analysis.

Results: The initial results of this study showed a consistent upward trend in Plin2-positive and Plin2-IBA1 positive colocalization in E2/E2, E3/E3, and E4/E4 mice. Female mouse brain sections or older sections are expected to be more lipid-burdened than male brain sections or younger sections; in addition, mice on a Western diet or with the 5xFAD mutation are expected to be more lipid-burdened than mice on a chow diet or wild-type mice.

Conclusion: These findings suggest that APOE genotype may influence lipid droplet distribution in the brain. The results of this study will be used to generate a lipid droplet atlas as a free community-wide resource.

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Poster Number 31

The effects of FeTMPyP on neurovascular and hippocampal synaptic function in 30-month-old mice

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Postdoctoral Scholar

Background: As the global population ages and life expectancy rises, neurodegenerative diseases have become a growing concern, significantly affecting quality of life. Oxidative stress plays a key role in brain pathology and age-related cognitive decline, making it a promising therapeutic target. FeTMPyP (FeT), a peroxynitrite scavenger with antioxidant properties, has shown potential in reducing oxidative stress. This study hypothesizes that FeT may restore hippocampal synaptic function in super-aged mice, offering a potential strategy for combating cognitive decline in aging.

Methods: Middle aged and super-aged mice (30 months old) were randomly assigned to a vehicle or Fe treatment group. Cranial window installation was installed to perform Laser speckle contrast imaging (LSCI). FeT (10 mg/kg) was administered via subcutaneous injection twice a week for 4 weeks. At the end of the treatment, all mice were euthanized by decapitation, and brains were harvested for extracellular recordings and dendritic spine analysis.

Results: Aged mice showed impaired long-term potentiation (LTP), reduced synaptic strength (EPSP/FV: 1.95±0.68 vs 0.23±0.11, *p=0.0364*), and decreased dendritic spine density in CA1 and dentate gyrus. FeT partially restored LTP and synaptic strength (0.72±0.15, *p=0.0362*), and significantly increased spine density in CA1 (11.87±0.96 vs 5.52±0.97, *p=0.0003*) and DG (7.82±1.96 vs 3.68±0.70, *p=0.0256*). Furthermore, the distribution of all spine types—including stubby, mushroom, long thin, and filopodia—was significantly higher in CA1, while only mushroom-type spines were significantly increased in the DG of FeT-treated mice compared to the vehicle group. Neurovascular response to whisker stimulation was reduced in aged mice compare to young mice (119.75±4.53 vs 107.18±2.16, *p=0.1414*) and modestly improved after FeT treatment.

Conclusion: FeT treatment improved hippocampal synaptic function and strength in super-aged mice, also enhancing neurovascular function, suggesting its potential as a therapeutic intervention for oxidative stress-related cognitive decline in aging.

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Poster Number 32

Genome-wide analysis of short tandem repeat expansions in Alzheimer's disease

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Graduate Student

Background: Alzheimer's Disease (AD), the leading cause of dementia in older adults, has established genetic risk factors including mutations in *APP*, *PSEN1*, *PSEN2*, and *APOE*. While Short Tandem Repeats (STRs) are highly mutable sequences implicated in neurodegenerative disorders including Huntington's disease, amyotrophic lateral sclerosis (ALS), and spinocerebellar ataxias such as SCA1 and SCA2, among others, their contribution to AD pathogenesis remains understudied despite representing approximately 3% of the human genome.

Methods: We analyzed whole-genome sequencing data from the Alzheimer's Disease Sequencing Project (ADSP) cohort comprising 5,022 AD cases and 5,524 controls. Using GangSTR and ExpansionHunter for genome-wide STR genotyping, we implemented stringent filters for call rate (>90%), Hardy-Weinberg equilibrium, and read support (≥10x coverage). Analysis incorporated age, sex, and first 10 principal components for population stratification correction, with case-control association analysis performed using logistic regression and multi-threshold testing approaches. Validation involved processing samples through ExpansionHunterDenovo to extract case-specific outliers from relevant genes identified by logistic regression analysis.

Results: We identified significant STR expansions in dinucleotide, trinucleotide, and tetranucleotide sequences mapped to neurologically relevant genes (*MTNR1A*, *ATG4B*, *THAP4*, *BOK*, *DUSP10*). Effect sizes ranged from OR=2.08-6.09, with strongest associations in *THAP4* (OR = 6.09, $p = 8.2\times10^{-6}$) and *MTNR1A* (OR = 3.41, $p = 1.1\times10^{-6}$). These genes demonstrate established associations with neurodegenerative disorders, including altered *DUSP10* expression in AD brain tissue, previous *THAP4* correlation with AD, *BOK* association in murine AD models, and *MTNR1A* and *ATG4B* implications in AD pathogenesis.

Conclusion: Our findings provide compelling evidence for STR expansions contributing to AD pathogenesis, representing the largest STR-GWAS to date in AD. Future validation will employ functional studies using induced pluripotent stem cells (IPSCs) to determine the impact of these mutations and machine learning-optimized threshold selection.

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Poster Number 33

Astrocytic insulin signaling as a regulator of astrovascular integrity in Alzheimer's disease

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Postdoctoral Scholar

Background: Alzheimer's disease (AD) often coexists with cerebrovascular pathology, including cerebral amyloid angiopathy, exacerbating gait dysfunction. Emerging evidence suggests that astrocytic insulin signaling may play a key role in modulating vascular function, yet its impact on cerebrovascular integrity is not fully explored. This study aims to elucidate how astrocytic insulin receptor (IR) overexpression (OE) affects vascular dynamics and astrocyte-vascular (astrovascular) coupling in a model of amyloidosis.

Methods: We overexpressed a constitutively active, truncated human IR β-subunit (IRβ) in sensorimotor cortical astrocytes of amyloidosis (5XFAD) and control mice. Longitudinal in vivo two-photon imaging assessed vascular morphology, remodeling, and astrocytic density, vasoreactivity. Gait performance was quantified by ambulation speed, stride time, length deviation, average stride length, and paw placement.

Results: Two-photon imaging showed Astrocytic IRβ OE resulted in vascular alterations, including changes in vascular morphology and reductions in both vessel and astrocytic density. Notability, synchronicity of S1 astrocytic calcium increases in both Control and 5XFAD mice with astrocytic IRβ OE. Vasoreactivity response rate (%) was decreased, particularly in 5XFAD mice. Gait analysis revealed significant reductions in locomotor speed ($p=0.0002$) but without changes in stride length or balance.

Conclusion: Constitutive activation of astrocytic IRβ modifies cerebrovascular structure, impairs vasoreactivity, and ultimately alters locomotor behavior, supporting a role for astrocytic insulin signaling in regulating astrovascular integrity in AD-related pathology. Ongoing work includes mechanistic analysis of IR signaling pathways (pAKT, AKT, IRS-1, IGF-1R) and morphological validation in Cxcl12-GFP mice to further define astrocytic contributions to cerebrovascular remodeling.

Acknowledgments: This work was supported by the National Institutes of Health (P01AG078116 to OT).

Poster Number 34

Astrovascular coupling in awake 5xFAD mice: relationship to ambulation status, calcium, sex, and aging

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Staff

Background: Evidence points to dysregulated Ca^{2+} in neurons and astrocytes in models of amyloidosis. While most of these data were obtained in vitro or in vivo under anesthesia, less work has investigated these variables in awake ambulating mice.

Methods: Astrocytic Ca^{2+} fluctuations (GCaMP8f) were imaged concomitantly with vasoreactivity in S1 on a two-photon microscope during rest and ambulation. Single cell resolution variables were extracted using continuous wavelet transform measure.

Results: Along with increases in Aβ accumulation, we found significant reductions in measures of astrocyte functional connectivity, pairwise correlations, and network synchronicity in older 5xFAD mice, with greater decreases in females. Results align with altered gait and reduced astrovascular coupling.

Conclusion: The results provided here are novel and demonstrate that age and sex are major risk factors for AD; however, central astrovascular dysregulations appear to exist in response to reduced, rather than elevated astrocyte Ca^{2+} transients.

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Poster Number 35

Induced eIF5A hypusination increased neurodegenerative and bioenergetic impairments associated with TDP-43 pathology in a transgenic animal model.

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Postdoctoral Fellow

Background: Eukaryotic translation initiation factor 5A (eIF5A) is a highly conserved protein involved in gene regulation and protein synthesis. eIF5A undergoes a unique post-translational modification of the lysine 50 residue to hypusine. Hypusination of eIF5A (eIF5A^{Hyp}) is a two-step process where deoxyhypusine synthase (DHS, 1st and rate limiting step) and deoxyhypusine hydroxylase (DOHH) via utilization of spermidine. Our group has demonstrated direct integrations of TDP-43 with eIF5A^{Hyp} and proposed eIF5A^{Hyp} as a driver of TDP-43 sequestration in the cytoplasm and stress granules of neurons.
Methods: Non-transgenic (Non-Tg), hemizygous and homozygous human TDP-43 over-expression mice (TAR4 and TAR4/4) were used. At 12 months old, Non-Tg and TAR4 mice were injected with rAAV9-empty capsid, GFP-eIF5A, or flag-DHS+DOHH (DHS/DOHH) bilaterally in anterior cortex and hippocampus. Hippocampi were collected and analyzed by western blot, bulk RNA-seq, Nanostring or GCMS metabolomic analysis
Results: eIF5A^{Hyp} levels increased in TAR4 and TAR4/4 mice in a step-wise manner and were significantly correlated with pTDP-43 levels. eIF5A over-expression produced minor transcriptomic or metabolomic changes. However, DHS/DOHH induced endogenous hypusination significantly enriched genes related to mitochondrial and neuronal function associated with neurodegenerative diseases; synaptic vesicle movement, axon-dendrite structure, nonsense mediated decay based on RNA-seq and Nanostring analysis. Additionally, neurogenesis, autophagy, and long-term potentiation pathways were downregulated. ADD at least one sentence regarding RNA-SEQ mataobolic genes here. Quantitative enrichment analysis of polar metabolites indicated significantly impaired amino acid utilized by TCA cycle (glutamate, aspartate, isoleucine) and bioenergetic metabolism.

Conclusion: Increased hypusination is a driver of neurometabolic impairments in the brain that precedes early neurodegenerative changes and potentially drives TDP-43 pathology in vivo. We posit that eIF5A^{Hyp} is a novel biomarker of TDP-43 proteinopathy.

Acknowledgments: Funded by CNS-MET COBRE, P20GM148326-01; NIA-R01AG8470-01; NIH/NIA-ADRC, P30AG072946-03, T32 AG078110, and SBCoA start-up funds

Poster Number 36

Selective APOE2 expression in hepatocytes does not mitigate APOE4 associated Alzheimer's disease pathology

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Graduate Student

Background: Apolipoprotein E4 (*APOE4*) is the strongest genetic risk factor for late-onset Alzheimer's disease (LOAD), while *APOE2* reduces LOAD risk relative to the most common *APOE3* allele. The highest concentration of ApoE in the body is produced by the hepatocytes of the liver. Although hepatocyte-derived ApoE does not cross the blood brain barrier (BBB), recent studies have shown evidence that it still contributes to LOAD pathology, including amyloid accumulation, BBB dysfunction, and cognitive impairments. This will be the first study to test whether the beneficial effects of peripheral ApoE2 expression can help mitigate the harmful effects of cerebral ApoE4.

Methods: Our lab is employing a novel *APOE*4-Switch-*APOE*2 (*APOE*4s2) mouse model which uses the Cre-LoxP system. Cre is delivered via AAV with a hepatocyte-specific promoter, resulting in mice with ApoE4 expression in the brain but ApoE2 expression in the liver. Efficiency of this strategy was confirmed by proteomics and Western blots on plasma with ApoE isoform specific antibodies. Cognitive function was measured by the Y-maze and the contextual and cued fear conditioning tasks. Amyloid plaque load levels, microgliosis, and astrogliosis were quantified via IHC.

Results: Western blots show efficient expression of ApoE2 in the plasma of AAV-injected animals which persists for at least 12 months. Hepatic expression of ApoE2 did not significantly improve outcomes related to learning and memory in the fear conditioning and Y-maze tasks. We observed a trend of reduced amyloid in mice with peripheral ApoE2 expression compared to controls, but this did not reach statistical significance. We did observe significantly more amyloid pathology in female mice compared to males, consistent with findings across the field of AD.

Conclusion: Western blot data confirm that our AAV-Cre strategy in *APOE*4s2 mice results in highly efficient and long-lasting recombination in the liver. Our results thus far have indicated that hepatic ApoE2 expression is not sufficient to reduce brain related AD pathology. Future studies will investigate BBB integrity and transcriptomic changes following the hepatocyte-specific E4 -> E2 allele switch.

Acknowledgments: NIH T32 AG078110; Alzheimer's Association (ABA-22-972169).

Poster Number 37

APOE genotype interacts with diet and sex to modify hepatic health

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Postdoctoral Scholar

Background: Variation in the apolipoprotein E (*APOE*) gene is the strongest risk determinant for late-onset Alzheimer's disease (LOAD). Among the three common alleles (*ε2, ε3*, and *ε4*), the *ε4* allele confers a dose-dependent increase in risk, with homozygotes having up to a 12-15 fold higher risk compared to *ε3* carriers. While *APOE* genotype has been extensively studied in the context of brain health, its role in peripheral metabolism remains comparatively understudied. This is particularly relevant for the liver, the primary site of APOE synthesis and a central regulator of lipid and energy metabolism. The goal of this work was to determine how *APOE* genotype and diet influence hepatic metabolic pathways using an unbiased proteomic approach.

Methods: We used C57BL/6NTac male and female *APOE* targeted replacement (TR) mice homozygous for the human *APOE3* or *APOE4* alleles. Mice were maintained on a standard chow diet until 4 months of age, at which point they were switched to a low-fat diet (LFD) or high-fat diet (HFD) for 4-5 months. At 8-9 months of age, serum and liver samples were collected for downstream analyses, including unbiased proteomics.

Results: Biochemical analysis revealed that *APOE4* mice displayed reduced hepatic APOE expression and elevated serum APOE. Liver triglyceride levels were also lower in *APOE4* mice while serum levels remained relatively unchanged. Interestingly, levels of hepatic $A\beta_{42}$ were lower in *APOE4* mice with additional sex and diet interactions. Our data also show that *APOE* genetic variation interacts with diet and sex to alter the liver proteome. While many of these changes are unsurprisingly driven by sex differences, *APOE* genotype and diet also drove alterations in ribosomal translation, lipid metabolism, mitochondrial pathways, and immune-related profiles.

Conclusion: These findings demonstrate that *APOE* genotype significantly influences liver metabolism and interacts with diet and sex to shape the hepatic proteome. Ongoing work includes liver metabolomics and serum and liver lipidomics to further interrogate the peripheral effects of *APOE* genetic variation.

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Poster Number 38

Sex-dependent effects of ketone therapy after TBI reveal a dichotomy in mitochondrial response and metabolism in an Alzheimer's disease model

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Graduate Student

Background: Cerebral hypometabolism contributes to brain energy deficits in Alzheimer's disease (AD). The ketone body beta-hydroxybutyrate (BHB), provides an alternative fuel when glucose metabolism is impaired. Managing cerebral hypometabolism reduces dementia risk, including after traumatic brain injury (TBI). We hypothesize that BHB treatment will improve mitochondrial function in APP/PS1 KI mice, potentially offering a therapeutic approach to addressing energy deficits in AD.

Methods: Eight-month old APP/PS1 knock-in mice received closed head injury or sham surgery using a stereotactic electric impactor. BHB was delivered via subcutaneously implanted mini-osmotic pumps, providing continuous infusion for 28 days at a rate of 0.25µL/hour. Mitochondrial respiration was assessed in neocortical and hippocampal tissue and oxygen consumption rates (OCR) for Complexes I, II, and V were quantified.

Results: BHB significantly enhanced Complex I and II-driven respiration in female mice, regardless of injury, with a 16.9% increase in Complex I OCR and a 14.1% increase in Complex II OCR in CHI females. In contrast, male sham mice exhibited a 10.1% reduction in Complex II OCR with BHB treatment. Hippocampal mitochondrial function showed minimal response to BHB across groups.

Conclusion: These findings highlight reveal a sex-dependent dichotomy in ketone metabolism and mitochondrial response after a TBI. While females exhibited improved mitochondrial efficiency with BHB, males showed limited or negative responses. This sex-specific divergence underscores the need for precision approaches when targeting metabolic dysfunction in TBI and AD and supports the therapeutic potential of ketone-based interventions in females at risk for TBI-induced neurodegeneration.

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Poster Number 39

NOX2 at the blood- brain barrier: A new therapeutic target for Alzheimer's disease?

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Graduate Student

Background: Blood-brain barrier dysfunction is a key contributor to cognitive decline in Alzheimer's disease (AD). One factor that drives barrier dysfunction is oxidative stress. We recently identified NOX2, an isoform of NADPH oxidase, as a central source of Aβ-induced oxidative stress at the blood-brain barrier. The goal of this project is to identify signaling steps underlying NOX2-mediated barrier dysfunction. We hypothesize that Aβ activates NOX2, leading to oxidative stress that upregulates matrix metalloproteinases, which in turn degrade tight junction proteins and ultimately cause barrier dysfunction.

Methods: Mouse capillaries were isolated according to our established protocol. Isolated capillaries were divided into three groups: 1) Ctrl, 2) 100nM Aβ40, 3) 100nM Aβ40 plus 1mM PhoxI2 for 24 hours at room temperature. The same experiment was conducted for Aβ42. Following incubation, samples were lysed and used for ELISA to quantify protein expression levels of NOX2, 4-HNE, MMP9, MMP2, and Claudin-5. Bradford protein assay was used to determine protein concentrations in each sample and normalize the data obtained with ELISA. Isolated brain capillaries were also used for immunohistochemistry to stain for NOX2 and NOX4.

Results: We detected NOX2 and NOX4 protein expression in isolated mouse brain capillaries by immunostaining, confirming that both NOX isoforms are expressed at the blood-brain barrier. We found that capillaries exposed to Aβ40 and Aβ42 had significantly increased NOX2 protein levels compared to control capillaries. We also show that inhibiting NOX2 with PhoxI2 attenuates Aβ-mediated increase of the oxidative stress marker 4-HNE in capillaries. PhoxI2 also abolished Aβ-mediated increase of MMP9 and MMP2 protein levels and restored Claudin-5 to control levels. Importantly, PhoxI2 prevented Aβ-mediated capillary leakage.

Conclusion: Our data indicate that Aβ activates NOX2, which induces oxidative stress, thereby increasing MMP9 and MMP2, degrading tight junctions, and leading to capillary leakage. These findings highlight NOX2 as a critical mediator of Aβ-induced barrier dysfunction and suggest that NOX2 could be a potential therapeutic target to prevent blood-brain barrier dysfunction in Alzheimer's disease.

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Poster Number 40

Roles of CPTA in immunometabolic regulation of microglial responses to amyloid beta

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Undergraduate Student

Background: Alzheimer's disease (AD), a leading cause of dementia, is characterized by amyloid-beta (Aβ) plaques, tau tangles, and neuroinflammation. Microglia, central nervous system resident macrophages, regulate Aβ clearance and inflammatory signaling through dynamic metabolic adaptation. Fatty-acid oxidation (FAO), regulated by CPT1A, fuels mitochondrial β-oxidation, whereas etomoxir (ETO) inhibits this process. The mechanisms by which CPT1A modulates microglial responses to AD-like inflammation remain unclear. We hypothesize that FAO, via CPT1A, is a significant regulator of disease-associated microglial phenotypes that are responsible for restricting AD pathological burden.

Methods: Murine BV2 microglia were cultured in DMEM/F12 with 10% FBS and 1% penicillin-streptomycin at 37 °C and 5% CO_2. Cells received 50 μM ETO for 3h followed by a 24h LPS or Aβ challenge before cell lysate was collected for qPCR and lipidomic analyses. RNA was isolated using the Qiagen RNeasy Plus Micro Kit, quantified on a QuantStudio 7 Pro, and analyzed in PRISM. Lipid extracts were processed by LC-MS-based lipidomics through the CNS-MET COBRE Core.

Results: Differential gene expression regulating lipid metabolism, FAO, β-oxidation, and inflammation demonstrated metabolic-immune response interplay. Lipidomics revealed significantly reduced lipid abundance following ETO, indicating a stronger pharmacologic than inflammatory effect consistent with transcriptomic findings.

Conclusion: Inhibiting FAO alters microglial metabolic and inflammatory responses to neuroinflammatory stress. Defining these mechanisms may reveal therapeutic strategies to modulate microglial metabolism and slow AD progression.

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Poster Number 41

Pleiotropic architecture of Alzheimer's disease and narcolepsy: Insights at the gene and expression levels

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Graduate Student

Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid-β accumulation, tau hyperphosphorylation, and progressive cognitive decline. Narcolepsy is an autoimmune disorder marked by loss of orexin neurons, leading to disrupted wakefulness. Recent evidence that dual orexin receptor antagonists (e.g. suvorexant) reduce CSF amyloid-β and phosphorylated tau suggests that wakefulness regulation may modulate AD pathology. It is thus plausible that AD and narcolepsy share common genetic and transcriptomic mechanisms via pleiotropy, which, if elucidated, could shed light on shared risk pathways.

Methods: GWAS summary statistics for AD and for narcolepsy were used to perform harmonization and quality control first. At the genetic level, genome-wide genetic correlation will be used to estimate pleiotropic SNPs through methods such as PLACO, and aggregate GWAS signals to gene and pathway level via MAGMA to pinpoint overlapping risk genes and pathways. At the expression (transcriptomic) level, eQTL-based prediction models (TWAS) will be applied to test whether genetically predicted gene expression is associated with each trait, and colocalization analyses will be performed to validate whether overlapping GWAS & eQTL/TWAS signals share the same causal variant(s). Finally, results across genetic and expression levels will be integrated to define shared loci, genes, and pathways.

Results: Work is still in progress. We anticipate detecting a significant genetic correlation between AD and narcolepsy, and identifying SNPs with pleiotropic effects. Shared risk genes are expected to emerge via MAGMA as well as via TWAS, particularly ones involved in immune regulation, protein clearance/proteostasis, inflammatory response, and wakefulness/orexin signaling pathways. Colocalization analyses are expected to support shared causal variants for some of these genes, reinforcing the overlap.

Conclusion: This study aims to map the pleiotropic architecture linking Alzheimer's disease and narcolepsy at the genetic and expression levels. The findings could improve understanding of how wakefulness modulation impacts AD pathology, highlight biomarker candidates, and suggest therapeutic targets that lie at the intersection of sleep-wake regulation, immune function, and neurodegeneration.
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Poster Number 42

Investigating locus coeruleus pTDP-43 immunoreactivity in the aged human brain

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Undergraduate Student

Background: The locus coeruleus (LC) is located in the brainstem (mostly in the pons) and is the only known source of norepinephrine innervation in the human brain. The LC is also the earliest known site of Tau pathology in Alzheimer's disease (AD). However, very little is known about TDP-43 pathology in the LC in human aging and how that pathology relates to limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) and AD neuropathologic changes (ADNC). To address these knowledge gaps, we evaluated TDP-43 pathology in the LC and queried the associations between LC TDP-43 pathology and clinical and pathological data.

Methods: Brain tissue was analyzed from a convenience sample of 134 particip-ants who came to autopsy as part of the University of Kentucky AD Research Center community-based cohort. Each individual included had neuropathologic features assessed using state-of-the-art methods. Non-ADNC tauopathies and non-LATE-NC TDP-43-proteinopathies were excluded. Sections of pons were stained immunohistochemically for phosphorylated Tau (pTau) and phosphory-lated TDP-43 (pTDP-43). Whole slide images were digitized at 40x magnification and analyzed using a HALO AI DenseNet classifer to quantify neurofibrillary tangle (NFT) density in manually defined regions of interest. The severity of pTDP-43 immunoreactivity was scored visually by a neuropathologist.

Results: Among the 134 brains analyzed, 21% (n=28) had pTDP-43 pathology in the LC. For the pTDP-43+ cases, the pathologic burden was relatively modest (2.2 +- 1.9 pTDP-43+ lesions seen per positive LC). The LC pTDP-43 pathology tracked generally with LATE-NC stages, but the correlation was imperfect. LC pTDP-43 was only weakly associated with ADNC. By contrast, the large majority of included cases demonstrated pTau pathology in the LC (94%; n=126) and LC tauopathy correlated strongly with ADNC severity.

Conclusion: We show for the first time that LC pTDP-43 pathology is relatively common and is generally associated with LATE-NC in the same brains. The LC has been implicated in human mental health conditions often comorbid with dementia. Developing an understanding of how underlying pathologies correlate with common mental disorders is integral to our understanding of aged brains.

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Poster Number 43

Microglia-selective expression of APOE2 improves remyelination even in the presence of CNS APOE4.

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Graduate Student

Background: During demyelination, microglia upregulate expression of *APOE*, the gene encoding for the brain's primary lipid transport protein apolipoprotein E (ApoE), which also mediates microglial engulfment and elimination of myelin debris. Compared to the E3 allele of *APOE*, the E2 allele decreases risk for Alzheimer's disease (AD), while the E4 allele increases AD risk and is associ-ated with an increased severity and progression of multiple sclerosis. Previous work shows that mice expressing E2 exhibit improved microglial function and remyelination compared to mice expressing E4. However, whether microglial-derived ApoE is responsible for driving these differences following demyelination, and if microglia-selective expression of E2 is sufficient to provide protection, is unknown. We sought to determine if microglial replacement of the E4 allele with E2 can rescue myelin loss and promote remyelination, even in the presence of continued E4 expression by other central nervous system (CNS) cells.

Methods: E4 to E2 allelic "switch" mice ($4s2^{M}$) and Cre-negative controls (4s2-) received tamoxifen at 6-weeks to induce a microglia-selective transition from expression of E4 to E2 (Tmem119-$CreERT^{2}$). At 8-weeks, mice were given either lysophosphatidylcholine (LPC) corpus callosum injections (euthanized 10 d.p.i) or cuprizone (CPZ) diet for 5 weeks before sacrifice (demyelination) or return to standard chow for 1 week (remyelination). Histological assessment of myelination, gliosis, lipid droplets, and lipidomics were performed on brain tissue.

Results: We found that microglial E2 replacement decreased astrogliosis following LPC-demyelination, improved remyelination, lowered microgliosis and astrocytic lipid droplet load following CPZ-remyelination with subtle alterations to the CNS lipid profile.

Conclusion: Our results indicate that microglia-specific E2 expression, in the presence of continued E4 expression, may provide protection against myelin loss via cell and non-cell autonomous mechanisms.

Acknowledgments: NIH R01AG081421, R01AG080589, COBRE P20 GM148326

Poster Number 44

ZeBRA: Reliable test-free screening for preclinical Alzheimer's disease via deep pattern discovery in individual electronic health records

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Graduate Student

Background: Early detection of Alzheimer's disease and related dementias (ADRD) is critical, but current screening methods rely on costly and burdensome tests. The Zero-burden Risk Assessment (ZeBRA) score is a novel point-of-care AI-leveraged pattern discovery platform that uses routine electronic health record (EHR) data for individuals, to make personalized predictions of ADRD onset up to a decade before clinical diagnosis, without requiring new bloodwork, imaging, or cognitive assessments.

Methods: ZeBRA was trained on a nationwide U.S. insurance claims dataset (487,989 ADRD cases; 12,483,718 controls). The model was validated retrospectively on independent cohorts from the University of Chicago and NIH All of Us. ZeBRA identifies longitudinal comorbidity patterns associated with ADRD onset. Prospective evaluation was conducted through limited pilot testing with Montreal Cognitive Assessment (MoCA) scores.

Results: ZeBRA achieved AUC = 93.3% for 1-year and 83.1% for 10-year prediction, with consistent performance across age, sex, race, and ethnicity. In pilot testing, ZeBRA scores correlated with MoCA (Pearson's R = −0.78). Compared to existing EHR-based models, ZeBRA showed higher accuracy and broader generalizability, including detection of high-risk individuals lacking conventional risk factors.

Conclusion: ZeBRA is a scalable, low-cost tool for early and pre-clinical ADRD screening. Its strong predictive power and independence from specialized testing make it practical for population health and for enriching presymptomatic clinical trials.

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Poster Number 45

Glioblastoma-derived extracellular vesicles induce neuroinflammatory responses

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Graduate Student

Background: Glioblastoma (GBM) remains an incurable cancer, characterized by high recurrence and severe therapy-derived cognitive impairments. We found that GBM patients exhibit high numbers of extracellular vesicles (EVs) enriched in 4HNE adductions caused by the high ROS levels in GBM, particularly after radiation (RedoxEVs). Since EVs function as molecular intermediaries, we hypothesize that GBM-EVs could be key mediators driving therapy-associated neurotoxicity in GBM patients.

Methods/Results: We used radiation to increase 4HNE content. High levels of 4HNE in RedoxEVs were confirmed by western blotting, immunogold labeling and mass spectrometry. Then, we administered NonRedoxEVs and RedoxEVs intranasally. Mice treated with RedoxEVs showed a delay in object exploration and increased 4HNE adductions and CD68 expression in their brains.To control the EVs' delivery to the brain, we injected RedoxEVs intracranially. These mice exhibited cognitive deficits, DNA damage in cerebral tissue, decreased neuron markers, and elevated p50 and pro-inflammatory cytokines. Mechanistically, RedoxEVs are internalized by microglia, causing pronounced microglial activation and release of pro-inflammatory cytokines and H2O2 as mediators. To assess the downstream neurotoxic effect of H2O2, RedoxEVs were added to a co-culture setting with microglia and neuron cells. Neuron viability was reduced when exposed to microglia activated by RedoxEVs. Additionally, mice with RedoxEVs-derived cognitive deficits demonstrated elevated pro-inflammatory cytokines and CD68 expression. Consistently, proteomics analysis revealed that RedoxEVs are enriched in proteins that activate the NFkB pathway. Next, we explored whether the adverse effects induced by RedoxEVs could be mitigated. Treatment with BMX-001 (an MnSOD mimetic in clinical trials for high-grade gliomas) reduced RedoxEVs-derived microglial activation. This highlights the therapeutic potential of redox regulation in the brain microenvironment.

Conclusion: Our data indicate that RedoxEVs induce microglia-mediated neurotoxicity and cognitive alterations, and these negative effects may be mitigated by using redox-active antioxidant therapies like BMX-001.

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Poster Number 46

Species-specific isoform subcellular localization of CCAAT/Enhancer Binding Protein-β (C/EBPβ) under inflammatory stress.

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Undergraduate Student

Background: Neuroinflammation is a major player in neurodegenerative diseases, including Alzheimer's Disease (AD), yet its regulatory mechanisms remain poorly understood. CCAAT/Enhancer Binding Protein-β (C/EBPβ) is a transcription factor that controls cytokine and inflammatory mediator expression and is translated into three isoforms—LAP1, LAP2, and LIP. LAP1 and LAP2 generally act as transcriptional activators, whereas LIP functions as a dominant negative, though context-dependent activator roles. Elevated C/EBPβ levels have been observed in AD, predominantly in glial cells, where it has been linked to δ-secretase activation, APP cleavage, tau pathology, and APOE4 regulation. However, critical gaps remain: the cell-type specificity and subcellular distribution of each isoform under inflammatory stress, species-specific differences, and the impact of isoform ratio (e.g., LAP to LIP ratio) on neuroinflammation. The objectives of the current study are to investigates C/EBPβ isoform expression and localization across cell types and species, and their association with AD pathology.

Methods: Subcellular fractionation was performed using postmortem human brain tissue, mouse brain tissue, and multiple cultured cell lines (SH-SY5Y, H4, HeLa, HMC3, BV2, and HepG). Cells were subjected to inflammatory stress prior to fractionation. Tissue and cells were homogenized using sequential hypotonic and hypertonic buffers with mild detergent, followed by differential centrifugation to separate cytosolic and nuclear fractions. Equal amounts of protein from each fraction were resolved on 4–20% gradient SDS-PAGE and transferred to membranes for immunoblotting. C/EBPβ expression was examined using six different commercially available antibodies.

Results: Distinct patterns of C/EBPβ isoform expression and localization were observed across different cell types and species under inflammatory stress. In human brain tissue and human-derived neuronal cell lines, a modified form of the LIP isoform was predominantly detected in the cytosolic fraction. In contrast, neither LIP nor its modified form was observed in any subcellular fraction from mouse brain tissue or mouse-derived cell lines.

Conclusion: These findings suggest that C/EBPβ isoforms exhibit cell type– and species-specific regulation under inflammatory stress, indicating their distinct functional roles in stress-induced cellular responses.

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Poster Number 47

APOE4 drives changes in glial reactivity after low-dose Aducanumab immunotherapy

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Graduate Student

Background: Anti-amyloid monoclonal antibodies, such as Aducanumab and Lecanemab, are the first disease modifying therapies for AD. Despite this benefit, amyloid related imaging abnormalities (ARIA), findings of fluid effusion or microbleeds on MRI, are key adverse effects sometimes associated with severe symptoms and death. While the cause of ARIA is unknown, there is a strong link with APOE4 (E4). E4 is the strongest genetic risk factor for late onset AD, making it critical to understand the mechanisms of E4 driven ARIA.

Methods: Nine month old human APOE-expressing mice (E2, E3, or E4) crossed to the 5XFAD model of amyloidosis ("EFAD") received 12 weeks of a low dose (1.56 mg/kg) treatment with chimeric Aducanumab (chAdu) or IgG isotype control. Mice underwent MRI and images were mapped to reference atlases for functional assessments ARIA pathology, with microbleeds quantified on SWI imaging. Histological assessment of microbleeds (Prussian Blue), plaque (AmyloGlo) and associated gliosis (IBA1, GFAP, CD68) were performed in parallel with vascular labeling (isolectin). A group of six female E4FADs underwent single cell RNA sequencing, with data analysis in R.

Results: Low dose treatment with chAdu was sufficient to induce clearance in E4 FADs. This decrease in plaque load was associated with an increase in both parenchymal- and vascular-associated microgliosis in E4FADs only. Increases in overall and vessel-associated GFAP were also observed in E4FADs. Single cell RNA sequencing revealed several transcriptomic changes in immune and vascular cell types after chAdu treatment. Specifically, we found an upregulation of early DAM-like microglia, and a decrease in homeostatic microglia after chAdu treatment in our single cell dataset, with communication signals between CNS myeloid cells and peripheral T-lymphocytes.

Conclusion: Even at low doses, APOE modulates microglial and astrocyte reactivity, especially associated with parenchymal plaque and vasculature, after anti-Aβ therapy. These findings provide a window into the potential mechanisms of E4 driven ARIA and associated pathologies.

Acknowledgments: TL1TR001997

Poster Number 48

Population-specific and shared transposable element insertions associated with Alzheimer's disease in a case-control study

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Graduate Student

Background: Alzheimer disease is the most common neurodegenerative disease, affecting around 7.1 million Americans. While highly heritable with many associated genes identified, much of the heritability remains unexplained. Transposable elements are interspersed repeats capable of moving around our genome; comprise ~50% of the human genome with L1, A*lu*, and SVA remaining active. Although usually silenced through various defense mechanisms, new insertion events can cause disease or alter gene expression. This study aims to explain some of the genetic underpinnings of Alzheimer's disease by focusing on an understudied class of genetic variation.

Methods: We conducted a case-control study using Alzheimer's Disease Sequencing Project (ADSP) data. The Mobile Element Locator Tool (MELT) generated the VCF files and identified TE insertions (A*lu*, LINE1, SVA) from the vcf files. After quality filtering and population stratification, the dataset included 139 African cases/85 controls and 421 European cases/340 controls. Fisher's test identified significant loci, and odds ratios quantified effect sizes.

Results: Our preliminary analysis identified a total of 132 statistically significant LINE1 insertions, 52 statistically significant SVA insertions and 686 statistically significant A*lu* insertions ($p < 0.05$), including population-specific (African-only, European-only) and shared insertions. Some insertions were enriched in cases, others in controls, revealing both common and population-specific associations with Alzheimer's disease.

Conclusion: This study demonstrates that transposable element insertions represent a significant source of genetic variation associated with Alzheimer's disease, with both shared and population-specific patterns. Moving forward, we plan to prioritize these significant insertions by identifying nearby annotated genes to explore their functional roles in the disease process.

Acknowledgments: Alzheimer's Disease Sequencing Project data.

Poster Number 49

Analyzing neurovascular structural and functional damage with multiphoton microscopy

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Graduate Student

Background: Cerebrovascular pathology is highly comorbid with Alzheimer's disease (AD). However, the study of this pathology in the living brain is limited. While post-mortem thin-section staining is useful for diagnosis, this technique is not optimal for studying structural and functional disruption of the vessels. To move past this limitation, we performed intravital multiphoton imaging to observe vascular architecture and neurovascular response in AD mouse models.

Methods: Cranial window surgery was performed in young (3-6 months) and old (24 months) wild-type and AD (Tg2576) mice to observe vascular architecture using two-photon multiphoton microscopy. Cerebral amyloid angiopathy (CAA) and Aβ plaque build-up was labeled with methoxy-X04 while the vasculature was visualized with rhodamine dextran. Neurovascular coupling was measured in awake mice using air-puff stimulation on contralateral whiskers.

Results: The predisposition of Aβ also increased blebbing and saccular vessel aneurisms. Architectural tortuosity such as curved, folded, and looped vessels increased in aged mice and were more prominent in Tg2576. Neurovascular function was impaired in aged wild-type mice, and severe impairment was found in vessels with CAA pathology.

Conclusion: These results represent the vascular structural deformation and functional disruption in ADRD brains. Multiphoton microscopy is an approach translational to the pathogenesis and pathophysiology of AD and vascular-related neurodegeneration.

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Poster Number 50

Bioenergetic consequences of CPT1 inhibition (Etomoxir) on microglial response to Aβ challenge

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Undergraduate Student

Background: Microglia are the resident immune cells of the central nervous system (CNS) and play a key role in the pathogenesis of neurodegenerative disease. In the presence of amyloid beta (Aβ), microglia undergo metabolic reprogramming, initially shifting toward aerobic glycolysis while retaining the capacity for Fatty Acid Oxidation (FAO). The enzyme Carnitine Palmitoyltransferase 1 (CPT1) is the rate-limiting step for FAO, and its function is critical for maintaining metabolic flexibility. We hypothesize that pharmacological inhibition of CPT1 with Etomoxir will compromise the microglial ability to cope with metabolic stress induced by Aβ, leading to greater mitochondrial dysfunction.

Methods: Immortalized murine microglia (BV2 cells) will be cultured under standard conditions. Cells will be pre-treated with the CPT1 inhibitor Etomoxir, followed by a challenge with Aβ oligomers to induce metabolic stress. Mitochondrial function and substrate utilization will be assessed in real time using Seahorse analysis, focusing on parameters of FAO, basal respiration, and maximal respiratory capacity. Data will be normalized to protein content and analyzed with PRISM software.

Results: Data collection is ongoing. Based on prior findings, we expect that Aβ treatment alone will decrease basal OXPHOS and spare respiratory capacity. We further anticipate that Etomoxir pre-treatment will exacerbate this Aβ-induced dysfunction, resulting in a significantly lower maximal respiratory capacity and greater dependence on glycolysis compared to Aβ treatment alone. The Seahorse analysis will confirm that this reduced capacity is specifically due to FAO inhibition.

Conclusion: This study will clarify the functional role of CPT1-mediated FAO in microglial defense against Aβ pathology. Defining whether blocking FAO increases microglial susceptibility to Aβ stress may reveal CPT1 as a critical target for preserving microglial metabolic health in neurodegenerative disease.

Poster Number 51

tPA alters inflammatory protein expressions differentially with sex and across age ranges

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Medical Student

Background: Beyond their ability to degrade thrombi, thrombolytics such as tPA may also mediate neuroprotection by mitigating neuroinflammation and secondary post-ischemic injuries through currently unknown mechanisms. Moreover, the role patient sex and age play in these responses due to thrombolytic action is yet to be understood. By utilizing the Blood and Clot Thrombectomy Registry and Collaboration (BACTRAC), we aimed to evaluate differences in the intravascular expression of cardiometabolic and inflammatory proteins in the acute ischemic stroke (AIS) environment following thrombolytic administration based on patient sex and age.
Methods: AIS patients enrolled in BACTRAC treated with mechanical thrombectomy (MT) for AIS between June 2017 and June 2024 were included. Arterial blood samples were collected from systemic circulation and intracranial vessels distal to occluded arteries before recanalization. O-link proteomic assays quantified the expression of 276 cardiovascular, cardiometabolic, and inflammatory proteins from isolated plasma.
Results: Patients who received thrombolytics (n=60) displayed notable sex-based differences in the intracranial expression of SLAMF1 (Females 1.24 ± 0.79 vs. Males 1.71 ± 0.73; $p<0.05$) and NTproBNP (Females 4.65 ± 1.86 vs. Males 3.14 ± 2.01; $p<0.05$), as well as the expression of IL17C (Females 1.45 ± 0.89 vs. Males 1.92 ± 0.80; $p<0.05$) in systemic blood. Thrombolytic patients were divided into four age ranges (≤52., 53 to 66, 67 to 82, ≥83). Intracranial expression of NTproBNP was found to be significantly different across the four defined age groups (one-way ANOVA, $F(3,27)=3.09$, $p<0.05$) with the younger two age groups showing lower expressions than the older two age groups. Systemic expression of CST5 was found to be different across the four age groups (one-way ANOVA, $F(3,56)=4.69$, $p<0.01$) with expression increasing in a stepwise fashion as patient age increased.
Conclusions: This study provides an initial evaluation of the sex and age differences in proteomic response to thrombolytics in AIS patients undergoing MT. Our findings suggest that there are possible underlying metabolic and inflammatory pathways that are differentially affected by thrombolytics based on sex and age ranges. Future work will evaluate if these differences translate to functional and cognitive AIS outcomes.
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Poster Number 52

Progressive behavioral and cognitive deficits in APP-SAA KI mice: A longitudinal, sex-specific study

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Undergraduate Student

Background: Cognitive decline, sleep disturbances, and deficits in activities of daily living are hallmarks of Alzheimer's Disease (AD). Many studies have focused on individual behaviors of mice with AD pathology such as sleep, nesting, and memory. However, these behaviors have been shown to be linked and progressively worsen over time. Our study examined them together longitudinally using knock-in models that closely mimic human AD genetics.

Methods: We evaluated APP-SAA knock-in and wild-type mice across three cohorts (n = 119 total). Cohort 1 was monitored longitudinally from 2–19 months for sleep, circadian rhythms, and nesting behaviors. Cohort 2 consisted of younger mice (4 months old) which established early spatial learning and memory using the radial arm water maze (RAWM) to assess. Cohort 3 included older mice (8 months old) evaluated in RAWM with nesting.

Results: Female KI mice exhibited progressive reductions in light-phase sleep beginning at 10 months, accompanied by increased sleep fragmentation and reduced circadian stability at later ages. Nesting behavior declined with age in both sexes but showed earlier and more pronounced impairments in KI females. In the RAWM, young KI mice performed similarly to WT in acquisition and retention, but older KI females showed significant deficits in reversal learning, indicating impaired cognitive flexibility. Locomotor activity was largely normal, with only a minor female-specific reduction in mice aged 10 months.

Conclusions: These results demonstrate that APP-SAA KI mice display sex and age dependent behavioral alterations. While there were deficits in sleep, nesting, and cognitive flexibility in older mice across Cohorts 1 and 3 these results were notably female-biased. Together, these findings establish APP-SAA KI mice as a valuable model for studying the interplay between circadian disruption, ethological behaviors, and memory decline in patients with AD.

Poster Number 53

Investigation of the patho-clinical profile of citrullinated TDP-43 in LATE-NC: A case study

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Staff

Background: TDP-43 (TAR DNA-Binding Protein 43) is implicated in the clinical and pathological course of various neurodegenerative diseases, including Limbic predominant age-related TDP-43 encephalopathy (LATE). Phosphorylation is one of the most studied post-translational modifications (PTM) of pathological TDP-43. Though using specific phospho-Serine TDP-43 epitopes (ie. pS409/410 or pS403/404) is effective in identifying TDP-43 pathological hallmarks, utilization of irreversible PTMs could potentially provide a better biomarker for early differentiation of TDP-43 proteinopathies or disease severity. Our laboratory has identified citrullination (citR) of eleven (11) arginine epitopes in TDP-43 protein, followed by generation of six (6) citR-specific TDP-43 antibodies, characterized in various systems models. We hypothesize that activity of this irreversible PTM increases with pathology; thus, understanding citrullinated TDP-43 patterns can provide information on disease-staging and severity.
Methods: *Human Tissue:* (Control and LATE positive) Hippocampus tissue was provided by the UK-ADRC Brain Bank at SBCoA. Sections were used to investigate citR TDP-43 profiles across a spectrum of LATE-NC severity. *Immunohistochemistry (IHC)***:** We investigated the morphological patterns of citR TDP-43 inclusions using custom, site-specific citR-TDP-43 antibodies (citR83, citR191, and citR268/272 TDP-43) on paraffin-embedded formalin-fixed (PFFE) tissue sections. Tissue was also stained with pS409/410 TDP-43 (Clone 1D3, Biolegend, Cat #829901) per conventional protocols.
Results: Our IHC analysis demonstrated that epitope-specific profiles of citR TDP-43 expressed at different levels across HPC neuronal CA1-CA3 and DG layers. We further revealed that citR TDP-43 conformers manifested novel morphologies based on disease severity, and displayed different spatio-temporal hippocampal profiles. We confirmed pS409/410 TDP-43 increases according to disease stage and also demonstrated spatial differences following moderate and severe LATE-NC presentation.
Conclusion: This small-scale “case study” provides promising data towards utilization of citR TDP-43 as a biomarker for early detection of pathology across LATE-NC severity. Future studies will include a larger patient cohort across 1-3 stages of LATE-NC, AD with LATE-NC, and FTDs to establish the citR TDP-43 patho-clinical profile disease progression and clinical utilization.
Acknowledgements: This work was supported by NIH/ NIA R01s: 1R01AG084670-01

Poster Number 54

The role of community engagement in neurological research among disproportionately affected adults: Lessons from the CHAMP Health and Resource Fair

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Staff

Background: Community engagement has long been an underutilized strategy when conducting dementia research, especially for the recruitment of high-risk communities such as refugees. Due to exposure to adverse life events and limited access to health resources, refugees are shown to be at a critically risk of experiencing poor brain health. Thus, we created CHAMP: Championing Healthy Aging in Multicultural Populations Health and Resource Fair. CHAMP is a community-researchers partnership aimed to promote modifiable risk behaviors and early health and cognitive screening among aging refugees. .

Methods: On August 9, 2025, the Health and Aging from Multicultural Perspectives Lab (HAMPLAB) hosted the inaugural CHAMP Health and Resource Fair at the Healthy Kentucky Research Building. Twenty-two vendors participated in the fair, including the Lexington Senior Center, Bluegrass Lions Diabetes Project and the Alzheimer's Association. Over 200 people and 18 volunteers attended the event. Complimentary services provided at the fair includes health screening (e.g., A1C and blood pressure measurements), fresh food produce, and back-to school supplies.

Results: 38% of the 55 participants screened for A1C exhibited elevated levels. Many of these individuals were not previously diagnosed with prediabetes or diabetes and were offered counselling and follow up. Also, over 100 people were screened for high blood pressure, and 62 eligible middle-older age adults signed up for research participation. These results indicate the importance of community-based events in which high-risk individuals can be identified and presented with practical next steps.

Conclusion: The CHAMP Health and Resource Fair illustrates the dual benefit of community engagement: advancing public health awareness through immediate health feedback and strengthening recruitment for ongoing research initiatives.

Acknowledgments: UK ASCEND (Achieving Success in Community-Engaged research to elimiNate Disparities) is supported by National Institutes of Minority Health and Health Disparities (P50MD019476), HAMPLAB, Lexington Senior Center, and Empucate International.

Poster Number 55

Loss of astrocytic endfeet in 5xFAD mice over time

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Staff

Background: Cerebrovascular dysfunction and reactive astrocytosis are well characterized hallmarks of Alzheimer's disease (AD) and related dementias, although astrocyte endfeet coverage of cerebral vessels through disease progression and normal aging remain unknown.

Methods: Here we utilized weekly longitudinal intravital two photon imaging over a 12-week time course to investigate astrocyte endfeet and cerebral vascular changes in 5xFAD mice, and wild-type (WT) littermates injected with an astrocyte specific Gfa2-EGFP AAV. Images from the individual astrocytes and vessels were obtained from the identical brain region each week.

Results: We found that 5xFAD mice appeared to be losing astrocyte endfeet from 5-8 months of age compared to WT while the astrocyte number and volume remained relatively unchanged. The cerebrovasculature in both WT and 5xFAD mice remained unchanged during this time course.

Conclusion: These data suggest that examining the individual cellular compartments of astrocytes and their interactions with the cerebrovasculature may provide insight into mechanism of blood brain barrier breakdown resulting in neurocognitive impairment.

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Poster Number 56

Does Lecanemab impact blood-brain barrier function?

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Graduate Student

Background: Monoclonal antibodies have emerged as a cornerstone of modern therapeutics, with lecanemab (Leqembi™) and donanemab (Kisunla™) recently receiving FDA approval for use in patients with early symptomatic Alzheimer's disease (AD). Both antibodies reduce brain amyloid burden in patients with the hope of slowing cognitive decline, highlighting their therapeutic potential. However, their use is associated with amyloid-related imaging abnormalities (ARIA), typically detected by MRI, which reflects damage and increased permeability of large leptomeningeal and cerebral arteries. Whether these antibodies also impact small capillaries that comprise the blood-brain barrier is currently unknown, representing a critical gap in our understanding of their cerebrovascular effects. The goal of our study is to address this knowledge gap by investigating the effect of lecanemab on blood-brain barrier integrity and function.

Methods: We isolated brain capillaries from 8-week-old CD1 mice (male, n=20 per experiment) using an established protocol (Hartz et al., 2018, Journal of Visualized Experiments). Isolated capillaries were resuspended in DPBS buffer supplemented with pyruvate and glucose and divided into four treatment groups: 1) Control, 2) 0.25 µg/mL lecanemab, 3) 0.5 µg/mL lecanemab, and 4) 0.5 µg/mL goat anti-mouse IgG1 (IgG control). Capillaries were incubated at room temperature for 24 hours, centrifuged, and frozen for subsequent downstream analyses. Lecanemab concentrations were based on CSF levels measured in patients enrolled in an early-phase clinical trial (Logovinsky et al., 2016, Alzheimer's Research & Therapy). Lecanemab was obtained from Thermo Fisher Scientific (#MA5-59917; research grade replica of Eisai's clinical antibody).

Results: Planned endpoints include immunohistochemical staining, ELISA, and transport activity assays to assess changes in blood-brain barrier proteins responsible for barrier function and integrity. Specifically, we will determine 1) protein expression levels of the tight junction proteins (ZO-1, occludin, Claudin-1, and Claudin-5), 2) transport activity levels of P-glycoprotein, a transporter involved in Aβ clearance, and 3) adhesion molecules involved in inflammatory responses in capillaries such as ICAM-1.

Conclusion: We anticipate that capillary exposure to lecanemab will reduce tight junction protein expression levels, lower P-gp transport activity, and increase adhesion molecule expression. Data from this project may help inform future studies focused on the potential impact of lecanemab on blood-brain barrier function and integrity in Alzheimer's disease.

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Poster Number 57

Spatial TDP-43 dysregulation contributes to mitochondrial respiratory dysfunction after severe CCI: implications for the eIF5A pathway

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Staff

Background: Traumatic brain injury (TBI) and neurodegenerative diseases share overlapping pathological features, yet the mechanisms driving cognitive decline remain unclear. Transactive response DNA-binding protein 43 (TDP-43) is a nuclear RNA/DNA binding protein that regulates RNA processing. Cytoplasmic mislocalization and aggregation of TDP-43 represent a toxic gain of function mechanism in both TBI and other NDs. Additional hallmarks of sustained injury include oxidative stress, excitotoxicity, synaptic loss, and mitochondrial dysfunction. We have identified eukaryotic initiation factor 5A (eIF5A) as a regulator of TDP-43 aggregation and mislocalization. eIF5A is post-translationally modified at lysine 50 by hypusination, a modification linked to TDP-43 pathology.
Methods: Aged (17–22 mo) male and female heterozygous TAR6 mice (hTDP-43 expressing line) underwent controlled cortical impact (CCI) to model severe TBI or sham surgery. Brains were collected 24 h post-injury. Whole-brain homogenates were analyzed by Western blot using antibodies against TDP-43, pTDP-43 (S409/410), citrullinated TDP-43 (R83, R191, R268/272), GFAP, citrullinated GFAP (R416), and UCHL1. Immunohistochemistry was performed to assess total TDP-43 and eIF5A^{hypK50}. Mitochondrial function was evaluated using the Seahorse XF OXPHOS assay on freshly isolated mitochondria.
Results: Immunohistochemistry revealed increased eIF5A^{hypK50} and spatial TDP-43 expression in non-Tg mice following severe CCI. TDP-43 overexpression promoted mitochondrial dysfunction after injury, with Complex III impairment in the anterior cortex of both non-Tg and TAR6 mice and Complex I impairment in TAR6 mice. Hippocampal Complex I deficits were also observed in TAR6 mice following CCI. CCI reduced TDP-43 citrullination at R191 and R268/272 in the anterior cortex, with a selective reduction of R268/272 in the hippocampus. GFAP cit^{R416} increased in both regions, accompanied by decreased total GFAP in the hippocampus. The reduction in hippocampal TDP-43 seen in sham TAR6 mice was absent after CCI. UCHL1 levels were reduced in the hippocampus of TAR6 mice compared to WT but were unaffected by CCI.
Conclusion: These findings highlight region- and complex-specific vulnerabilities driven by TDP-43 pathology in the context of traumatic injury and suggest that eIF5A hypusination may contribute to mitochondrial dysfunction in TBI.
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Poster Number 58

Exploring associations between formal music knowledge and autopsy-confirmed neuropathological changes in a community-based sample of older adults

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Undergraduate Student

Background: Older adults are at risk of cognitive impairments that drastically affect an individual's lifestyle and health. Music making is increasingly recognized for its potential to facilitate brain plasticity and mitigate or prevent age-related cognitive decline. However, the neuropathologic mechanisms underlying the protective association between formal music knowledge (FMK) and cognitive impairment have not been studied to our knowledge. We aim to explore the association between FMK and autopsy-confirmed neuropathology, clinical diagnosis, and global clinical dementia ratings (CDR).

Methods: A subsample of participants from a 2012 study in the UK Sanders-Brown Center on Aging ADRC cohort were categorized as high FMK, medium FMK, and low FMK. The presence or absence of ADNC, LATE-NC, LBD, CAA, atherosclerosis, infarcts, and ARTAG pathological findings were compared between FMK groups using chi-square. An OLS Linear Regression was used to assess the correlation between CDR ratings and neuropathology amongst FMK groups.

Results: 74 participants met criteria and came to autopsy. Only the presence of ARTAG was more likely in low FMK individuals than those with high FMK ($p=0.048$), but ARTAG was only available for a subsample of 28; the subsample was older at death (89.3 vs 85.2, $p = 0.03$) but did not differ from the rest of the sample in sex, education, or FMK distribution. Although there was not a significant difference in last ante mortem CDR ratings between groups, the low FMK group was more likely to have a diagnosis of MCI or dementia prior to death ($p = 0.023$).

Conclusion: FMK appears to be protective for clinical status and perhaps ARTAG, an astroglial pathology, may be related to cognitive reserve indicated by FMK. Further research is needed to determine the mechanism behind FMK and protected cognitive health.

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Poster Number 59

Redefining tau pathology staging through AI-driven digital neuropathology: An updated framework from the Sanders-Brown Center on Aging

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Postdoctoral Fellow

Background: The Sanders-Brown Center on Aging (SBCoA) and University of Kentucky Alzheimer's' Disease Research Center (UK-ADRC) team has pioneered digital neuropathology for over a decade, leading efforts to integrate quantitative methods into routine neurodegenerative disease assessment. To enhance the precision, reproducibility, and clinical relevance of tau pathology evaluation, we developed and implemented a digital pathological framework using HALO software, integrating machine learning-driven tissue classification, tissue segmentation, and stringent quality control, representing a methodological advancement with direct implications for research and diagnosis of neurodegenerative diseases.

Methods: Archival brain tissue from the UK-ADRC biobank was reanalyzed using HALO modules optimized for tau detection and quantification of tau pathology. This pipeline enables region-specific quantification of tau pathology in defined neocortical areas. Both pathological burden (percent area) and tangle counts were derived, and sampling strategies assessed to determine the minimum regional representation required for accurate staging. Standardized analytic protocols were disseminated to a collaborating academic center to evaluate inter-institutional reproducibility.

Results: Compared to previous methods, the AI-assisted framework yielded greater analytic stability and closer alignment with clinical features. Evaluation of anatomical sampling confirmed that a streamlined panel of neocortical regions preserves pathologic fidelity while increasing procedural efficiency. Furthermore, external validation demonstrated high reproducibility, supporting its utility as a standardized tool for collaborative neuropathologic assessment.

Conclusion: This study establishes a computationally enhanced, anatomically resolved approach to tau quantification, positioning SBCoA to create a data-driven, standardized revision of neocortical tau staging. By transitioning from descriptive frameworks to biologically and clinically anchored metrics of disease, we aim to redefine staging criteria that more accurately reflect the severity and spatial distribution of tau pathology. Such refinement is critical for improving diagnostic resolution, enabling multicenter harmonization, and strengthening the neuropathologic foundations of Alzheimer's disease research.

Poster Number 60

Characterizing Bioenergetic Status of Neurons and Astrocytes Using 2P Imaging Techniques

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Graduate Student

Background: By characterizing brain energy dynamics, metabolic processes integral to maintaining and regulating homeostatic equilibrium can be addressed in healthy and diseased states. With the advent of commercially available nanosensors used to evaluate metabolic processes with high spatial and temporal resolution, and the accessibility of 2-photon microscopy, energy dynamics can be investigated in live, awake animals. We used PerecevalHR (ATP:ADP) and Peredox (NADH:NAD+) to assess metabolic status in astrocytes in control and 5xFAD mice during rest and movement using 2-photon imaging. A subset of animals received an injection of the norepinephrine (NE) sensor nLightG to evaluate the role of NE release onto neurons on vascular function.

Methods: Animals were either injected with PercevalHR (1 uL or 2 uL; GFAP promoter) Peredox (1 uL; Gfa104 promoter), or nLightG (0.5 uL; Syn promoter). On the day of imaging, animals were anesthetized briefly, received a retro-orbital injection of rhodamine dextran, and head-fixed under the objective lens. Awake animals were then imaged across excitation wavelengths (790 nm – 975 nm). During imaging, measures of sensor fluorescence intensity and animal velocity were captured

Results: Peredox and PercevalHR were expressed inconsistently in cells, making it difficult to evaluate bioenergetics across animals. However, nLightG expressed readily in neurons and showed robust responses to changes in animal state.

Conclusion: These findings suggest that with current methods and resolution ATP or NADH levels are stable in astrocytes during ambulation, perhaps highlighting a solid metabolic phenotype in these animals. Further investigations will evaluate NE dynamics in astrocytes and vascular smooth muscle cells to assess the role of NE in neuro- and astrovascular coupling.

Acknowledgments: This project was supported by P01 AG078116.

Poster Number 61

Modeling hearing state transitions in later life using multi-state Markov Chain Models: A longitudinal analysis of NACC data

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Graduate Student

Background: Hearing loss is increasingly recognized as a modifiable risk factor for cognitive decline and dementia in later life. However, little is known about how hearing states evolve over time in relation to cognitive changes, particularly in populations at risk for or living with dementia. Traditional longitudinal models do not adequately capture the dynamic, multi-state nature of hearing. This study uses multi-state Markov chain models to examine transitions between hearing states over time, incorporating cognitive and dementia-related factors.

Methods: This study uses longitudinal data from the National Alzheimer's Coordinating Center (NACC) to develop a discrete-time Markov model. The model defines four hearing states, defined annually at each visit: (1) hearing, (2) hearing impaired, (3) non-hearing or functionally deaf without hearing aid, and (4) death. Multinomial logistic regression models for each state transition will be estimated using SAS PROC NLMIXED. Covariates include demographic, cognitive, and health-related factors. Death is modeled as an absorbing state, and right-censoring will be addressed through inverse probability weighting.

Results: Analyses are currently in progress and will be completed in time for conference presentation. Preliminary results will estimate transition probabilities and identify key covariates associated with hearing state changes.

Conclusion: This study will offer novel insights into how hearing and cognitive decline may intersect, informing early intervention strategies to reduce dementia risk and improve quality of life in aging populations.

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Poster Number 62

Defining the role of tribbles pseudokinase 3 in Alzheimer's disease and related dementias

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Undergraduate Student

Background: Tribbles pseudokinase 3 (Trib3) is a protein that coordinates metabolic and inflammatory crosstalk to control cellular survival in response to stress. Predominantly studied in the cancer field, it remains relatively understudied in the aging brain. Nonetheless, a handful of reports have implicated it in various neurodegenerative contexts, including Parkinson's disease, Alzheimer's disease, Type 2 Diabetes, and epilepsy. Numerous insults can trigger increases in Trib3 expression which in turn can cause cell death. This makes manipulation of Trib3 an attractive target to prevent or blunt neurodegeneration across multiple neuropathological contexts, including those commonly found in patients with Alzheimer's disease and related dementias (ADRD).

Methods: We have begun to characterize Trib3 expression in human ADRD databases, AD brain tissue, and mouse models of AD dementia. This has included examining the SEA-AD database, as well as banked tissue by western blot and immunohistochemistry.

Results: Interestingly, we have found that Trib3 expression increases at the message level across numerous cell types in the human brain, including neurons, oligodendrocytes, and microglia. We have also found increased protein level of Trib3 in the hippocampus of a mouse model of mixed amyloid and vascular pathologies.

Conclusion: Work is ongoing to define the region- and cell-type specificity of Trib3 changes in human tissue in association with common neuropathological features (*e.g.*, amyloid plaques and tau tangles). Given its central role in both immune and metabolic response to stress, Trib3 may be a heretofore unrecognized contributor to ADRD pathogenesis. Ultimately, the intent is to determine whether Trib3 is a feasible therapeutic target to preserve neural function in the context of ADRD.

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Poster Number 63

Knockout of Perilipin-2 affects lipid droplet and microglial dynamics

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Graduate Student

Background: Lipid dysregulation plays a key role in neurodegenerative disease progression. Perilipin-2 (Plin2), a lipid droplet (LD)-associated protein, is elevated in Alzheimer's disease (AD) brains and linked to peripheral conditions like NAFLD and cancer. In AD, microglia can adopt a lipid-accumulating state which impairs function and may contribute to pathology. To explore how Plin2 influences this response, we generated a Plin2 knockout BV2 cell line and examined its role in microglial lipid accumulation following AD-relevant stimuli.

Methods: WT and Plin2 KO BV2 microglia were treated with control, oleic acid (250 μM), amyloid-β (1.5 μM), myelin debris (15 μg/cm²), or dead neurons. LDs were stained with Lipi-Green, quantified using HALO, and analyzed in Prism. Phagocytosis assays involved oleic acid ± pHrodo-zymosan particles. Lipidomics was performed following 24-hr treatments using methanol:butanol extraction and LC-MS analysis; data were processed via MetaboAnalyst and LipidomicsR. Bulk RNA-seq was performed on identically treated samples, sequenced by Novogene, and analyzed using Partek and clusterProfiler R.

Results: Plin2 KO microglia formed fewer LDs across all treatment conditions. Knockdown of Plin2 in microglia increased their phagocytic capacity. Lipidomic profiling revealed reductions in triacylglycerols and diacylglycerols, yet increased cholesterol esters. Transcriptomic analysis showed upregulation of oxidative phosphorylation and suppression of inflammatory pathways, particularly after amyloid-β exposure.

Conclusion: Loss of Plin2 reprograms the microglial phenotype—enhancing phagocytosis, reducing lipid droplet accumulation, and shifting transcriptional programs toward oxidative metabolism and reduced inflammation. These findings establish Plin2 as a key regulator of microglial lipid handling and immune function. Modulating Plin2 or related lipid pathways may represent a viable therapeutic strategy to influence microglial behavior in the context of AD.

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Poster Number 64

Targeting mPGES-1 and 5-LOX to repair blood-brain barrier dysfunction in epilepsy

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Graduate Student

Background: Seizures cause barrier leakage and neuroinflammation that contribute to drug-resistant epilepsy. Glutamate released during seizures activates 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2), producing leukotrienes and prostaglandins that drive matrix metalloproteinase (MMP)-mediated tight junction degradation leading to barrier leakage. Thus, blocking leukotriene and prostaglandin synthesis by inhibiting the 5-LOX and COX-2 pathways holds promise for repairing BBB dysfunction in epilepsy. Microsomal prostaglandin E synthase-1 (mPGES-1), the enzyme downstream of COX-2, is an attractive target, as its inhibition may provide a better safety profile than COX-2 inhibition. Here, we hypothesize that dual COX-2/5-LOX and mPGES-1/5-LOX inhibition with small-molecule inhibitors will repair barrier leakage.
Methods: We determined mPGES-1 localization in isolated mouse and rat brain capillaries using immunohistochemistry. Seizures were induced in 8-week-old female Wistar rats using the lithium-pilocarpine protocol. Rats were used 48 hours (acute) or 15 months (chronic) post-induction when spontaneous recurrent seizures were observed via piezo/video monitoring. Animals were dosed with the 5-LOX inhibitor Zileuton (ZLT; 5 mg/kg, IP, BID), the COX-2 inhibitor Celecoxib (CEL; 10 mg/kg, IP, BID), and/or the mPGES-1 inhibitor UK4b (10 mg/kg, IP, QD). Capillary leakage was assessed using a previously established assay (Hartz, 2004). Barrier leakage markers (MMP-2, MMP-9, S100β) were quantified from serum samples using ELISA.
Results: In rats with acute seizure, treatment with CEL, ZLT, or UK4b inhibitors alone did not return MMP-2, MMP-9, and S100β levels to control. Only dual inhibitor combinations, CEL/ZLT and UK4b/ZLT, reduced MMP-2 and MMP-9 to control levels. In chronic seizure animals, dual UK4B and ZLT administration significantly reduced MMP-2, MMP-9, and S100β to control levels compared to untreated chronic seizure animals.
Conclusion: Our findings demonstrate that dual inhibition of mPGES-1/5-LOX (UK4b/ZLT) and COX-2/5-LOX (CEL/ZLT) effectively repairs barrier leakage in both acute and chronic seizure rats. We are currently investigating the impact of dual UK4b/ZLT therapy with antiseizure drugs on seizure burden in chronic epilepsy.
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Poster Number 65

Glyburide repurposing targets KATP channels to reduce tau pathology

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Graduate Student

Background: Neurodegeneration and neuroinflammation drive Alzheimer's disease (AD) and other tauopathies. Since microglial activity is linked to cellular metabolism and inflammation, modulating it via ATP sensitive potassium (KATP) channels may offer therapeutic benefits. This study tests whether KATP channel inhibition with glyburide affects tau pathology, neurodegeneration, and neuroinflammation.

Methods: Slow-release glyburide or placebo pellets were implanted in 5-month-old P301S PS19 and WT mice for three months. Interstitial fluid (ISF) tau and lactate were measured via in vivo microdialysis. After treatment, tau pathology (AT8) and inflammatory markers (Iba1, GFAP) were assessed. Transcriptomic and pathway analysis was performed to evaluate therapeutic efficacy with glyburide treatment.

Results: Glyburide reduced ISF tau and trended toward lower lactate, suggesting reduced tau release and inflammation. Transcriptomic data showed increased macroautophagy, mitochondrial ATP production, and protein synthesis, indicating enhanced neuronal function while inflammation related pathways were downregulated. These changes were associated with reduced somatic AT8+ tau, altered tau distribution, and fewer astrocytes and microglia.

Conclusions: Glyburide modulates tau pathology, reduces neuroinflammation, and supports neuronal health via KATP channel inhibition in a sex-dependent manner. Targeting neuroimmune and metabolic pathways may offer therapeutic potential in tauopathies.

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Poster Number 66

Cell type-specific IL-1R1 signaling shapes subacute hippocampal synaptic function after closed-head injury

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Graduate Student

Background: Interleukin-1 receptor type-1 (IL-1R1) signaling has been implicated in post-traumatic neuron dysfunction, yet its neuron- vs endothelial-specific contributions remain unclear.

Methods: In 4–6-month-old male and female mice, we tested how IL-1R1 loss in CaMKIIα+ neurons or Slco1c1+ endothelial cells alters hippocampal function 1 wkpi vs sham. At 7 dpi, acute slices underwent field potential recordings in CA1 and DG, generating IO curves for basal synaptic strength. Parallel slices received DiOlistic labeling for quantification of dendritic spine density in CA1 and DG.

Results: At 1wkpi, CA1 of WT-CHI mice showed reduced basal synaptic strength, reduced spike threshold, & decreased spine density. These deficits were restored in nKO-CHI, but partially preserved in eKO-CHI, which showed milder depression, reduced spike threshold, and partial spine recovery. In DG, WT-CHI exhibited the expected hyperexcitable shift (greater basal strength, lower spike threshold), which was normalized in nKO-CHI and remained modestly lower in eKO-CHI. Dendritic spine changes were limited and directionally matched physiological effects.

Conclusion: At one week post-CHI, neuronal and endothelial IL-1R1 each show distinct, region-specific relationships with hippocampal synaptic function, suggesting complementary roles in post-injury dysfunction.

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Poster Number 67

STONE-LAVA: Multimodal quantification of cellular, network, and vascular activity

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Graduate Student

Background: Modern two-photon datasets demand tools that quantify a variety of signaling and physiological processes with subcellular resolution and spatial context**.** In astrocytes, signals arise on different timescales and interact with nearby structures (e.g., arterioles) and brain states. Existing workflows separate preprocessing from parameter definition, and include separate tools for cell event signal analysis, and other outcomes such as vessel geometry and motion. As a result, these analyses fail to converge spatially relevant information, and introduce methodological variation into the results.

Methods: We developed STONE-LAVA, a unified toolkit for multimodal data analysis. Its current version couples a framework to identify and quantify activity from subcellular compartments (somata, branches, and endfeet), with a process that models vascular motion and spatially correlates activity with perivascular cell signals. The pipeline performs machine learning approaches to segment cells into active compartments, and combine activity into cell networks among compartments/regions of interest. These networks are then spatially and temporally related to relevant experiment details such as stimulation and vascular activity. Sequential event timing experiments were conducted on processes such as neurovascular coupling, cell network activation, and cerebral blood flow in models of AD and cerebrovascular disease.

Results: STONE-LAVA revealed elevated spontaneous astrocyte Ca^{2+} event rates across somata, processes, and perivascular regions in 5xFAD mice, alongside attenuated stimulus-evoked vasodilation and reduced astrocyte–vessel coupling relative to controls. Standardized exports enabled rapid secondary analyses that resulted in findings that were featured on the cover of The Journal of Neuroscience (Oct 1, 2025). A provisional patent covering STONE-LAVA methods has also been filed.

Conclusion: STONE-LAVA converts complex two-photon movies into interoperable, analysis-ready datasets while explicitly linking cell sub compartment activity to vascular geometry and dynamics. By unifying segmentation, event detection, and coupling analytics with reproducible exports, the toolkit enables comprehensive hypothesis testing in neurovascular biology and clarified AD-related (de)coupling phenotypes. This open, framework lowers the barrier to rigorous intravital cell signaling–vascular research and enables comparisons across experiments, disease models, and laboratories.

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Poster Number 68

Exploring mechanisms of long-term cognitive impairment in sepsis survivors

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Undergraduate Student

Background: Sepsis is a potentially fatal systemic response to an infection. A majority of sepsis survivors experience a condition known as post-sepsis syndrome (PSS) including physical and cognitive impairment. Previously we developed a mouse PSS model in which sepsis surviving mice demonstrate long-term muscle weakness accompanied with mitochondrial dysfunction. The objectives of the current study were to examine whether our PSS model also exhibits cognitive impairment and identify potential causes of cognitive impairment after sepsis.

Methods: Sepsis was induced by abdominal infection followed by repeated antibiotics treatment and fluid resuscitation beginning 12 hours later. Fear conditioning memory tests were performed on both sepsis survivor and control mice three-four weeks after sepsis induction. Five weeks after sepsis induction, hippocampus tissues were collected for gene expression profiling by bulk RNA sequencing analysis.

Results: Results of the fear conditioning tests showed significant memory impairment in sepsis survivor mice. RNA sequencing analysis followed by Gene Ontology (GO) pathway analyses revealed significant differences between sepsis survivor and control mice. The top five most up-regulated gene pathways in sepsis survivors were all related to neuronal cell growth while the top five most down-regulated gene pathways included four mitochondrial respiration related pathways and one ribosomal translation pathway. Five out of 13 mitochondria-encoded protein-coding genes were also down-regulated suggesting mitochondrial damage and dysfunction.

Conclusion: These ongoing analyses suggest that sepsis survivor mice have long-term cognitive impairment which involves reduced mitochondrial and ribosomal functions with altered synaptic cell growth in the hippocampus.

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Poster Number 69

Utilizing the Clinical Dementia Rating Scale to assess social function in older adults with dementia as a tool to alleviate caregiver burden

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Staff

Background: As the number of older adults with Alzheimer's Disease and Related Dementias (ADRD) grows, so does the number of caregivers. Caregivers for people with dementia (PWD) are often unpaid family members providing care in the home. Social engagement is not only a protective factor against cognitive decline, but it is also a factor affecting caregiver burden. Previous studies demonstrate that social function in people with ADRD significantly affects caregiver burden. This study aimed to evaluate the relationship between caregiver burden and social function as measured by the Clinical Dementia Rating scale (CDR), a short and accessible measure.

Methods: Using a secondary analysis of data collected from participants with ADRD and their primary caregivers enrolled in a non-pharmacological randomized controlled trial (NCT05722743), Spearman correlational analyses evaluated the relationship between social function as measured by the community affairs and behavior subcategories of the CDR and caregiver burden, as assessed by the Zarit Burden Interview (ZBI).

Results: Data were analyzed from 24 participants with ADRD and their caregivers. Participants with ADRD consisted of 16 females, 8 males, $\bar{x}$ age of 78.58, with a $\bar{x}$ Global CDR of 1.77 (SD=0.86). Caregivers were comprised of 20 females, 4 males, $\bar{x}$ age of 61.42 (SD=11.22), and were most often spouses (n=11) or children (n=11) to their care partners. Analyses indicate significant positive correlations between impairments in behavior and community affairs with increased burden (rho=0.58, p=0.003; rho=0.54, p=0.007).

Conclusion: These findings emphasize the role of social functioning in people with ADRD as highly influential in caregiver burden. Furthermore, the CDR is a well-established and accessible instrument, whose potentially novel use as a measure of social functioning integrates easily into its current use. Due to the direct and indirect importance of social function for PWD and their caregivers, clinicians could use the CDR to identify any deficits in the community affairs and behavior subcategories in order to offer specific strategies to enhance social engagement and social functioning.

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Poster Number 70

Investigating the effect of astrocytic insulin receptor overexpression on beta-amyloid load and gait in a model of amyloidosis

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Staff

Background: Gait dysregulation is a hallmark of Alzheimer's Disease (AD) pathology, which affects the primary somatosensory cortex (S1), and can serve as a potential early indicator. An amyloid mouse model (5xFAD) was selected to investigate the correlation between the accumulation of amyloid-beta plaques and gait dysregulation in young and aged mice. Evidence from the literature suggests that insulin receptors of astrocytes may play a critical role in downstream signaling and function. To explore the pathology of amyloidosis across age, genotype, and sex, immunofluorescence (IF) was performed on mouse brain sections containing the somatosensory cortex (S1) region to visualize astrocytes, plaque load, and insulin receptor function in 5xFAD mice compared to wild type (WT).

Methods: Mice were singly or dually injected via craniotomy with a combination of AAV5-Gfa104-GCaMP8f and AAV5-Gfa104-Luciferase or AAV5-Gfa104-hIRbeta-HA in the S1 region 4 weeks prior to walking on a homemade, three-plane visualization gait apparatus. Matlab and ImageJ were utilized to quantify gait parameters. Coordinates acquired from each mouse were used to determine the average stride length, stride length deviance, average speed, stride time deviance, paw precision index, deviance from center, number of steps per cm, and number of steps per second.

Perfused brains were then sectioned at 40 μm using a cryostat. Immunofluorescence was conducted on sections, probing for S100β, amyloid-beta, HA-tag/IR-beta, and insulin-degrading enzyme (IDE). Sections were Z-stacked using a confocal microscope and condensed to measure plaque area. An ROI containing the section was chosen to quantify plaque area, measuring three sections per mouse. Significance was determined using 3-way and 2-way ANOVAs.

Results: Significant genotype differences were observed in nearly every measure taken from the gait analysis, along with an increase in plaque load, in the 5xFAD versus the WT models. 5xFAD mice appear to have a larger deviation from WT mice, especially in females, aligning with clinical data.

Conclusion: Our preliminary data suggest that IROE-injected 5xFAD mice appear to have no reduction in overall gait function when compared to their luciferase counterparts. The impact of IROE on inflammation and insulin signaling function is an ongoing area of research.

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Poster Number 71

Integrative analysis of multi-tissue molecular QTLs identifies novel causal genes for coronary artery disease

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Graduate Student

Background: Genome-wide association studies (GWAS) have identified numerous DNA variants associated with disease risk; however, the molecular mechanisms linking these variants to disease remain largely unknown.

Methods: To address this gap, I integrated expression quantitative trait loci (eQTL) data, which connect genetic variants with gene expression levels, to identify causal risk genes for coronary artery disease (CAD). A novel Bayesian variable selection method, causal-TWAS (cTWAS), was applied to prioritize risk genes from GWAS results (n = 1,165,690 participants of predominantly European ancestry) with lower false-positive rates than commonly used approaches. Three tissues (aorta, coronary artery, tibial artery) and three molecular traits (expression, splicing, stability) were jointly analyzed, incorporating relevant SNPs into the model.

Results: This analysis prioritized 21 putative causal genes, based on posterior inclusion probability and CAD relevance, out of 65 candidates. Many identified genes had not previously been linked to CAD but were biologically plausible. For example, *PHACTR1*, which regulates vascular smooth muscle contraction and endothelial function, emerged as a strong candidate.

Conclusion: The findings highlight novel CAD-associated genes and provide insights into the molecular mechanisms underlying genetic risk. Importantly, the cTWAS approach is broadly applicable to other complex traits and tissues, such as those involved in brain development and neurodegenerative diseases, offering a powerful framework for uncovering causal genes across diverse disorders.

Poster Number 72

Cre-mediated deletion of the transcriptional factor NFATc3 in a □-amyloid mouse model of Alzheimer's Disease.

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Graduate Student

Background: Astrocytes mediate neuronal health, connectivity and homeostasis, and their morphological and biochemical conversion into a reactive state reduces their protective function as the brain becomes more susceptible to degenerative diseases. Calcineurin (CN) is a Ca^{2+}-dependent phosphatase that drives NFAT (nuclear factor of activated T cells) transcription factor activity. Hyperactive CN-NFAT signaling is found in reactive astrocytes and is associated with cognitive decline in Alzheimer's Disease. Specific ablation of CN-NFAT signaling in astrocytes may be a promising strategy for reducing the pathophysiology of neurodegenerative disorders in humans.

Methods: 5XFAD transgenic mice have been bred into the NFATc3 floxed model to generate 5XFAD; $NFATc3^{fl/fl}$ and $NFATc3^{fl/fl}$ mice for this study. A subset of these mice was injected retro-orbitally with an AAV-Cre for astrocyte-specific expression of Cre recombinase (PHP.eB-Gfa104-Cre-4x6T). Ai9 reporter mice were also used to examine the level of Cre activity. Mice were perfused with PBS, and brains were harvested and fixed in 4% paraformaldehyde for 24 hours followed by placing in 30% sucrose. Sectioning was done at 40 □M for immunofluorescence studies. For biochemical studies, brains were flash frozen in liquid nitrogen for RNA analysis.

Results: Cranial window placement on Ai9 mice followed by retro-orbital injection of AAV-Cre showed strong expression of TdTomato beginning within 2 weeks as determined by two-photon microscopy. Cross-sections of Cre-injected Ai9 brains revealed high specificity of TdTomato expression within astrocyte populations throughout the cortex and hippocampus. AAV-Cre injection into mice with floxed NFATc3 alleles showed reduction of NFAT expression.

Conclusion: AAV-Cre can be administered via retro-orbital injection for rapid conversion of floxed alleles within a 2-week time period. Moreover, the specificity of the AAV allows for recombination within astrocyte populations.

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Poster Number 73

Motor network integrity predicts physical and cognitive performance in older adults at risk for Alzheimer's disease

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Postdoctoral Scholar

Background: Physical exercise (PEx) is a promising strategy to mitigate cognitive decline, yet meta-analyses show only modest cognitive benefits in older adults, underscoring the need to identify factors limiting its efficacy. The motor network (MN) is structurally vulnerable early in Alzheimer's disease (AD) risk. This study determines if baseline MN cortical volume and thickness predict physical and cognitive function in sedentary older adults at high AD risk.

Methods: We analyzed baseline data from 434 cognitively normal, sedentary adults (age 60-85) in the NIH-funded rrAD trial (NCT02913664). MRI, performed on five different 3T systems at four clinical sites, included 3D T_1-weighted MPRAGE to quantify cortical volume and thickness, as well as diffusion MRI to assess brain microstructural integrity and connectivity in key regions (precentral/postcentral gyri, superior frontal, and anterior cingulate cortices). Outcomes included cognitive (MMSE, PACC, NIH-Toolbox, DCCS) and physical (peak VO_2, 10m-walk dual task) tasks. Pairwise relationships were assessed using Spearman correlations (ρ).

Results: MN volume at baseline positively correlated with overall cognitive status (DCCS, MMSE, PACC, NIH-Toolbox Composite), but showed no clear linear association with physical performance (peak VO2 or 10m-walk dual task). In contrast, MN cortical thickness showed stronger positive correlations with executive function (DCCS and PACC) and was strongly associated with all physical performance measures at baseline (e.g., higher thickness predicted better peak VO2 and 10m-walk dual task speed).

Conclusion: Baseline motor network structural integrity, particularly cortical thickness, is a significant predictor of both physical and cognitive function in older adults at AD risk. MN integrity may serve as a crucial biomarker differentiating individuals' potential to benefit from PEx. Further analysis of two-year follow-up data will determine if baseline MN integrity moderates PEx-induced changes.

Acknowledgments: R01 AG49749, R56 AG074613, RF1 AG084134.

Poster Number 74

HALO AI characterization of microglia morphological changes after TBI in AD-relevant mouse model

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Undergraduate Student

Background: Traumatic brain injury (TBI) can trigger a neuroinflammatory response that persists long-term and may contribute to the onset of neurological conditions like Alzheimer's disease (AD). However, the extent to which a single mild TBI alters the trajectory of AD-related pathology remains unclear. In this study, we evaluated whether a closed head injury (CHI) administered in early adulthood affects the progression of microglia pathology in APP/PS1 knock-in (KI) mice, a genetically predisposed model of AD.

Methods: Both APP/PS1 KI mice and wild type (WT) received CHI or sham surgery at 4-5 months of age, a time point preceding the typical onset of Aβ plaque formation in KI mice. Brain tissue was analyzed for microglia reactivity (IBA1) at 1-, 4-, 8-, and 11-months post-injury. An AI classifier using HALO software was developed to assess ramified, hypertrophic, and dystrophic microglia populations within 4 brain regions (focus-area of injury, hippocampus, neocortex, corpus callosum), representing a novel application of AI to microglia phenotyping designed to mitigate human subjectivity in morphological assessment.

Results: Burden (% IBA1+ positive area) and counts of ramified, hypertrophic, and dystrophic microglia show a prominent genotype effect, with region-dependent differences associated with CHI in select timepoints.

Conclusion: Such investigations advance our understanding of microglial pathology in injured and diseased brains, and this approach can be extended to investigate other glial reactivity and amyloid burden to further understand the roles they play in neurodegeneration.

Acknowledgements: Research was supported by Department of Defense under award number AZ190017.

Poster Number 75

Participant factors associated with transitions to and from Subjective Memory Complaint: Results from the National Alzheimer's Coordinating Center' Uniform Data Set (2005-2025)

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Postdoctoral Scholar

Background: Subjective Memory Complaint (SMC) is considered a prodromal stage in the pathway to dementia, preceding Mild Cognitive Impairment (MCI). However, its predictive utility as a clinical state remains unclear. In the current study, we aimed to estimate transition probabilities between SMC and other states on the continuum from normal cognition to dementia.

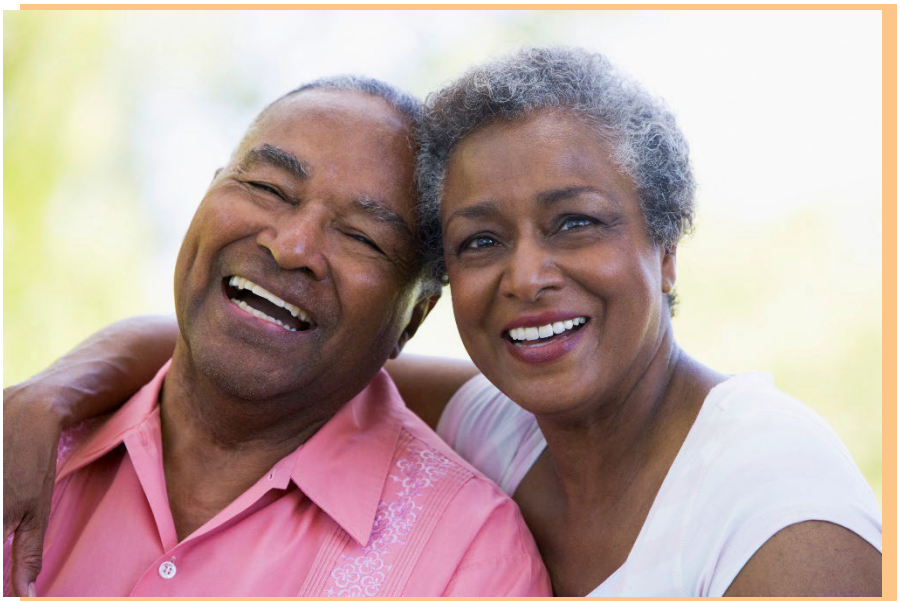
Methods: A retrospective cohort of initially dementia-free research participants was created using data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set, drawn from visits occurring between September 2005 and March 2025. Using Markov chain analysis with multinomial logistic regression models, we estimated the probabilities of transition between different cognitive states (Normal, SMC, MCI, Impairment non-MCI, Dementia, and Death without dementia), as well as the factors associated with the transitions.

Results: Included participants (N=27,140) had an average of 5 annual visits, and 18.2% reported SMC at least once during the study period. About 25% of participants with SMC transitioned to worse cognitive states (MCI: 11%; Impairment, non-MCI: 3.5%; or dementia: 10.6%) during follow-up. However, participants with SMC more frequently remained in the SMC state (32.5%) or transitioned back to Normal cognition the next year (38%). Transition probabilities were similar by sex. Factors associated with the transitions varied by sex and the state-specific transition; for example, females *APOE* ε2 carriers were less likely to transition to SMC from Normal cognition. Depression was strongly associated with transition from SMC to a worse cognitive state for both men and women.

Conclusion: This study provides additional evidence that SMC is meaningful cognitive state on the pathway to dementia. Its predictive utility is still limited by the fact that a higher proportion of individuals with SMC remained stable or returned to normal cognition than declined during the study period, and depression was strongly associated with decline from SMC. More textured measures of SMC may yield different results with fewer false positives.

Acknowledgments: This study was partially supported by the UK ADRC, NIH/NIA P30AG072946.

Sanders-Brown Center on Aging



The Sanders-Brown Center on Aging (SBCoA) was established in 1979, and received funding as one of the original ten National Institutes of Health Alzheimer's Disease Centers in 1985. Internationally acclaimed, the SBCoA is recognized for its contributions to the fight against brain diseases that are associated with aging.

Our vision: The University of Kentucky Sanders-Brown Center on Aging will be recognized locally and nationally as a premier, vitally productive and innovative aging center that effectively translates research findings into interventions and information that will benefit older adults.

ALZHEIMER'S DISEASE FACTS

Normal Age-Related Memory Changes

- Missing a monthly payment
- Forgetting which day it is and remembering later
- Sometimes forgetting which word to use
- Losing things from time

Warning Signs of Dementia

- Poor judgment and decision making
- Inability to manage a budget
- Losing track of the date or the season
- Misplacing things and being unable to retrace steps to find

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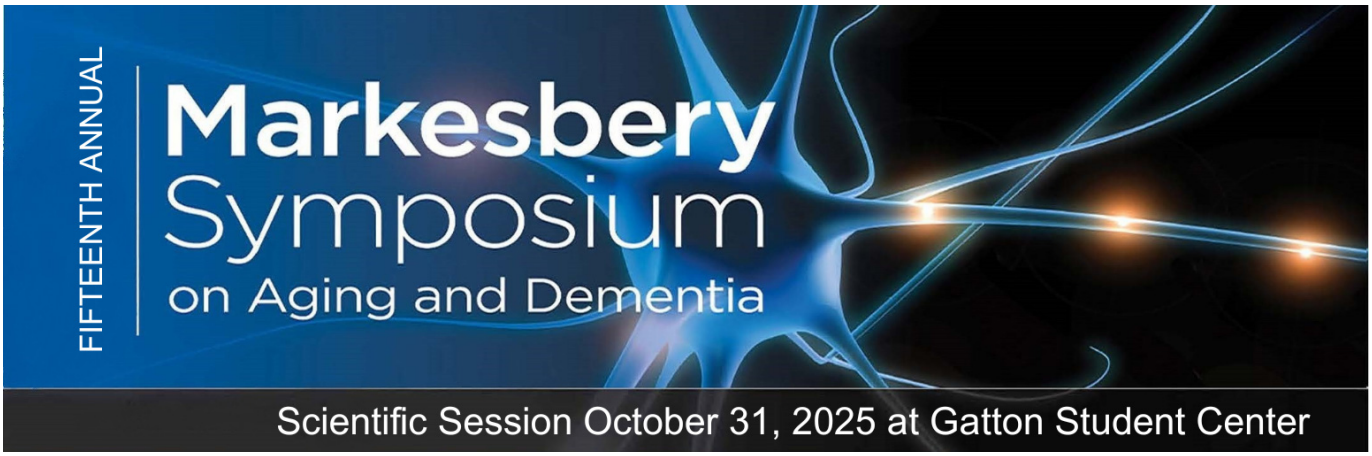
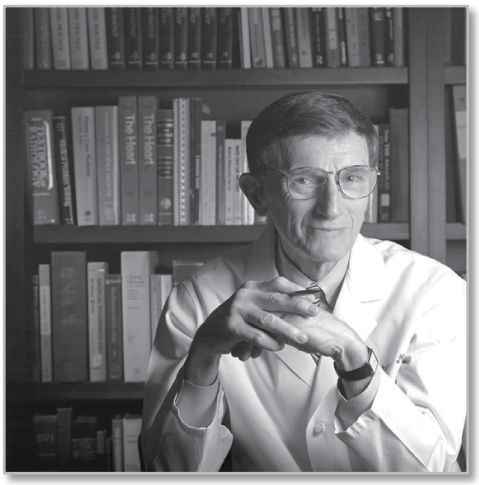
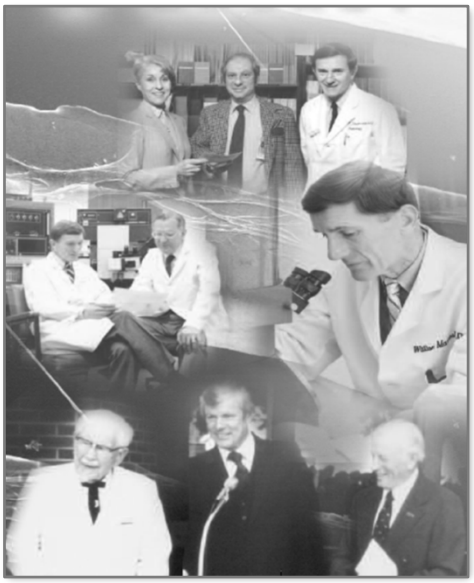


WILLIAM R. MARKESBERY, MD (1932-2010)

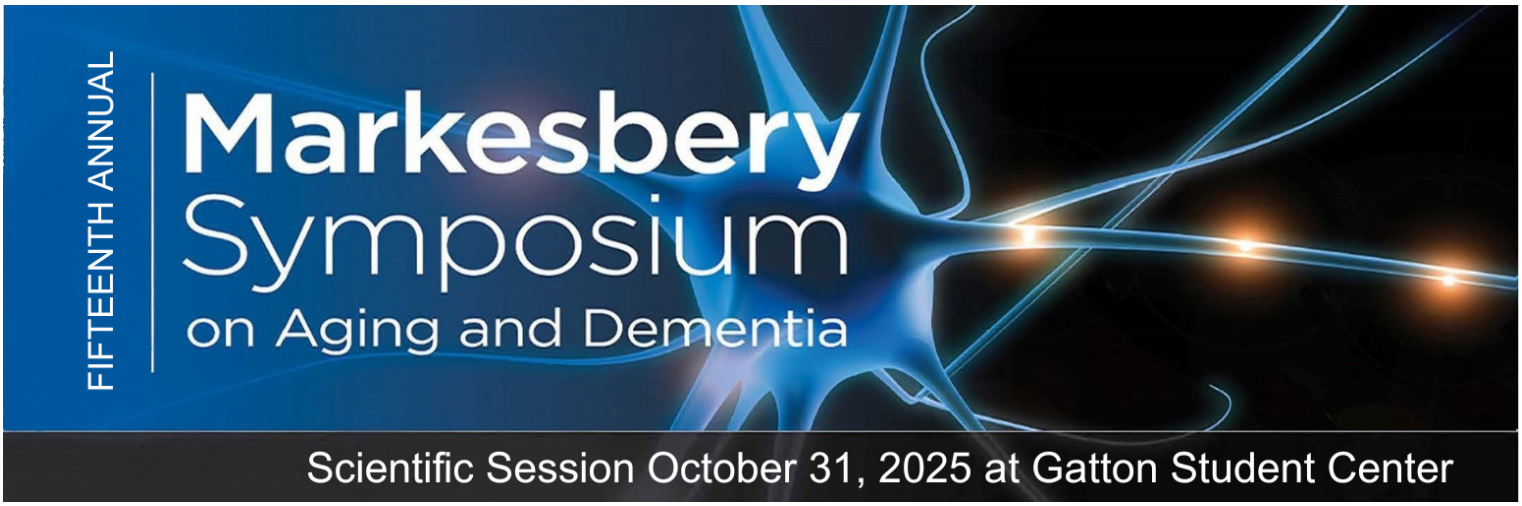




The Markesbery Symposium on Aging and Dementia is named in honor of William R. Markesbery, MD, a gifted scientist and internationally recognized neurologist and neuropathologist. Dr. Markesbery's creativity and commitment to aging research provided the impetus for the University of Kentucky to establish the Sanders- Brown Center on Aging in 1979 and name him as the first director. He held that position until his death in January 2010.

In 1985, Bill Markesbery became the director of the Alzheimer's Disease Research Center, one of the original 10 National Institute on Aging (NIA)-funded centers in the United States, with a primary focus on neuropathology. After more than 40 years, the Alzheimer's Disease Research Center continues to be funded by NIA, a remarkable achievement that demonstrates the strength and caliber of this program. During his academic career, Dr. Markesbery published more than 400 scientific papers and was one of the world's leading experts on Alzheimer's disease and oxidative stress. He will always be remembered as a compassionate and caring physician, a brilliant researcher, and an inspirational leader.

Notes



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