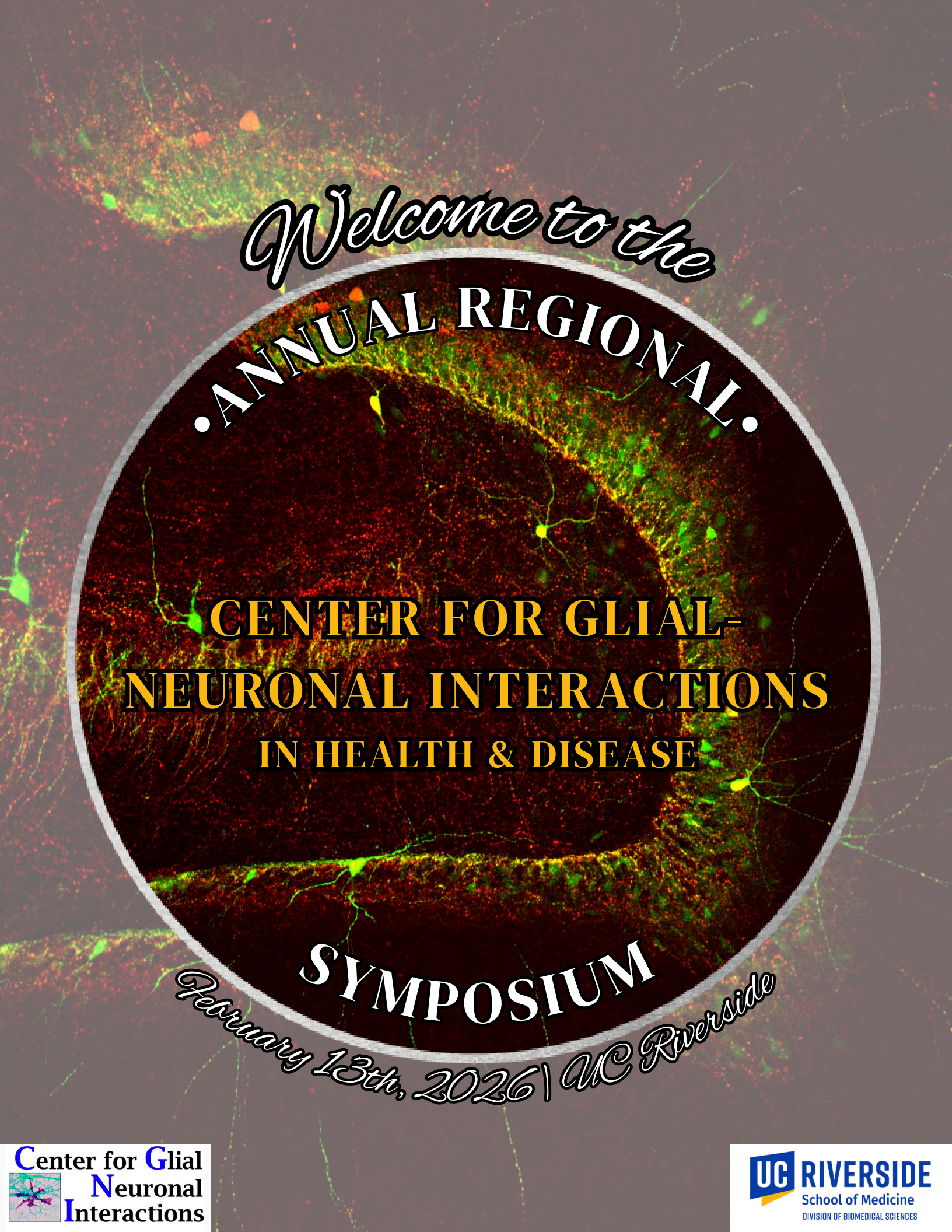


Center for Glial Neuronal Interactions

UC RIVERSIDE School of Medicine
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# Center for Glial Neuronal Interactions

The **CGNI Faculty** would like to thank our sponsors. Without your many contributions, this event would not be possible.

**Our Sponors:**

- UCR School of Medicine & Division of Biomedical Sciences
- Journal for Neuroinflammation & Springer Nature
- UC Riverside Neuroscience Graduate Program

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BMC

SPRINGER NATURE

**Cover image by Chia-Wei (George) Yeh, *Interdepartmental Graduate Program in Neuroscience, (Dr. Viji Santhakumar Lab, Molecular Cell & Systems Bio Dept.).*** This image of the mouse hippocampal dentate gyrus features the axo-axonic cells, also called the chandelier cells, labeled with eYFP-expressing virus. Parvalbumin staining (red) marks fast-spiking interneurons in the dentate gyrus, and eYFP signals (green) mark labeled chandelier cells, a subpopulation of parvalbumin-expressing interneurons in the dentate gyrus.

# Welcome to the 19th Annual SoCal Symposium on Glial-Neuronal Interactions in Health and Disease

*We are delighted to celebrate all of you, the more than 200 registrants from a dozen institutions who have joined us here today. We come together as a community with diverse scientific expertise, perspectives and life experiences. We celebrate the discussions, the questions, the explorations of potential new collaborations between 50 poster presenters, our invited speakers and all attending. Indeed, it is all about the interactions, and together we will go far!*

*So, who are we who choose to join? Few researchers have the ability to be true experts in all cells and all systems involved in developing, maintaining, defending and repairing the nervous system. Collaborative research between experts of relevant fields is often impeded by field specific jargon, cultures and the lack of forums friendly to those from "outside." The Center for Glial-Neuronal Interactions (CGNI) is dedicated to providing an interactive and welcoming forum facilitating innovative collaborations between neuro- and glial-centric researchers as well as with researchers from outside the field of neuroscience. The ultimate goal is to define the multi-factoral processes contributing to the health and dysfunction of the nervous system.*

*How did we start? October 26, 2007, we launched this symposium to provide a regional forum for individuals with neuro-centric, glial-centric or disease-centric research focus (as well as for all who find themselves in between) to present their ongoing research and initiate collaborations across disciplines and between organizations. The multiple interdisciplinary and collaborative interactions evident in this year's posters and speaker presentations confirm the need for participation of diverse researchers to solve problems of brain health and disease.*

*At this time of year, we also honor and remember Glenn Hatton. Glenn was one of CGNI's co-founders and an early and fearless advocate of crossing "scientific borders" to pursue how glia and neurons interact. We encourage you to follow his example of interdisciplinary research. Please take advantage of the poster sessions and discussion periods to meet new colleagues, explore new ideas and perhaps start a new collaboration. We provide you with the names, affiliations and email contact information for the registrants of this symposium at the end of this booklet to facilitate interactions well after the close of our symposium.*

*We thank the generous support of our sponsors that allows us to continue to provide this interactive forum without a registration fee. We thank Pica Preston and the entire team of staff and student volunteers for their invaluable and tireless support in so many aspects of this forum.*

*If you wish to join in our in person monthly meetings on the second Friday of each month, please let us know (biomedsci@medsch.ucr.edu). We would love to have you join us.*

Thank you all for your active participation in this symposium and we hope to see you again next year for our **20th Annual CGNI Symposium on February 12, 2027**!

**The 2025-2026 Executive Committee**
**UCR Center for Glial-Neuronal Interactions**

# 19th Annual Regional Symposium on Glial-Neuronal Interactions in Health and Disease

## February 13, 2026

## School of Medicine Education Building II, Rooms 104/106 - UC Riverside

**Agenda:**

| | |
|---|---|
| *9:00 - 9:45am* | ***Registration. Badge pick-up. Poster set-up.*** |
| *9:45 - 10:00am* | ***Symposium Opens***<br>***Welcome Opening Remarks***<br>Monica Carson, PhD., Professor and Chair<br>Division of Biomedical Sciences, School of Medicine<br>S. Sue Johnson Presidential Endowed Chair in Glial-Neuronal Interactions<br>Center Director, Center for Glial-Neuronal Interactions<br>University of California, Riverside |
| *10:00 - 11:00am* | ***Keynote Lecture***<br>**Matt J. Campen, PhD., MSPH, Distinguished Professor**<br>College of Pharmacy<br>University of New Mexico Health Sciences Center<br>**"Minding the Nanoplastics"** |
| *11:00 - 11:45am* | ***Presentation I***<br>**Megan M. Herting, PhD., Associate Professor**<br>Population and Public Health Sciences<br>Keck School of Medicine<br>University of Southern California<br>**"Windows of Vulnerability: Air Quality and the Adolescent Brain"** |
| *11:45am - 1:15pm* | ***Lunch and Poster Session*** |

***Afternoon session I, moderator: Dr. Viji Santhakumar, Vice Chair & Professor, Molecular Cell & Systems Bio Dept***

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|---|---|
| *1:15 - 2:00pm* | ***Presentation II***<br>**Melissa Rosenkranz, PhD., Associate Professor of Psychiatry**<br>Distinguished Chair in Contemplative Neuroscience at the Center for Healthy Minds<br>University of Wisconsin-Madison<br>**"Beyond the Airways: The Neural Effects of Asthma"** |
| *2:00 - 2:45pm* | ***Presentation III***<br>**Pamela J. Lein, PhD., Distinguished Professor and Chair**<br>Department of Molecular Biosciences<br>University of California, Davis<br>**"Evolving role of microglia following acute organophosphate intoxication: time and phenotype matter"** |
| *2:45 - 3:15pm* | ***Afternoon break and Poster Session*** |

***Afternoon session II, moderator: Dr. Andre Obenaus, Professor, Biomedical Sciences***

| | |
|---|---|
| *3:15 - 4:00pm* | ***Presentation IV***<br>**M. Kerry O'Banion, MD., PhD., Professor of Neuroscience**<br>Del Monte Institute for Neuroscience<br>University of Rochester School of Medicine & Dentistry<br>**"Influence of Sex and Cytokines on Microglia and their Modulation of Amyloid Pathology"** |
| *4:00 - 4:45pm* | ***Glenn Hatton Lecture***<br>**Prof. Dr. Thomas Langmann, Professor and Chair**<br>Laboratory for Experimental Immunology of the Eye<br>Department of Ophthalmology<br>University of Cologne<br>**"Microglia in retinal degeneration and pathological angiogenesis"** |
| *4:45- 5:00pm* | ***Trainee awards and Closing Remarks*** |

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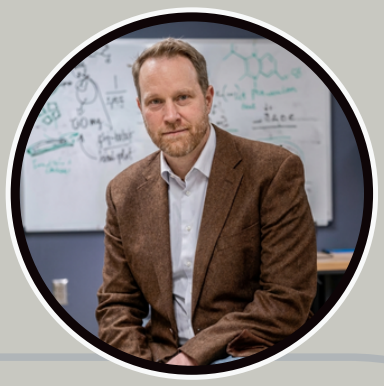
# THE 19TH ANNUAL REGIONAL SYMPOSIUM ON GLIAL-NEURONAL INTERACTIONS IN HEALTH AND DISEASE SPEAKER BIOS

## MATTHEW J. CAMPEN, PHD, MSPH (KEYNOTE SPEAKER)

**Distinguished Professor, College of Pharmacy**
**University of New Mexico Health Sciences Center**



Dr. Matthew Campen is a Distinguished Professor in the University of New Mexico College of Pharmacy. He received his bachelor's degrees in biochemistry and psychology from Virginia Tech, then completed an MSPH and PhD in Environmental Science and Engineering from the University of North Carolina School of Public Health. Following a postdoctoral fellowship in the Johns Hopkins University School of Medicine, Dr. Campen moved to New Mexico and worked for several years as a toxicologist at the Lovelace Biomedical Research Institute. In 2009, he moved across town to accept a faculty position at the University of New Mexico College of Pharmacy.

Dr. Campen has been instrumental in establishing multidisciplinary, programmatic research programs at UNM, including several NIH-funded centers, such as the UNM Center for Metals in Biology and Medicine and the Southwest Center for Advancing Clinical and Translational Innovations. His research expertise is largely focused on how inhaled pollutants like ozone, particulate matter, and carbon monoxide can cause toxicity beyond the lungs, including neurological and placental health effects. He began researching the problem of microplastics about 5 years ago and found the science at the interface of plastics and human health was immature. He has worked to better understand the nature of exposures, dosimetry, and toxicity using approaches that incorporate real human/clinical samples.

## MEGAN M. HERTING, PHD

**Associate Professor of Population and Public Health Sciences**
**Keck School of Medicine**
**University of Southern CaliforniaUniversity of Southern California**

Dr. Megan Herting is an Associate Professor in the Department of Population and Public Health Sciences and the Director of the Herting NeuroImaging Laboratory at the University of Southern California. Her research focuses on how lifestyle and environmental factors, particularly air pollution, influence brain development, cognition, and mental health in children and adolescents. Using multi-modal MRI, cognitive assessments, and neuropsychological testing, she leads multiple NIH-funded projects examining air pollution's effects on neurodevelopment and psychopathology risk.

## MELISSA ROSENKRANZ, PHD

**Associate Professor of Psychiatry**
**Distinguished Chair in Contemplative Neuroscience at the Center for Healthy Minds**
**University of Wisconsin-Madison**

Dr. Melissa Rosenkranz is an Associate Professor in the Department of Psychiatry and holds the Distinguished Chair in Contemplative Neuroscience at the Center for Healthy Minds. She earned a Ph.D. in Psychology from the University of Wisconsin-Madison in 2008 and a Bachelor's of Science degree, also from UW-Madison, in 1997. Since that time she has worked to develop a mechanistic understanding of how the contents of the mind influence physiological processes in the body and how the activities of the immune system shape how we experience the world. Melissa has amassed multi-disciplinary expertise at the intersections of psychology, neuroscience, immunology, endocrinology, and contemplative studies, leveraging a diverse array of methods from brain imaging to molecular biology. With federal funding from NCCIH and NHLBI, her work has identified both neural and immune signaling pathways that connect airway inflammation in the lungs of individuals with asthma to the psychological experiences of stress and emotion. Extending these relationships across the lifespan with funding from NIA, Dr. Rosenkranz's work also reveals links between chronic systemic inflammation, neuroinflammation, neurodegeneration, and long-term cognitive decline and dementia.

Importantly, Melissa's work goes beyond basic science. She also examines the mind as a novel treatment target in chronic inflammatory diseases. She has shown, for example, that 8-weeks of training in mindfulness-based stress reduction improved asthma control and reduced airway inflammation in patients with asthma, particularly those with elevated symptoms of depression. She is currently working to expand this work and to accelerate its translation into the clinic.

## PAMELA J. LEIN, PHD

**Distinguished Professor and Chair, Department of Molecular Biosciences**
**University of California, Davis**

Dr. Pamela (Pam) Lein is Distinguished Professor of Neurotoxicology and Chair of the Department of Molecular Biosciences in the University of California, Davis (UC Davis) School of Veterinary Medicine. She also holds a faculty appointment in the UC Davis MIND Institute. Dr. Lein earned a B.S. in Biology from Cornell University in Ithaca, NY, a M.S. in Environmental Health Sciences from East Tennessee State University in Johnson City, TN, and a Ph.D. in Pharmacology and Toxicology from the University of Buffalo in Buffalo, NY. She completed postdoctoral training in Molecular Immunology at the Roswell Park Cancer Institute in Buffalo, NY. Her research focuses on the cellular and molecular mechanisms by which environmental contaminants contribute to the pathogenesis of neurodevelopmental and neurodegenerative disorders. Dr. Lein has been continuously funded by the U.S. National Institutes of Health for over 30 years, and she has >300 peer-reviewed publications and book chapters. She is actively engaged in teaching and mentoring veterinary, graduate and undergraduate students in neuropharmacology and neurotoxicology. Her service activities include Co-Editor-in-Chief of the journal NeuroToxicology and Executive Committee of the International Neurotoxicology Association.

## M. KERRY O'BANION, MD, PHD

**Professor of Neuroscience**
**Del Monte Institute for Neuroscience**
**University of Rochester School of Medicine & Dentistry**

Dr. M. Kerry O'Banion is Professor and Vice-Chair of Neuroscience, Professor of Neurology, and a member of the Del Monte Institute for Neuroscience and the Wilmot Cancer Center at the University of Rochester School of Medicine & Dentistry in Rochester, New York. His research focuses on neuroinflammation and glial cell biology, emphasizing cellular interactions in in neurodegenerative disorders, including Alzheimer's disease, as well as in CNS radiation exposure, and how these contribute to pathology and cognitive deficits in preclinical models. Originally trained as a molecular virologist, Dr. O'Banion received his MD and PhD in Microbiology degrees from the University of Illinois, Champaign-Urbana and carried out postdoctoral work as a Wilmot Cancer Fellow at the University of Rochester that contributed to the discovery of cyclooxygenase-2 (COX-2) as a critical mediator of inflammation. Dr. O'Banion has trained 5 postdoctoral fellows and 28 graduate students, including six MD-PhD students. His research has been supported by NIA, NINDS, NIDA, NIAID, NCI, NASA and the Department of Energy. In addition to his research, Dr. O'Banion has directed Rochester's Medical Scientist Training (MD-PhD) Program since 2000 and co-directs an NIA funded T32 in Aging and Alzheimer's disease.

## PROF. DR. THOMAS LANGMANN (GLENN HATTON LECTURE)

**Professor and Chair, Laboratory for Experimental Immunology of the Eye**
**Department of Ophthalmology**
**University of Cologne**

Prof. Dr. Langmann is a leading ophthalmologist and immunologist at the University of Cologne (Uni Köln) and University Hospital Cologne (UK-Köln), heading the Lab for Experimental Immunology of the Eye. He specializes in retinal diseases such as macular degeneration (AMD) and diabetic retinopathy (DR), focusing on the critical role of the immune system (microglia/macrophages) in these conditions, aiming for new immunomodulatory therapies, and he is the Vice Dean for Critical Infrastructures.

# Poster Abstracts

## 1. Targeting Astrocytes in the Auditory System

**Analisia Dean**

California State University, Fullerton

Astrocytes are bushy, star-shaped glial cells that can be found throughout the brain where they support neurons and regulate neural function. Although astrocytes were assumed to be homogenous across brain regions, new studies show regional diversity. An area where astrocytes remain understudied is the auditory system. To address this gap in knowledge, we investigated astrocytes in 3 auditory processing regions: the cochlear nucleus, the inferior colliculus, and the auditory cortex. Using mouse models, genetic tools, and immunohistochemistry of astrocyte markers, we compared astrocyte abundance and marker expression across the specific regions. Fluorescence imaging and cellular quantification were used to analyze astrocyte population and determine if the amount of astrocytes differed between the auditory regions. Our findings indicate that there are regional differences in astrocyte marker expression and astrocyte population numbers across the cochlear nucleus, the inferior colliculus, and the auditory cortex. These results suggest that astrocytes in the auditory system display unique characteristics rather than being uniform throughout the entire CNS. Future research will investigate the relationship between astrocytes and neurons within the auditory system and compare the interactions between other sensory systems. This research will allow us to further understand how diverse cell types support hearing and auditory processing.

## 2. Optical stimulation of midbrain dopamine neurons enhances adaptive decision-making.

**Brandon Oliver**

University of California, Riverside

Midbrain dopamine (DA) release in the striatum is crucial for reward-based learning. Reversal learning, a measure of behavioral flexibility, assesses adaptation to changing environments and relies on this DA circuit. During early reversal learning, phasic striatal DA may facilitate updating stimulus-/response-reward associations and improve decision-making. We investigated striatal DA dynamics during a probabilistic reversal learning (PRL) task and probed the causal role of DA release in flexible decision-making. Using fiber photometry and a genetically encoded DA sensor (GrabDA), we recorded DA changes in the dorsal (DS) and ventral (NAc) striatum in male and female mice (N = 17) trained to discriminate between two levers with differing reinforcement probabilities (80% vs. 20%). Once expert level performance was achieved, reinforcement probabilities were switched or reversed across levers. Compared to pre-reversal, DA release was increased at the start of reversal trials in the DS (p < 0.001) and following correct-rewarded choices in both DS (p < 0.01) and NAc (p < 0.05), supporting striatal DA mediated response-outcome updating. We then use closed-loop optogenetics to stimulate dopaminergic afferents to these striatal regions on the first correct-rewarded response to assess whether boosting reward-evoked DA release on the new correct lever facilitates learning the new contingency. Compared to tdTomato controls, stimulating DA neurons in both SNc-DS (n = 19; p < 0.001) and VTA-NAc pathways (n = 30; p < 0.05) resulted in significantly improved reversal performance and choice strategy. These findings underscore the critical role of striatal DA in adaptive decision-making.

**3. Repeated Closed Head Injuries Alter Brain Bleed Patterns Elicited by Single Injury in Juvenile Male Mice.**

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

School of Medicine, University of California, Riverside

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

Funding: NIH NINDS 1RF1NS138032 to A. Obenaus and P. Territo

**4. Can adult gene re-activation alone or combined with controlled sound exposure normalize EEG and behaviors in a mouse model of Fragile X Syndrome?**

**Anna Norman**, Farooq N., Sahni A., De Arman J., Goel A., Razak K.A., Ethell I.M.

Biomedical Sciences, School of Medicine, University of California, Riverside

Fragile X Syndrome (FXS) is a neurodevelopmental disorder with no known cure, that is associated with epigenetic silencing of Fragile X Messenger Ribonucleoprotein 1 (Fmr1) gene. Impaired behaviors in FXS can stem from hyperexcitable cortical circuits manifesting in electroencephalogram (EEG) phenotypes that are remarkably similar between the mouse model of FXS and the human condition across different brain areas. The main goal of this study was to test if gene re-activation alone or combined with sensory manipulations can lead to positive functional outcomes in adult mice.

Fmr1FloxNeoCAG-CreERT2 mice were treated with tamoxifen to achieve gene re-activation. In addition, a subset of mice were exposed to14 kHz pure tones (5 Hz repetition rate, 70 dB SPL) alone or combined with tamoxifen treatment. We studied cortical activity using clinically relevant EEG recordings as well as locomotor and exploratory behaviors using open field test. We found that synchronization to frequency-modulated sound, chirp, was significantly improved in the frontal cortex of KO mice following gene re-activation, however, there was no effect of sound exposure. Behavior testing revealed significant improvements in exploratory behaviors but not hyperactivity following both adult gene-reactivation and sound exposure.

Summarizing, our results show that adult gene re-activation as well as adult controlled acoustic exposure had positive effects on functional cortical responses and behaviors in KO mice. These findings prove that therapeutic and sensory interventions in adulthood can result at least in partial improvements of functional outcomes and open new possibilities for treatments of adult humans with FXS.

**5. The role of astrocytic volume-regulated anion channel (VRAC) in neuronal excitability and astrocyte volume regulation.**

**Chrissy Lopez and Paul Pham**

University of California, Riverside

Astrocytes are a type of glial cell with a variety of functions, including maintaining ion and neurotransmitter concentrations in the fluid-filled extracellular space (ECS). Fluctuations in the composition of the ECS, such as reduced osmolarity or increased potassium, induce astrocyte swelling and can negatively impact neuronal function. Prolonged ECS constriction occurs in a variety of pathological states, including glutamate-mediated excitability, a hallmark of seizure-like activity. One channel implicated in the astrocyte volume response is the volume-regulated anion channel (VRAC), which may also be involved in volume-driven increases in neuronal excitability. VRAC is activated in response to cell swelling and is thought to regulate cell volume and osmolarity by releasing anions and glutamate, along with water, into the ECS. Our lab has previously observed that application of a hypoosmolar solution triggers an increase in neuronal excitability, but the underlying mechanism remains unknown. To investigate the role of VRAC in astrocytic volume regulation and neuronal excitability, we have generated a conditional knockout to selectively remove VRAC in astrocytes (VRAC cKO). We have found that the role of VRAC on astrocyte volume is highly context-dependent. While elevated extracellular potassium has little effect on astrocytic volume responses, VRAC activation is profoundly consequential for astrocyte volume regulation under reduced extracellular osmolarity. Notably, we did not observe a classic regulatory volume decrease (RVD) in either swelling condition or genotype. Our experiments have also suggested that astrocytic VRAC does not affect neuronal excitability through efflux of glutamate into the ECS. Future experiments will explore other potential astrocyte contributions to neuronal glutamatergic activity, such as the connexin hemichannels.

## 6. Hypoosmolar Conditions Produce a Unique Pattern of Hyperexcitability in Adult CA1 Hippocampal Neurons.

**Rhiannon Rivas**

University of California, Riverside

Rapid onset cellular edema in the brain leads to a reduction of the brain's extracellular space (ECS) and increases neuronal excitability, which is a critical factor underlying hyperexcitable conditions including epilepsy. Using whole-cell patch clamp electrophysiology, we recorded electrical currents in CA1 pyramidal neurons in live hippocampal slices from mice. In adult mice (P56-84), there emerges a pattern of activity with some similarity to the ictiform activity commonly observed in epilepsy. The ictiform bursts are observable in 30% - 40% hypoosmolarartificial cerebrospinal fluid (ACSF), but not in 17% hypoosmolar ACSF. Additionally, this activity does not appear to be appreciably impacted by the neuronal volume regulated anion channel (VRAC). VRAC is an outwardly-rectifying anion channel which primarily allows for the movement of chloride out of cells, creating an osmotic gradient that leads to a reduction in cellular volume. Using a NEX1-Cre promoter, we selectively ablated the SWELL1 gene which encodes for the essential LRRC8A subunit of VRAC, in cortical neurons. Despite the potential dysregulation of neuronal volume, these cells do not display a substantial increase in ictiform-like activity compared to control animals. Conversely, our data suggests that targeted knockout of neuronal VRAC reduces the frequency of synaptic events, especially small events (mEPSCs). We are performing additional experiments across a host of conditions to determine potential context dependency of neuronal VRAC. Overall, our results present an interesting avenue for further investigation into the impact and degree of swelling on neuronal hyperexcitability, as well as the role of neuronal VRAC in epileptiform conditions.

**7. Microglia-extracellular matrix remodeling in a mouse model of vascular dementia and its relationship with memory deficits.**

**Mia Donato**

University of California, Los Angeles

Vascular Dementia (VaD) is the second leading cause of dementia cases worldwide. Cognitive training strategies have shown promising results in ameliorating age-associated cognitive decline and in some cases VaD-related deficits. Whether such enrichment strategies are effective in mouse models of VaD remains unknown. Microglia have critical surveillance and phagocytic functions throughout the brain and spinal cord, and play central roles in driving responses to VaD. One feature of microglia responses to VaD is remodeling of the extracellular matrix (ECM), a complex network of proteins and carbohydrates involved in cellular communication and structural support. This study tests whether engaging in foraging-based enrichment alters microglia and ECM status in a mouse model of VaD. 36 mice were assigned to control-sedentary, VaD-sedentary, or VaD-foraging groups, each of which underwent saline control or VaD-inducing vasoconstrictor surgery. The mice completed behavioral phenotyping before and after a four-week sedentary or foraging-enrichment period. Brain tissue from select mice was sectioned and histochemically stained for tyrosine hydroxylase (dopaminergic neurons), wisteria floribunda agglutinin (ECM), and IBA1 (microglia). Our results indicate that VaD mice exhibit decreased spontaneous alternation on a T maze, suggestive of cognitive deficits in frontal cortical networks. Here we present preliminary results of microglia density and ECM abundance in the nucleus accumbens, anterior cingulate cortex, and motor cortex and highlight possible links with T maze performance. The results from this research will contribute to a greater understanding of how VaD impacts brain function and whether behavioral enrichment changes non-neuronal structures supportive of cognition in individuals with VaD.

## 8. Longitudinal Brain Maturation In hAβKI Mice Reveals Sex-Specific Cortical Differences.

**Anh Le**

University of California, Riverside

Objectives: The MODEL-AD consortium (model-ad.org) develops new mouse models of Alzheimer's disease (AD) that are more reflective of sporadic AD than currently available models. A humanized amyloid beta knock-in (hAβKI) mouse has been developed and is used as a base model onto which risk alleles for AD can be added. Here, we characterized age- and sex-dependent changes in hAβKI mice using high resolution neuroimaging of whole brain and regional volumes relative to age and sex matched C57BL/6J (WT) mice.

Methods: In this longitudinal study, male and female WT and hAβKI mice (N=5-6 per group) were scanned in vivo by MRI (T2-weighted imaging) at 6, 12, and 18 months at 9.4T. Whole brain and regional volumes were derived at each age using a modified Australian Mouse Brain Mapping Consortium (AMBMC) brain atlas.

Results: Whole brain volumes significantly increased between 6 and 18 months in all groups. At 6 months, female hAβKI mice had significantly smaller cerebrum volumes compared to the female WT, with no other genotype-dependent differences at 12 or 18 months. Cortical analysis revealed that male hAβKI mice had significantly reduced volumes in the anterior cingulate and parietal cortex regions at 12 months relative to WT males.

Conclusions: Sex-specific differences in brain volume trajectories were observed with male hAβKI mice exhibiting age-dependent cortical alterations despite increasing whole brain volumes. The pre-frontal and parietal region involvement supports early cortical implications in AD.

Funding: NIH NIA 1U54AG054349 (PI LaFerla, Tenner)

**9. A Single Concussion in Juvenile Mice Induces Sex-Specific Acute Cerebrovascular and Blood-Brain Barrier Dysfunction.**

**Nathan Nguyen**

University of California, Riverside

Objectives: Concussions may disrupt the blood-brain barrier (BBB), contributing to neurological and behavioral impairments. However, the temporal dynamics of BBB dysfunction following concussion during developmentally vulnerable periods remain understudied. This study aimed to characterize the acute time course of BBB disruption and cerebrovascular alterations following mild traumatic brain injury (TBI) in juvenile mice.

Methods: Male and female C57BL/6 mice at postnatal day 17 underwent sham procedure or a single closed-head injury (CHILD). BBB permeability was assessed using intravenous Evans Blue dye at 1h, 6h, 1d, 3d, and 7d post-injury. Cerebrovascular architecture was visualized using our vessel painting, and MRI-based T2 relaxation mapping was performed at 1d post-injury to assess injury-related alterations in brain tissue.

Results: A single early-life concussion produced hyperacute structural and potential functional changes to the cerebrovasculature. CHILD resulted in disrupted physiological and developmental trajectories with reduced brain volumes, and sex-dependent alterations in T2 relaxation times (increased in females; decreased in males). BBB permeability was significantly elevated within hours of injury and was associated with cerebrovascular reductions with males exhibiting a more pronounced BBB disruption and vascular alterations than females. Small penetrating cortical vessels appeared to be more vulnerable to injury-induced changes compared with larger, more resilient pial vessels.

Conclusions: A single concussion is sufficient to induce hyperacute BBB dysfunction and cerebrovascular alterations in juvenile mice, potentially preceding long-term developmental deficits. The observed sex differences underscore the importance of considering sex as a biological variable in pediatric TBI research.

Funding: This project was funded by NIH NINDS 1R01NS119605 to AO, JB.

## 10. Dual Roles of SARM1 in Axonal Degeneration and Immune Regulation in a Mouse Model of Multiple Sclerosis.

**Samarth Bhat**

University of California, Riverside

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS) characterized by inflammatory demyelination and axonal degeneration. Sterile alpha and Toll/interleukin receptor motif–containing protein 1 (SARM1) plays a central role in axonal degeneration and neuronal cell death. Although SARM1 inhibition has emerged as a promising neuroprotective strategy, SARM1 knockout (KO) mice do not display reduced axonal damage in all neurodegenerative disease models. An underexplored function of SARM1 as a negative regulator of immune activation and Toll-like receptor signaling raises the possibility that SARM1 deletion may exert opposing effects on neurodegeneration and inflammation. To test this hypothesis, we examined the impact of SARM1 deletion in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. In vivo axonal integrity was assessed using visual evoked potentials (VEPs), while axon health, demyelination, and immune responses were evaluated by immunohistochemistry (IHC) and cytokine analyses. SARM1KO mice exhibited comparable EAE clinical disease but mitigated axon degeneration compared to WT EAE mice. Similarly, VEP recordings revealed faster signal conduction through the optic pathway during SARM1KO EAE. Naïve SARM1KO splenocytes showed elevated pro-inflammatory cytokine and chemokine release relative to WT controls, although these differences were attenuated following EAE induction. In contrast, IHC demonstrated increased immune cell infiltration within the CNS of SARM1KO mice. Together, these findings indicate that while SARM1 promotes axonal degeneration, it also modulates immune responses in a context-dependent manner. These results support exploration of SARM1 as a therapeutic target in MS while underscoring the need to better define its immunoregulatory mechanisms.

**11. Spatiotemporal stimulus information is systematically encoded in V1 and is regulated by Parvalbumin and Somatostatin interneurons.**

**Sam Post, William Mol, Anubhuti Goel**

University of California, Riverside

Spatial features of visual encoding have been well studied, but little research has investigated the temporal features of visual encoding. To address this, we recorded Pyramidal, Somatostatin (SST) and Parvalbumin (PV) activity in L2/3 of V1 using 2p Ca2+ imaging as mice were passively exposed to sequences of time varying stimuli (pairs of 300 ms drifting sinusoidal gratings separated by 400, 800, or 1600 ms ISIs). The first stimulus in the pair was one of four randomized orientations (180o, 225o, 270o, 315o) while the second stimulus was always 180o. We hypothesized that activity elicited by the first stimulus would "leak" into that elicited by the second, thereby altering the population's trajectory as a function of time. We found that encoding of the second stimuli in the pairs, despite being identical, systematically varied as a function of both the duration between the first and second grating as well as the orientation of the leading stimulus. In effect, there was a transient memory trace in V1 which depended upon the preceding spatiotemporal information. This differential encoding results from different state space trajectories and is regulated by both PV and SST neurons, likely due to each's short term plasticity profiles. Our results provide a mechanism for how sequences of stimuli are encoded in a primary sensory area, such as in music or language, which may differ from that used in encoding discrete stimuli.

## 12. Pathway specific recruitment of dentate gyrus CCK interneurons is compromised after status epilepticus.

**Mahboubeh Ahmadi**

University of California, Riverside

The hippocampal dentate gyrus (DG) is a critical site for memory processing, integrating object and spatial information from lateral and medial entorhinal cortex (LEC/MEC) respectively. Granule cells (GCs), the principal excitatory output neurons of the DG, exhibit sparse activity largely due to robust feedforward and feedback inhibition mediated by interneurons. Among these, cholecystokinin-expressing interneurons (CCK INs) play a key role in shaping synaptic input and regulating memory encoding. In epilepsy loss of interneurons, results in heightened excitatory activity and aberrant circuit reorganization. However, the mechanisms by which epilepsy alters DG circuitry, particularly with regard to CCK INs, are not fully understood. This study investigates whether CCK IN recruitment and synaptic function are disrupted after status epilepticus (SE).
Adult CCK-Cre transgenic mice received repeated low-dose kainic acid injections every 20 minutes to achieve Racine stage 4–5 seizures followed by diazepam after 2 hours to model SE. Saline injected controls and post-SE CCK-Cre mice received AAV injections to selectively express eGFP in GABAergic CCK INs in the DG and ChR2 in the LEC or MEC projection neurons. Five weeks later, whole-cell recordings were obtained from eGFP expressing CCK INs in acute hippocampal slices. Optically evoked excitatory post synaptic currents (oeEPSCs) were elicited by stimulating ChR2-labeled LEC/MEC axons.
In control mice, MEC driven oeEPSC amplitudes were significantly higher than LEC evoked EPSCs (amplitude in pA, LPP: 0.11±0.04 in 15 cells, MPP: 0.29±0.07, in 14cells; p < 0.01, Mann–Whitney test). Notably, CCK INs exhibited pathway specific differences in short-term plasticity with responses to LEC input trains (10Hz) eliciting multi-pulse facilitation while responses to MEC input trains showed multi-pulse depression (p < 0.003, two-way ANOVA). Following SE, MEC-driven excitation of CCK INs was significantly reduced compared to controls (amplitude in pA, control: 0.29±0.07 in 14 cells, SE: 0.02±0.01, in 14cells; p < 0.001, Mann–Whitney test). Additionally, responses to MEC inputs trains (10 Hz) exhibited greater multi-pulse depression after SE compared to controls (p < 0.03, two-way ANOVA), suggesting presynaptic dysregulation of MEC inputs after SE.
These findings suggest that MEC input to CCK INs might be selectively impaired early after SE, potentially undermining feedback inhibition of the DG circuit and contributing to cognitive dysfunction. Due to their sensitivity to neuromodulators, CCK INs are promising therapeutic targets for restoring inhibition and improving cognitive function.

## 13. Phenotypic analysis of digging and nesting behavior in developing and adult Fmr1 KO mice.

**Navroop Kaur Sandhu**

University of California, Riverside

Fragile X Syndrome (FXS) is a leading known genetic cause of intellectual disability with symptoms that include increased anxiety and social and sensory processing deficits. Many behavioral studies have been performed in mouse models of FXS, but robust behavioral phenotypes reliably distinguishing WT vs. Fmr1 KO mice have been elusive. In the present study, we analyzed two simple behaviors (nest building and nest removal digging) in developing and adult WT and Fmr1 KO mice. We found that both P21 and P91 Fmr1 KO mice have altered nest building and nest removal digging behaviors compared to age-matched WT mice, possibly modeling increased anxiety following changes in environment. These behavioral phenotypes were observed in both male and female Fmr1 KO mice. Together, these findings define a robust set of behavioral phenotypes in young and adult mice that can serve as translational targets for genetic and pharmacological manipulation in phenotypic rescue studies.

## 14. Cumulative Effects of Alzheimer's Disease Risk Factors on Cerebrovascular Morphology.

**Hung Phan**

Department of Biomedical Sciences, University of California, Riverside

The focus of the MODEL-AD consortium is to develop Alzheimer's disease (AD) mouse models that mimic the sporadic human disease. The human amyloid β knock-in (hAβKI) mouse was developed as a base model onto which other risk alleles, such as humanized tau (hMAPT) and humanized APOE4 (hAPOE4) could be added. We aimed to test our hypothesis that layering of AD risk factors can lead to cerebrovascular changes.

To analyze vascular features in different novel mouse models across age and sex, we utilized our vessel painting technique on a) C57BL6/J (WT), b) hAβKI.hMAPT, and c) hAβKI.hMAPT.hAPOE4 mice. We undertook classical vascular analysis (vessel density, length, junctions…) axially in brains of both sexes at 4, 12, and 18 months of age.

At 4 months, we observed a trending increase for both sexes in vessel density and average vessel length in hAβKI.hMAPT mice relative to the WT. No significant differences were reported in hAβKI.hMAPT.hAPOE4 relative to WT at 4 months. At 12 months, no significant differences between genotypes nor sex were found. However, by 18 months there was a significant increase in vessel density and vessel length between WT and hAβKI.hMAPT mice that was even more pronounced in the hAβKI.hMAPT.hAPOE4 mice.

Our results in AD mouse models suggest that aging and addition of AD risk alleles impacts vascular features particularly late in life. In the late stages of life, we found a cumulative effect of AD risk factors, with more radical changes in hABKI.hMAPT.hAPOE4 compared to hAβKI.hMAPT.

## 15. ACE2 Administration Promotes Vascular Remodeling in Mouse Model of Traumatic Brain Injury.

**Alan Thai**

University of California, Riverside, Biomedical Sciences

Traumatic brain injury (TBI) is a public health concern, with 2.5 million people sustaining injury every year and over 70,000 fatalities annually. Individuals with TBI are at higher risk of Alzheimer's disease and report a decline in memory, attention, and problem solving. Currently, the leading treatments only manage symptomatic conditions without preventing neurodegeneration. Moreover, the vasculature is vulnerable to damage after TBI. The objective of this study was to assess if post-TBI ACE2 treatment could blunt vascular loss and promote vascular regrowth, vasodilation, and eventually cognitive function.

To test this theory, 2-month-old C57B16 adult male mice were subjected to a closed head (CHI). ACE2 reconstituted in sterile phosphate-buffered saline (PBS) treatment was immediately administered and continued for 4 continuous days. CHI vehicle mice were given PBS. At 5 days post injury, mice were perfused fluorescent stain.. Dil stained brains underwent cerebrovascular assessment of vascular networks, including classical vascular features (density, length etc) and the fractal analyses for vascular complexity.

In CHI ACE2-treated mice we observed enhanced vascular remodeling characterized by increased vessel density and improved network organization compared to vehicle-treated controls. Fractal analysis revealed a higher frequency peak and leptokurtic, indicating increased vascular abundance and uniformity. AngioTool analyses further supported these findings, demonstrating increases in vessel length in the ACE2 treatment group.

These results suggest ACE2 treatment following CHI may promote angiogenesis and restoration of cerebrovascular integrity. Targeting the RAS/MasR axis may represent a promising disease-modifying strategy to mitigate TBl-induced vascular dysfunction and reduce long-term secondary sequelae.

## 16. The Effect of Mitochondria Modifying Agents on Neuronal Dysfunction within the Cerebellum of Multiple Sclerosis Mouse Models.

**Nicole Sameer D'Souza**

Division of Biomedical Sciences, University of California, Riverside, School of Medicine

Multiple sclerosis (MS) is characterized by inflammation and demyelination within the central nervous system, with metabolically active Purkinje cells (PC) of the cerebellum frequently affected. Thus, mitochondrial dysfunction is thought to contribute to PC degeneration and disease progression in MS. We hypothesized that mitochondria-modifying agents could improve PC health and disease outcomes. Using the experimental autoimmune encephalomyelitis (EAE) mouse model, we evaluated the therapeutic potential of the chloroindazole-based ERβ-selective ligand, K102, and the mitochondria-modifying agent M1. We evaluated cerebellar mitochondrial function and the effects of M1 and K102 using nCounter, spatial transcriptomics, and immunohistochemistry (IHC). In nCounter data, genes associated with microglia and complement activation were significantly upregulated in the EAE + Vehicle group, with reduced expression following K102 treatment. In contrast, spatial data also revealed upregulation of genes associated with mitochondrial dysfunction and apoptosis in lesioned vs non-lesioned areas of the cerebellum, with K102 treatment bringing expression of these genes down in lesions. Utilizing IHC we found that EAE mice had increased white matter demyelination and leukocyte infiltration in the cerebellum compared to mice treated with K102. Calbindin staining in normal control groups demonstrated intact PCs, whereas EAE mice exhibited Purkinje cell loss. In EAE, treatment with K102 or M1 lead to greater recovery compared to vehicle-treated controls. Overall, this suggests that modification of mitochondrial function may be a new avenue of therapeutic intervention to explore for people with MS.

## 17. Cortico-Accumbal Endocannabinoid Signaling Modulates Cocaine-Seeking.

**Jeffrey Delgado,** Brandon Oliver, Alexandra Arcenas, Leslie Estrada, Natalie Zlebnik

University of California, Riverside

Global rates of cocaine use reached an all-time high in 2023, with approximately 25 million people worldwide using cocaine. Moreover, as global supply surges, the upward trend of cocaine use is expected to continue increasing. Cocaine and other drugs of abuse lead to profound molecular and physiological changes within the nucleus accumbens (NAc), a key node in the brain's reward circuitry. In the NAc, glutamatergic terminals from the prelimbic (PrL) region of the medial prefrontal cortex (mPFC) synapse onto medium spiny neurons (MSNs) which integrate cortical inputs with dopaminergic signals from the midbrain. Previous studies have implicated the potentiation of these glutamatergic PrL projections to the NAc in promoting cocaine-seeking and relapse. Endocannabinoids (eCBs) function as retrograde spatiotemporal "homeostatic regulators" within this cortico-accumbal circuit by decreasing the likelihood of neurotransmitter release onto neurons experiencing extensive levels of activity. Importantly, studies have linked dysfunction of eCB signaling within this reward circuitry to vulnerability to cocaine-seeking and relapse. Recent data from our lab has shown that augmenting synaptic levels of the eCB 2-AG in the NAc by inhibition if its degradation enzyme MAGL reduces cue-induced cocaine seeking in mice trained to self-administer cocaine. Our current pilot studies examine spatiotemporal eCB dynamics within cortico-accumbal circuitry by expressing the GRABeCB-2.0 biosensor on PrL terminals in the NAc and imaging in real-time via fiber photometry while mice undergo cue-induced cocaine relapse. We hypothesize that dysfunctional eCB signaling within this circuit allows for the potentiation of glutamatergic input to the NAc and is critical for the pathogenesis of addiction-related behaviors. Further, we propose that pharmacologically restoring functional eCB signaling will normalize glutamatergic signaling within the NAc, thereby reducing cocaine-seeking.

**18. ACE2 treatment improves neurovascular morphology and function after mTBI: Functional Ultrasound Imaging and Ultrasound Localization Microscopy.**

**Annie Le**

University of California, Riverside

Traumatic brain injury (TBI) elicits an impaired cerebral vasculature leading to compromised blood flow depriving the brain of needed oxygen and nutrients. Mild TBI (mTBI) leads to impaired neurovascular coupling and damaged angioarchitecture with days of injury. Angiotensin-converting enzyme II (ACE2)-modulating drugs have been used to alleviate vascular pathologies due to their vasodilatory and anti-inflammatory effects. The ability of ACE2 to blunt neurovascular perturbations after TBI is not well understood. The current study examined the impact of ACE2 treatment in a rodent model of mTBI. Adult male mice (2 mo) were exposed to a mild closed head injury (CHI) and received daily ACE2 administration for four consecutive days. On day five, all mice underwent high-resolution in-vivo functional ultrasound imaging (fUSI) and ultrasound localization microscopy (ULM). fUSI enables dynamic observation of cerebral blood flow and volumes, while ULM provides high-precision mapping of microvascular architecture. Whisker stimulation was performed to assess cerebrovascular function and to visualize cerebral blood volume changes as an indirect measure of neuronal activity. ACE2 treatment in CHI mice enhanced neurovascular coupling and increased vessel branch length compared to the vehicle treated CHI mice. ACE2 decreased vein density with no observable differences in artery density. Notably, ACE2 treatment in CHI mice led to divergent artery and vein velocities that were not observed in the vehicle treated mice. In summary, ACE2 treatment alleviated TBI-induced cerebrovascular deficits. This study provides promising evidence for ACE2 modulation to treat TBI and use of fUSI/ULM to monitor treatment effects.

**19. Characterizing the role of C3a-C3aR Signaling in Glioblastoma Multiforme.**

**Maria Joana Araujo,** Cameron Fraser

University of California, Irvine

Glioblastoma (GBM) is the most aggressive form of malignant brain tumor with a high annual incidence of 10,000 new cases per year and median survival of less than 24 months. Current standard of care includes surgical intervention, chemotherapy (temozolomide), and radiotherapy; however, these interventions give patients additional months of increased lifespan. We previously identified that C3a-C3aR1 signaling plays important roles in human neural stem cells (NSC) in proliferation and maintenance of stemness. We have found parallel roles for C3a-C3aR1 signaling in glioblastoma stem cells (GSC), a critical population that drives aggressive tumor growth and recurrence following resection of the primary tumor. To confirm this signaling, we report the presence of this signaling pathway in 7 patient derived glioblastoma cultures. Moreover, we demonstrate that in vivo blockade of C3a-C3aR1 by RNAi decreases glioblastoma tumor volume and improves host survival in an orthotopic xenograft model. These data provide a foundation of evidence supporting the further development of C3a-C3aR1 targeting therapeutics.

**20. C3a-C3aR Signaling in Glioblastoma Multiforme as a Therapeutic Target.**

**Cameron Fraser,** Maria Joana Araujo

University of California, Irvine

Glioblastoma (GBM) is the most aggressive form of malignant brain tumor with a high annual incidence of 10,000 new cases per year and median survival of less than 24 months. Current standard of care includes surgical intervention, chemotherapy (temozolomide), and radiotherapy; however, these interventions give patients additional months of increased lifespan. We previously identified that C3a-C3aR1 signaling plays important roles in human neural stem cells (NSC) in proliferation and maintenance of stemness. We have found parallel roles for C3a-C3aR1 signaling in glioblastoma stem cells (GSC), a critical population that drives aggressive tumor growth and recurrence following resection of the primary tumor. To confirm this signaling, we report the presence of this signaling pathway in 7 patient derived glioblastoma cultures. Moreover, we demonstrate that in vivo blockade of C3a-C3aR1 by RNAi decreases glioblastoma tumor volume and improves host survival in an orthotopic xenograft model. These data provide a foundation of evidence supporting the further development of C3a-C3aR1 targeting therapeutics.

## 21. Estrogen dependent T cell regulation during Toxoplasma infection.

**Jose L. Martin**, Pedro A. Villa, Zoe A. Figueroa, Djurdica Coss, Emma H. Wilson

University of California, Riverside

Toxoplasma gondii (T. gondii) is an obligate intracellular parasite with the capacity to invade any nucleated cell in a wide range of host species, including humans. During chronic infection, T. gondii transitions into a dormant state and establishes a lifelong infection. Effective control of the parasite depends on a robust Th1-type response mediated by interleukin-12 (IL-12) and interferon-gamma (IFNγ), which are essential for activating macrophages and limiting parasite replication. For over 20 years we have known that female mice are more susceptible to Toxoplasma infection in part due to a decrease or delay in IL-12 production. This sex bias highlights the complex crosstalk between the immune and endocrine systems. Understanding how hormones such as estrogen influence host immunity during T. gondii infection will help identify the mechanisms driving sex-specific differences in pathology.

Our preliminary data demonstrate that female mice exhibit greater mortality, parasite burden, and IFNγ-producing CD4+ cells compared to male mice during infection. To address if these effects are due to hormonal factors, we utilized an ovariectomy (OVX) model in to eliminate endogenous ovarian hormones and directly assess its role on the immune response and disease outcomes compared to sham and male groups. Unexpectedly, OVX females exhibit higher serum IFN-γ levels and reduced peripheral parasite burden compared to sham females, suggesting that estrogen suppresses Th1 cytokine production and peripheral immune activation. We hypothesize that estrogen signaling through estrogen receptor α (ERα) dampens the immune response, impairing parasite clearance and increasing disease susceptibility. Understanding these mechanisms will enhance our broader understanding of endocrine regulation of immunity in parasitic infections.

## 22. C1q drives neural stem cell quiescence by regulating cell cycle and metabolism through BAI1.

**Zeina Elrachid**, Pedro A. Villa, Zoe A. Figueroa, Djurdjica Coss, Emma H. Wilson

University of California, Irvine

C1q levels in the central nervous system increase following inflammation and neurovascular trauma, yet the consequences of C1q signaling on the neural stem cell (NSC) regenerative response remain poorly understood. Here, we report that C1q drives NSC quiescence, a reversible state of cell cycle arrest characterized by reduced proliferation and metabolic activity, and investigate the mechanisms underlying this effect. We recently identified novel C1q receptor candidates that enable direct receptor-mediated regulation of NSC behavior. Among these is Brain Angiogenesis Inhibitor 1 (BAI1), which has no previously described role in NSC biology. We establish a direct, BAI1-dependent role for C1q in regulating NSC quiescence. Exposure of NSCs to purified human C1q at physiological concentrations significantly reduces proliferation and induces metabolic remodeling consistent with a shift from oxidative phosphorylation to aerobic glycolysis. Using CRISPR/Cas9-mediated deletion of BAI1, we demonstrate that loss of BAI1 reverses C1q-induced decreases in proliferation and metabolic function. Mechanistically, BAI1 mediates C1q internalization and promotes intracellular interactions between C1q and the mitochondrial protein p32/gC1qR. Increased C1q-p32 interactions reduce the availability of functional p32, resulting in altered NSC metabolism. Protein interaction assays further validate C1q binding to BAI1 and p32 individually and in complex. Together, these findings identify BAI1 as a critical mediator of C1q-driven NSC quiescence and reveal a novel mechanism linking complement signaling to metabolic regulation of NSC function.

**23. IFNγ resistant bradyzoite replication.**

**Nala Kachour**, Ehsan Aryan, and Emma H. Wilson

University of California, Riverside

An estimated one third of the human population is chronically infected with Toxoplasma gondii. Chronic infection, manifested by bradyzoite cyst formation in the brain, is harmless in immunocompetent individuals, but can reactivate and cause lethal toxoplasmosis in patients with primary or acquired immunodeficiencies. No therapies have been developed to eliminate chronic infection, partly because the mechanisms underlying its maintenance are not completely understood. Using an ex vivo model of recrudescence, we recently demonstrated that bradyzoites can follow at least two differentiation pathways following cyst recrudescence. They can follow the canonical pathway to generate fast growing, cell-lytic tachyzoites ('brady-tachy') or they can divide as bradyzoites and form new cysts ('brady-brady'). The brady-brady pathway is enhanced in astrocytes compared to other cells including fibroblasts and intestinal epithelial cells. Although our ex vivo model has been integral in understanding the parasite's dependence on the host cell during recrudescence, it is limited by the absence of an immune response. Since cyst recrudesence takes place during immune competency, it is likely that the presence of the protective cytokine IFNγ influences the survival of differentiating parasites. Thus, astrocytes infected with newly excysted ME49EW bradyzoites were treated with IFNγ. Indeed, we observed an increase in the proportion of brady-brady replicating parasites and a decrease in the proportion of brady-tachy replicating parasites in stimulated astrocytes. This research expands on our previous work by demonstrating that the brady-brady pathway exists in the presence of the main effector cytokine in Toxoplasma infection. Further investigation of the basis of this pathway may provide implications for therapeutic development targeting the chronic stage.

**24. “There, there buddy”: Role of Odor in Prosocial Allogrooming in Mice - A Pilot Experiment.**

**Cori Zuvia**

University of California, Riverside

Affiliative social touch is a prosocial behavior believed to provide comfort to stressed partners. In paired mice, this manifests as allogrooming, where a helper licks and nibbles the fur of a stressed conspecific partner. Stress-related allogrooming first requires detection of stress in a partner often via olfactory cues. We investigated the extent to which urinary odors facilitate allogrooming via a urinary odor transfer pilot experiment. Pooled stress urine was collected from donor mice (n = 6) subjected to foot shocks (1 s, 0.5 A). Control urine was collected prior to stress induction. Samples were applied to the hind fur of non-stressed partners to analyze allogrooming duration in paired mice (n = 3 pairs). Allogrooming duration increased (p = 0.0867) under stress urine conditions. Notably, this behavior extended to non-hind specific sites, whereas control urine elicited only hind localized allogrooming. Finally, we investigated the activity of the Medial Amygdala (MeA) following stress urine allogrooming as this brain region receives input from the olfactory system and has been critical for allogrooming. While not statistically significant in this pilot sample (p = 0.2609), a strong positive correlation was observed between allogrooming duration and c-Fos+ cells in the MeA (r2 = 0.8412). Together, our preliminary evidence shows that urinary stress cues are sufficient to elicit prosocial allogrooming. This urinary odor transfer model provides a viable method for studying stress-related social behavior. Future studies will characterize the metabolic and proteomic profiles of these odors and explore the roles of the main and accessory olfactory systems.

**25. EphB2 receptor forward signaling regulates PV interneuron inhibitory synapse development in hippocampus.**

**Salma Reyes-Garcia**

University of California, Riverside

Disruption of excitatory–inhibitory balance contributes to hyperexcitable neuronal networks in neurodevelopmental disorders. Although the receptor tyrosine kinase EphB2 is a major regulator of excitatory synapse development, its role in inhibitory circuit function remains unclear. Parvalbumin interneurons provide powerful perisomatic inhibition onto CA1 pyramidal cells, and changes in their synaptic efficacy strongly influence hippocampal network excitability. We previously showed that deletion of EphB2 from parvalbumin cells increases presynaptic parvalbumin/vGAT sites and strengthens parvalbumin-to-pyramidal cell connectivity in CA1, suggesting that EphB2 negatively regulates inhibitory output. Here, we directly examined how EphB2 forward signaling controls inhibitory synaptic function and behavior using genetic gain- and loss-of-function approaches. EphB2 kinase activity was manipulated with point mutants F620D (kinase-hyperactive) and K661R (kinase-dead). Whole-cell patch-clamp recordings from CA1 pyramidal cells revealed that kinase-dead K661R mice exhibit enhanced inhibitory input, reflected by increased spontaneous inhibitory postsynaptic currents, whereas kinase-hyperactive F620D mice show reduced inhibitory drive. These functional changes were accompanied by corresponding structural alterations: K661R mice displayed increased parvalbumin/vGAT and vGAT/gephyrin colocalization, higher puncta density in the stratum pyramidale, and tighter presynaptic–postsynaptic alignment, while F620D mice showed reduced overlap and more dispersed inhibitory synapses. Importantly, these synaptic and electrophysiological effects translated to behavior. Loss of EphB2 signaling in parvalbumin cells conferred protection against pentylenetetrazole-induced seizures, indicating reduced network hyperexcitability in vivo. Together, our findings demonstrate that EphB2 kinase activity in parvalbumin interneurons negatively regulates inhibitory synaptic strength, hippocampal excitability, and seizure susceptibility, highlighting EphB2 as a key modulator of inhibitory circuit function and excitatory–inhibitory balance.

## 26. Effects Of Snap-5114 Injection On Gaba Expression In FXS Mouse Model.

**Jordan Wimberly,** Victoria Wagner and Iryna Ethell

Division of Biomedical Sciences, University of California, Riverside

Fragile X Syndrome (FXS) is a genetic disorder caused by a loss of function of the FMR1 gene, leading to similar symptoms as autism, including sensory hypersensitivity and cortical hyperexcitability. Recent observations in humans and Fmr1 knockout (KO) animal models of FXS suggest symptoms are mediated by abnormal GABAergic signaling. As most studies have focused on neuronal mechanisms, the role of astrocytes in mediating defective inhibition in FXS is largely unknown. We found that KO mouse astrocytes have increased GABA and GABA synthesizing enzyme GAD 65/67. Astrocytes can transport GABA, affecting extracellular GABA levels, contributing to tonic inhibition. We hypothesized that KO astrocytes were releasing excess GABA and that would result in less active parvalbumin-positive (PV) inhibitory neurons. Using an astrocyte-specific Fmr1 knockout (cKO), we pharmacologically blocked astrocyte-specific GABA transporter GAT3 using SNAP-5114 or vehicle-treated mice prior to perfusion, and immunostained auditory cortex and frontal cortex for either GABA and astrocyte marker GS or PV and cFos, an indicator of recently active cells. There was a statistically significant increase in GABA levels for cKO SNAP treated mice in the auditory cortex and a statistically significant increase in GABA for both cKO SNAP and vehicle treated mice in the frontal cortex. This work can provide insight into astrocytic regulation of GABAergic signaling as a potential therapeutic approach for hypersensitivity in FXS.

## 27. Regulation of microglial inflammation.

**Vaidehi Gandhi**

University of California, Irvine

Microglia are the resident immune cells of the central nervous system (CNS) that adopt heterogeneous states to maintain homeostasis.1 However, in CNS injury, they adopt a sustained, proinflammatory state that inhibits regeneration.1 Understanding mechanisms that drive maladaptive activation is critical to developing neuroprotective therapies. C1q is a key activator of proinflammatory microglia1,2 that drives transcriptional and functional changes.2 While traditionally secreted, C1q also acts intracellularly in neurons3 and T cells.4 Similarly, transforming growth factor-ß signals intracellularly in an autocrine manner to epigenetically5 promote quiescence.6 Neutralizing C1q significantly reduces iMicroglial inflammatory gene expression upon LPS exposure, In prep suggesting that C1q is necessary to respond to inflammatory stimuli. Microglia are the primary producers of C1q in the CNS and upregulate C1q expression in response to stimuli, including paracrine C1q;1 this suggests that microglial C1q may regulate activation state through an autocrine mechanism.7 However, current C1q-neutralization approaches cannot distinguish between paracrine and autocrine effects.. To address this gap, I generated C1q KO iPSC lines using CRISPR RNP technology and differentiated them into iMicroglia. Here, I present a finding that autocrine C1q directly modulates microglial behavior, transforming our understanding of neuroinflammation.

## 28. Systemic Inflammation Induces a Sex-Specific Neural Failure of the Hypoxic Ventilatory Response.

**Alberto Munoz**

University of California, Riverside

Systemic inflammation is a key driver of respiratory failure in clinical conditions such as sepsis, yet the specific neural mechanisms underlying respiratory decompensation remain poorly understood. While metabolic suppression (hypothermia) often confounds respiratory studies in rodent models, we aimed to determine if inflammation directly impairs the central neural control of breathing independent of metabolic state. Adult male and female C57BL/6J mice were injected with Lipopolysaccharide (LPS, 1 mg/kg) or saline. Twenty-four hours post-injection, ventilatory responses to acute Hypoxia (10% O2) and Hypercapnia (5% CO2) were measured using whole-body plethysmography. LPS induced significant weight loss in both sexes, confirming systemic inflammation, but did not induce hypothermia at the time of testing, ruling out metabolic depression. Male LPS mice exhibited a significant failure of the Hypoxic Ventilatory Response (HVR), characterized by a ~40% reduction in minute ventilation driven specifically by an inability to accelerate respiratory frequency. In contrast, female LPS mice maintained a robust HVR via the preservation of tidal volume recruitment.. Crucially, the Hypercapnic Ventilatory Response (HCVR) was preserved in both sexes, indicating that respiratory motor neurons and muscles remained functional. These findings demonstrate that systemic inflammation causes a pathway-specific, sex-specific failure of the peripheral chemoreflex loop, likely targeting the integration of hypoxic signals within the brainstem rhythm-generating networks.

## 29. Role of LC modulation of DG in the regulation of dentate excitability and seizure susceptibility.

**Alekhya Chippada**

University of California, Riverside

The dentate gyrus (DG) is the first relay station in the hippocampus, receiving inputs from the cortex and relaying them to the other hippocampal subfields. Inhibitory neurons in the DG maintain low network excitability and limit the propagation of hyperexcitable signals or seizures. In addition to the local circuit, external circuits can influence DG activity levels through long-range projections. One such projection is from the locus coeruleus (LC), a region responsive to stress that releases noradrenaline in response to acute stress. Stress is a known trigger for seizure onset in both clinical and animal studies.

In the present study, combining acute restraint stress induction, immunohistochemistry (IHC) staining, and kainic-acid-induced seizure, we investigated the effect of acute restraint stress induction on the neuronal excitability of the DG

and LC areas and the potential effects on the seizure threshold. Our data revealed elevated cFos expression in the LC, indicating increased neuronal activity. Furthermore, the hippocampal DG area was co-activated by the stress treatments. Finally, stress induction shortened the latency to kainic-acid-induced seizure onsets. Taken together, our data reveal co-activation of the LC and DG in response to stressors, suggesting a neuromodulatory regulation of DG excitability by LC inputs, which promotes seizure onset.

**30. Impact of host glucose availability on Toxoplasma gondii bradyzoite growth following cyst recrudescence in murine astrocytes.**

**Arzu Ulu,** Arianne Leon, Nandini Mannem, Jose L. Martin, Sharon Morales, Kristina V. Bergersen, Michael W. White, Emma H. Wilson.

Division of Biomedical Sciences, University of California, Riverside

Toxoplasma gondii is a foodborne intracellular parasite that infects approximately one-third of the globe and establishes lifelong brain cysts that can reactivate in immunocompromised hosts. Using an ex vivo culture system to study events post-cyst recrudescence, we identified two developmental pathways: the canonical bradyzoite-to-tachyzoite transition and a previously unrecognized bradyzoite-to-bradyzoite (brady-brady) replication pathway. Notably, brady-brady replication occurs in primary astrocytes but not fibroblasts, highlighting a host cell–specific developmental program in brain-resident cells that store glucose as glycogen. To explore this host-cell dependence and the requirements for brady-brady replication we tested the role of host-cell glucose availability following recrudescence in primary astrocytes. We found that low glucose levels promote bradyzoite-to-tachyzoite replication, while high glucose supports bradyzoite replication as revealed by the upregulation of the bradyzoite marker, SRS9. Manipulation of glucose storage within the host cell using insulin or adrenaline demonstrated that high glucose storage expands SRS9+ brady-brady replicating vacuoles ($P = 0.02$ main effect with one-way ANOVA, $P = 0.03$ for PBS vs. Insulin), while adrenaline decreases their proportion ($P = 0.4$ for PBS vs. Adrenaline). Using our previously published scRNAseq data, we also show increased glucose transport and glycolytic activity in a subset of bradyzoites. These metabolic adaptations support the view that host cell glucose storage capacity plays a critical role in Toxoplasma cyst development and maintenance. Subsequently, this dependence likely contributes to persistent infection and increased disease risk. Overall, our findings highlight host nutrient availability as a potential therapeutic target to disrupt the Toxoplasma life cycle and limit recrudescence.

**31. Vagal deafferentation provides benefits in hippocampal cognitive function but not activity-driven fatigue characteristic of Gulf War Illness.**

**Elena Kozlova, Swartz**, D, Krishnapillai, Y., Elhajjaoui, Y., Alam, S., Lam, A., Luna, C., and Margarita Curras-Collazo

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Gulf War Illness (GWI) is a chronic condition marked by unexplained neurological and gastrointestinal symptoms affecting Gulf War Veterans. They experience cognitive deficits, chronic fatigue, neuroinflammation in combination with gut dysbiosis. It is, therefore, suspected that altered gut-brain signaling plays a prominent role in GWI. Cholecystokinin (CCK) A receptor-containing vagal afferent neurons (VANs) are emerging as important mediators of the gut-brain axis, making them potential targets for understanding GWI pathophysiology. Having validated deafferentation of inflammatory signaling via gut afferents using the CCK-SAP method, we subjected 70 mice to bilateral nodose ganglia (NG) injection with either CCK-SAP or sham treatment (BLANK-SAP). Vagal deafferentation in CCK-SAP mice was verified as reduced number of Cckar-expressing VANs in NG vs Blank-SAP treated mice using RNA in situ hybridization. Each group received either GW agents (GW) or vehicle plus stress (CON/S). Mice were tested on cognitive and exercise behavior tests at approximately post treatment (PT) day 60, 90, and 190. Deficits caused by GW agents on a novel object recognition (NOR) memory test, on which normal VEH/CON mice show enhanced exploration of novel objects (p<0.05-0.01), could be completely mitigated in treated GW mice (p<0.05-0.01). Habituation during a 1 hr exploration of an open field arena, observed in VEH/CON (p<0.05-0.01) but not GW mice, was not improved in GW+CCK-SAP mice. On a passive avoidance test vagal deafferentation appeared to improve associative learning since the average group latency to enter the dark aversive chamber was apparently greater in GW+CCK-SAP vs GW-SAP group (p<0.1). On a passive wheel running test GW agents reduced overall daily activity indicating reluctance to engage in locomotor activity; vagal deafferentation provided slight normalization. The phenotypic differences in GW mice were supported by enhanced astrogliosis measured in hippocampal CA1 subfield vs CON/S. In contrast, latency to exhaustion on an exercise endurance test revealed an apparent reduction (tire faster) in both GW-SAP and GW-CCK-SAP groups as compared to CON/S. Using Echo MRI at PT193 GW mice displayed reduced fat mass (p=0.06) compared to CON/S, and this was further reduced in GW+CCK-SAP mice (p<0.001), suggesting an altered metabolic profile produced by combined GW agent exposure and vagal deafferentation. Together, these results provide novel mechanistic information on the role of gut-brain axis in GWI pathophysiology and of potential therapeutic benefit provided by vagal deafferentation. Funding: DoD grant GW-180072 to M.C.C.

**32. In vivo cilium proteomics reveals new regulators of cortical development.**

**Eva Cai**

University of California, Riverside

In the developing brain, the primary cilia of radial glial cells extend from the surface of the lateral ventricle, serving as the signaling hub to integrate environmental cues critical for brain formation. Dysfunctions in ciliary proteins contribute to a wide range of brain structural abnormalities in ciliopathies, yet identifying the bona fide ciliary protein components in the brain remains a significant challenge. Here, using proximity labeling and quantitative proteomics, we systematically charted proteins localized to the cilia of radial glial cells in the dorsal and ventral regions of the embryonic brain. From this dataset, we identified cohorts of new molecules intrinsic to the cilia at distinct regions of the developing brain. We validated the cilium localization of several components of the translation machinery and studied the mechanistic roles of ciliary candidates previously linked to brain malformation, including Marcks, a key regulator of radial glial polarity, and Ckap2l, a protein associated with Filippi syndrome. These results revealed previously unrecognized ciliary mechanisms that regulate brain development. Thus, our brain proteomic dataset provides a unique resource for understanding ciliary functions in brain development and the molecular etiology of developmental disorders.

## 33. An Experimental Pipeline to Evaluate How Epileptic Circuit Changes Impact Interneuron Activity During Seizures.

**Francisco Javier Guevara Pantoja**

University of California, Riverside

Temporal Lobe Epilepsy (TLE) is a common seizure disorder affecting roughly fifty million people globally. A key area involved in epilepsy is the dentate gyrus (DG), part of the hippocampal circuit that plays a role in memory, learning, and detecting novelty. The DG's activity is tightly regulated by various GABAergic interneurons (INs) with different patterns of activity and projection targets, such as soma-targeting parvalbumin- (PV+) INs and dendrite-targeting somatostatin- (SST+) INs. TLE often involves significant reorganization of limbic circuits in both humans and animal models. However, it remains unclear whether decreases in inhibition from specific IN subtypes occur before seizures in chronic epilepsy or if activation of particular IN populations contributes to stopping seizures. To explore this, we developed an experimental and analysis pipeline that records electrographic seizures alongside cell-type specific interneuron activity. This approach allowed us to examine PV+ and SST+ interneuron activity during seizure onset and termination in both naive and epileptic mice. Our findings show that both PV+ and SST+ neurons exhibit increased calcium transients indicative of activity during seizures in these mice. Notably, PV+ interneurons tend to activate earlier in epileptic animals, but their activity during seizures is reduced in these mice. Conversely, SST+ interneuron activity unexpectedly increased during seizures in epileptic mice. These observations challenge the idea that a failure of inhibition triggers seizure initiation. Instead, they suggest that post-status epilepticus, there is subtype-specific plasticity: PV+ interneuron activity diminishes, while SST+ activity rises, highlighting complex interneuronal dynamics in epilepsy.

## 34. Role of LC modulation of DG in the regulation of dentate excitability and seizure susceptibility.

**George Yeh, Alekhya Chippada**

University of California, Riverside

The dentate gyrus (DG) is the first relay station in the hippocampus, receiving inputs from the cortex and relaying them to the other hippocampal subfields. Inhibitory neurons in the DG maintain low network excitability and limit the propagation of hyperexcitable signals or seizures. In addition to the local circuit, external circuits can influence DG activity levels through long-range projections. One such projection is from the locus coeruleus (LC), a region responsive to stress that releases noradrenaline in response to acute stress. Stress is a known trigger for seizure onset in both clinical and animal studies.

In the present study, combining acute restraint stress induction, immunohistochemistry (IHC) staining, and kainic-acid-induced seizure, we investigated the effect of stress on the neuronal excitability in the DG and LC areas and on the seizure threshold. Our data revealed elevated cFos expression in the LC, indicating increased neuronal activity. Furthermore, the hippocampal DG area was co-activated by acute stress. Finally, stress induction shortened the latency to the onset of kainic-acid-induced seizures. Taken together, our data reveal co-activation of the LC and DG in response to stressors, suggesting a neuromodulatory regulation of DG excitability by LC inputs, which promotes seizure onset.

**35. Effects of Aerobic Exercise on Nicotine Relapse in Mice.**

**Marian Abawi, Jasmin Gill,** Brandon L. Oliver, Andrew P. Villa, Leslie S. Estrada, Natalie E. Zlebnik

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Nicotine addiction remains a major public health concern, with persistently high relapse rates due to the lack of effective treatments. Understanding the neurobiological mechanisms underlying addiction and relapse is crucial for developing successful interventions. Nicotine recruits dopamine release within the brain's reward circuitry, causing the development of addiction as well as promoting relapse. Aerobic exercise potently modulates dopaminergic signaling within this circuitry and may serve as an effective intervention. This study investigates the therapeutic effects of aerobic exercise on dopaminergic mechanisms underlying nicotine relapse in mice.

To carry out this study, male and female adult C57BL/6J mice (50:50 ratio) were implanted with jugular vein catheters for intravenous nicotine self-administration and chronic brain probes to measure dopamine release in the nucleus accumbens. Mice were trained to nosepoke for intravenous infusions of nicotine via a jugular vein catheter for 14 days. Then the mice undergo a 21-day withdrawal or incubation period without access to self-administer nicotine. During abstinence, mice were provided with a homecage running wheel that was either locked (control) or unlocked. Subsequently, nicotine craving or "seeking" behavior was assessed to determine if prior exercise decreases vulnerability to relapse. Throughout nicotine self-administration and craving tests, phasic dopamine release is measured within the brain's reward pathway.

Preliminary findings indicate that mice with access to an unlocked running wheel exhibited lower signs of nicotine-seeking behavior compared to those given a locked wheel. The mice have also displayed reduced dopaminergic activity associated with nicotine craving. This suggests that aerobic exercise lowers the craving for nicotine during late withdrawal, potentially through modulation of dopaminergic signaling. These findings could pave the way for future research exploring the dopaminergic mechanisms of exercise in greater depth, supporting the development of non-pharmacological interventions aimed at reducing relapse.

**36. Crk adaptor proteins regulate cortical lamination.**

**Payton A. Rao**

University of California, Riverside

Proper neuronal migration during cortical lamination is essential for functional circuit development. Disruptions in this process lead to a host of neurodevelopmental disorders hallmarked by an array of functional deficits. Cortical migration requires Reelin, an extracellular signal that binds to its receptors in migrating neurons. The chicken tumor virus #10 regulator of kinase, or Crk, family of adaptor proteins (Crk and CrkL) are well-positioned to bridge Reelin signaling to actin and adhesion dynamics via interactions with components of the Reelin pathway as well as integrin adhesion complex (IAC) components and cytoskeletal regulators. Here, we investigated the role of Crk and CrkL in cortical lamination using conditional gene knockout strategies in mouse cortex. We established a Crk and CrkL double conditional knockout (dcKO) model and assessed effects on neuronal positioning using layer-specific markers at postnatal day 7 (P7). Loss of both Crk and CrkL led to severe cortical layering defects phenocopying Reelin mutants, with cortical layers appearing inverted compared to control animals. These results demonstrate that Crk and CrkL are required for proper cortical lamination and may act downstream of Reelin to coordinate neuronal positioning during cortical development. Future work will focus on molecular epistasis analysis to determine whether Crk and CrkL indeed act downstream of Reelin and testing the functional role of Crk proteins in cell adhesion and migration.

**37. Modulation of inhibitory tone by Fmr1 KO astrocytes in the mouse hippocampus.**

**Ritika Thapa**

University of California, Riverside

Fragile X syndrome (FXS) is a leading genetic cause of autism-like symptoms and intellectual disability, resulting from epigenetic silencing of the Fragile X messenger ribonucleoprotein (Fmr1) gene. Recent observations in FXS models suggest abnormal GABAergic signaling and excitation/inhibition imbalance may underlie FXS pathophysiology. The role of astrocytes in mediating defective inhibition in FXS is largely unknown. Our previous study showed effects of astrocyte-specific Fmr1 conditional KO (cKO) on cortical inhibitory circuit development using EEGs that was attributed to excess GABA synthesis by Fmr1 KO astrocytes. As the hippocampus plays an important role in spatial learning and social behaviors that are altered in FXS, in this study we focused on dissecting the mechanism of abnormal inhibition in the CA1 hippocampus using slice electrophysiology. While we observed a reduction in the expression of synaptic GABAA receptor subunits and overall density of GABAergic synapses in cKO, amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs) was enhanced. In contrast to changes in phasic inhibition, cKO did not affect tonic inhibition in pyramidal cells or expression of extrasynaptic GABAA receptors, unlike in global KO. Our study suggests that elevated levels of extracellular GABA due to abnormal transport may contribute to the enhanced power of sIPSCs and potentially affect parvalbumin (PV) cell activity. Acute inhibition of GABA transport enhanced PV expression and improved spatial memory but not impaired socialization in cKO mice. Our work supports astrocytes as key players in the development and regulation of hippocampal inhibitory circuits in FXS potentially through GABA transport.

**38. Modulation of neuroinflammation by methamphetamine – implications for HIV-associated brain injury.**

**Sakina Tayabally**

University of California, Riverside

Methamphetamine (METH) is a potent addictive substance with high abuse rates, particularly among people living with HIV (PLWH) on combination antiretroviral therapy (cART). The interaction between HIV and METH exacerbates HIV-associated neurocognitive impairment (NCI) and neuronal damage, potentially through inflammatory processes. Peripheral HIV-infected monocytes/macrophages infiltrate the brain, releasing neurotoxins and pro-inflammatory factors, while the virus also infects microglia. This study investigated the in vitro effects of METH on monocytic THP-1 cells, the human microglial cell line HMC3, and induced pluripotent stem cell-derived microglia. Stimulation with the HIV LTR-mimic ssRNA40 or HIV-1 infection revealed that METH elevated inflammatory enzymes such as MPO and MMP-9 while increasing infection levels. Concurrently, METH reduced the antiviral cytokine IFNβ, downregulated IFN-γ, and decreased CXCL10/IP-10 protein expression, impairing immune activation and antiviral responses. These findings suggest that METH diminishes neuroprotective and antiviral immune responses while promoting pro-inflammatory pathways, potentially accelerating HIV-associated neuropathology.

## 39. ERβ Activation and SARM1 Inhibition as a Dual-Target Therapy for MS.

**Sarah Sharif,** Denzel Cardenas, Stephanie Peterson, Micah Feri, Alexandria Huang, Samantha Edelstein, Sung Hoon Kim, John Katzenellenbogen, Seema Tiwari-Woodruff

University of California, Riverside

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by inflammatory demyelination and progressive neurodegeneration within the central nervous system (CNS). Damage to CNS axons and myelin results in visual dysfunction, motor impairment, and cognitive deficits. Current MS therapies primarily target immune suppression to reduce inflammation but fail to reverse established CNS injury or prevent ongoing axonal degeneration. Therefore, therapies that simultaneously modulate immune responses, promote remyelination, and protect axons are urgently needed. We have previously demonstrated that estrogen receptor beta (ERβ) ligand treatment induces immunomodulation and enhances remyelination in preclinical models of MS. In parallel, sterile alpha and Toll/interleukin-1 receptor motif–containing protein 1 (SARM1) has been identified as a critical mediator of programmed axon degeneration following injury and disease. Our recent work showed a significant reduction in axonal damage in adeno-associated virus–mediated SARM1 antisense–treated retinas during experimental autoimmune encephalomyelitis (EAE)–induced optic neuritis, as well as robust axonal protection with pharmacological SARM1 inhibitors. To improve therapeutic efficacy, we developed a novel dual-target compound (DC) designed to activate ERβ to modulate immune-mediated demyelination while simultaneously inhibiting SARM1 to prevent axonal degeneration. Candidate DCs were first screened using primary oligodendrocyte and neuronal cultures, followed by in vivo evaluation in the EAE mouse model of MS. Treatment with DC at two doses, as well as combined ERβ ligand K102 and SARM1 inhibitor NB-3 administered at peak disease, significantly reduced clinical scores and proinflammatory cytokine expression and improved visual evoked potential amplitudes compared to vehicle-treated EAE mice. Immunohistochemical analyses revealed increased oligodendrocyte numbers, enhanced axonal myelination, and improved neuronal survival. DC efficacy was dose dependent, warranting further Investigation.

**40. Paternal exposure to microplastics alters sperm small non-coding RNA landscape and elicits offspring metabolic dysfunctions in mice.**

**Seung Hyun Park,** Jianfei Pan, Xudong Zhang, Ting-An Lin, Qi Chen, Tong Zhou, and Changcheng Zhou

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Background and Purpose: Microplastics (MPs) are small plastic particles emerging as significant environmental pollutants and humans are ubiquitously exposed to MPs. Recent studies have associated MP exposure with the increased risk of chronic diseases in humans. MPs can also be detected in both male and female reproductive tissues in humans. However, the impact of parental MP exposure on offspring health is unknow. This study aimed to investigate the impact of paternal exposure to MPs on the metabolic health of F1 offspring in mice.
Methods: In this study, eight-week-old male C57BL/6J wild-type (WT) mice were exposed with 10 mg/kg body weight of MPs or vehicle control by daily oral gavage for 4 weeks before mating with unexposed female mice to generate F1 offspring. Total RNAs were isolated from sperm of F0 sires and subjected to PANDORA-seq analysis. F1 offspring from MP- or control-exposed F0 sires were fed a high-fat diet before euthanasia at 12 weeks of age.
Results: We found that paternal MPs exposure had sex-specific effects on diet-induced obesity in F1 offspring. Female F1 offspring from MP-exposed sires had decreased lean mass and exacerbated insulin resistance. PANDORA-seq revealed that MP exposure altered sperm tRNA-derived small RNA (tsRNA) and rRNA-derived small RNAs (rsRNA) profiles. Furthermore, microplastic-stimulated sperm tsRNAs/rsRNAs can induce early transcription changes in mouse embryonic stem cells, potentially contributing to paternal MP exposure-elicited metabolic disorders in offspring.
Conclusions: Our results suggest that MPs exposure may have intergenerational adverse impact on offspring metabolic health. also underscore the urgency of better understanding the health consequences of plastic exposure in humans.

## 41. Impact of aerobic exercise on the dopaminergic mechanisms of cocaine relapse.

**Sharlyn Donoza, Samantha Thayer-Pham**

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Cocaine induces the release of dopamine in brain reward pathways, facilitating the development of addiction and enhancing vulnerability to relapse after prolonged periods of abstinence. Aerobic exercise has been shown to significantly influence dopamine regulation within these pathways, suggesting its potential as an efficacious therapeutic strategy. This study examines the dopaminergic mechanisms and therapeutic potential of aerobic exercise in mitigating cocaine relapse in mice. To do this, male and female mice are outfitted with chronic brain probes to monitor mesolimbic dopamine release and trained to self-administer intravenous cocaine infusions. The mice are given either a locked or unlocked homecage running wheel during a 21-day withdrawal period that follows a 10-day cocaine administration regimen. Following the intervention, mice undergo rigorous behavioral assessments to evaluate their cocaine "seeking" tendencies, providing critical insights into their likelihood of relapse. Dopamine release dynamics in the reward pathway are continuously monitored during both the cocaine self-administration and the seeking tests to elucidate the impact of aerobic exercise on dopamine release patterns that underlie cocaine craving. Preliminary results indicate that mice with access to an unlocked running wheel showed less interest in seeking cocaine compared to their counterparts with a locked wheel. The results indicate that aerobic exercise may reduce cravings for cocaine during the later stages of withdrawal, highlighting the need for further research into dopaminergic mechanisms of non-drug behavioral treatments aimed at lowering relapse rates.

**42. Microplastic exposure exacerbates atherosclerosis development in lean LDL receptor-deficient mice.**

**Ting-An Lin**

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Microplastics (MPs) have emerged as ubiquitous environmental pollutants that can be detected in human atherosclerotic plaques and are associated with an increased risk of cardiovascular disease (CVD) and stroke. However, the impact of MP exposure on the cardiovascular system remains elusive. This study aimed to investigate the effects of MP exposure on atherosclerosis development in low-density lipoprotein receptor–deficient (LDLR-/-) mice. Four-week-old male and female LDLR-/- mice were fed a semisynthetic low-fat diet and exposed to 10 mg/kg body weight MPs via daily oral gavage for 9 weeks. Atherosclerotic lesions in the aortic root and brachiocephalic artery were analyzed, and single-cell RNA sequencing (scRNA-seq) of the whole aorta was performed to characterize MP-induced changes in vascular cell populations and transcriptional programs. Our results show that MP exposure did not affect adiposity or circulating lipid profiles in lean male or female LDLR-/- mice. Intriguingly, MP exposure significantly increased atherosclerosis in male but not female LDLR-/- mice. scRNA-seq analysis revealed that MP exposure altered the proportions and functional states of key atherogenesis-related cell types, particularly endothelial cells (ECs). Consistently, MP exposure induced pro-atherogenic gene expression in murine and human ECs in vitro. Together, these findings demonstrate sex-specific pro-atherogenic effects of MPs in a relevant animal model and reveal a direct impact of MP exposure on endothelial atherogenic gene expression. These results provide mechanistic insight into the association between MP exposure and increased CVD risk in humans.

## 43. Distinct Cue and Reward Encoding by D1- and D2-Expressing Medium Spiny Neurons in the Nucleus Accumbens.

**Jia Lee, Vikasini Kuppa,** Jeffrey Delgado, Brandon L. Oliver, Natalie E. Zlebnik

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The nucleus accumbens (NAc), a major target of dopamine in the mesolimbic reward pathway, is a critical interface for decision making, as it integrates reward-predictive cues with action execution. Within the NAc, medium spiny neurons (MSNs) are classified into two populations defined by dopamine receptor expression: D1R- and D2R-expressing MSNs. These populations receive overlapping glutamatergic and dopaminergic inputs but differ in neuromodulatory sensitivity. D1Rs are excitatory and D2R are inhibitory g-coupled protein receptors, ultimately creating opposing downstream effects, respectively, in the mesolimbic pathway. Therefore, these populations may support distinct contributions to reward-motivated behavior. However, how D1- and D2-MSNs in the NAc encode reward-predictive cues and rewards during learning remains unclear. Rather than encoding reward-related events in an opposing manner, recent work suggests that D2-MSNs respond to reward-related cues scale with learning, while D1-MSN activity remains unchanged across learning. To address this, we evaluated population activity of D1- and D2-MSNs in the NAc during a variable time-out operant task. During this task, a cue light signals the forthcoming onset of lever availability; the subject must then press the lever to receive a sucrose reward, followed by a variable inter-trial interval. Using cre-dependent GCaMP in D1-Cre and A2A-Cre (D2R proxy) mice paired with fiber photometry, cell type-specific calcium activity was aligned to cue and reward-related events. Our pilot study will offer insight into how NAc D1- and D2-MSNs differentially encode cue and reward events across learning, including whether population level calcium dynamics are stable or if they evolve with task proficiency.

## 44. Circuit Mechanisms of Dynamic Sensory Encoding and Sensory Plasticity Across Learning in Primary Visual Cortex.

**William Mol**

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In our environment, we are constantly presented with sensory information that predicts coincident or future outcomes and, as such, has a bearing on our behaviors. Adapting to novel stimuli, constructing new associative relationships, and contextually processing familiar stimuli require feature-specific selectivity and the construction of an internally generated model. Growing evidence has shown primary visual cortex (V1) to be adaptable and plastic, changing the nature of its population response and its representation of stimuli with both repeated exposure and across learning. Models like predictive processing posit a statistical updating of sensory responses, both as a consequence of past experience and of stimulus contingency. A key underlying principle of predictive processing, efficient coding, and the phenomena of V1 dynamically shifting pair well, positioning the earliest point in the cortical visual stream as a primary substrate for learned sensory contingencies. V1, in addition to bottom-up sensory information, receives rich input from top-down modulatory areas like the anterior cingulate cortex (ACC). This ACC -> V1 input has been shown to carry information about stimulus-specific valence and putative prediction errors, as well as being shown necessary for rule updating and attenuation to distractors in specific tasks. In this work, we use 2-photon calcium imaging of layer 2/3 of V1, targeting pyramidal cells and somatostatin-expressing interneurons (SST), and axon terminals of ACC in superficial layers of V1 throughout task learning. Our novel head-fixed task is a go/no-go sensory discrimination paradigm consisting of stimuli constructed by sequences of four different angles of sinusoidal drifting orientations. The first and last of these elements are relevant for sensory discrimination, and are reversed between rewarded and unrewarded sequences, and the middle two are of a constant identity and carry no information about stimulus valence. Examining responses to these sequences—and their individual elements—reveals cell-type specific shifts, contributing to overall gradual changes in population dynamics as learning progresses, as well as changes in interleaved task-disengaged passive exposure sessions.

## 45. Activated vs Non-activated Monocytes Effects on Neuronal Network Function in Different Stages of Multiple Sclerosis.

**Mahsa Khayat-Khoei**

University of California, Riverside

Background & Objectives: Multiple Sclerosis (MS) disease progression and smoldering MS pathology focus on neuro-axonal injury driven by chronic inflammation. The innate immune system, specifically peripheral monocytes, may contribute to this process. We aim to understand if human peripheral monocytes develop different functional properties and act differently once activated during different stages of the MS disease.
Methods: Healthy human induced pluripotent stem cell (iPSC)-derived neurogenin-2 (NGN2) neurons and primary healthy human astrocytes were cultured on microelectrode array (MEA) systems (16-electrode MEAs, 48-well plates). Human monocytes from relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and healthy controls (n=4 per group) were isolated and either were directly co-cultured with neuronal cultures on MEA or were activated using Human Recombinant Macrophage Colony-Stimulating Factor (MCSF) for six days and then added to the neuronal culture. We also had a control group of activated/non-activated monocytes media added to the culture. Recordings of cultures were initiated every 3 days and switched to every 6 hours for 72 hours on day 25, after starting the interventions. The neuronal activity was analyzed using our unique analysis pipeline.
Results: The NGN2 neurons (n=35,000 NGN2 cells/well) and primary astrocytes (n=10,000 cells/well) were maintained on MEA. We assessed the reliability of our in vitro platform by monitoring the cultures activity. With the growth of the culture, the number of active electrodes significantly increased (p=3e-7), with an increase in the mean firing rate (p=7e-6), and mean network burst rate (p=0.01) from days-in-vitro (DIV) 14 to 25. We detected random neuronal activity as early as DIV 2 which started bursting after DIV 19. The addition of non-activated monocytes or their media was not toxic to the cultures. Similar pattern was seen with activated monocytes media. There were no significant differences in cortical activity when MS or healthy non-activated monocytes (n=150,000 cells/well in 48well plates) were added to the cultures. In our preliminary study, we detected a suppression of neuronal connectivity by 60% when SPMS derived activated monocytes were added to the culture compared to RRMS (n=150,000 cells/well in 48well plate).
Conclusions: We confirmed that iPSC derived NGN2 neuronal cultures develop functional connectivity on MEA systems with bursting as soon as DIV19 which shows our in vitro model gives accelerated access to a reliable platform for studying neurological diseases. In our preliminary data, activated vs non-activated SPMS monocytes had different direct effects on cortical function. This approach could help reveal stage-specific mechanisms by which infiltrating innate immune cells may degrade neuronal function in MS.

**46. Prefrontal Neural Dynamics During Spatial Memory Coding and Retrieval.**

**Pedram Jokar,** Gregory Adame, Douglas Ralston, Jordan Steinhauser, Kylene Shuler, Daniel Connely, and Edward Korzus

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Spatial memory constitutes the ability to encode and retrieve environmental information, facilitating navigation and object localization, both of which are essential for adaptive behavior. Converging evidence robustly indicates that the interaction between the prefrontal cortex and hippocampus is vital for spatial memory. Studies employing lesioning, pharmacological interventions, and genetic techniques have elucidated the role of plasticity in hippocampal circuitry, particularly in neural processes associated with spatial memory, such as object location memory. Nevertheless, the mechanisms within the prefrontal cortex that underpin spatial memory are comparatively less understood. Prior research conducted by the Korzus Laboratory (Vieira et al., 2015) demonstrated that long-term memory encoding in the medial prefrontal cortex complements hippocampus-dependent spatial memory processes and may be integral to the broader neural network involved in integrating information required to discern subtle spatial differences and guide appropriate behavioral responses during the retrieval of spatial memories. However, the dynamics of prefrontal circuitry involved in spatial memory tasks remain to be elucidated.

In this preliminary study, we recorded one-photon calcium imaging in the medial prefrontal cortex of freely behaving mice during an Object Location Task (OLT) to assess prefrontal network dynamics that guide learning and short-term spatial memory retrieval. For behavioral performance assessment, we used automated scoring and analysis. We hypothesized that the network activity underlying exploratory behavior and preference for novelty (specifically, novel object location) would be reflected in prefrontal dynamics, and that distinct neuronal populations would be highly engaged during learning and memory retrieval phases. Preliminary analysis identified discrete neuronal populations within the prefrontal network involved in learning and spatial memory recall. Further investigations are expected to reveal subtle alterations within the OL population that influence mouse exploratory behavior during the appropriate selection of familiar and novel environmental features.

Reference: Vieira, P.A., and Korzus, E. (2015). CBP-Dependent memory consolidation in the prefrontal cortex supports object-location learning. Hippocampus 25, 1532-1540. 10.1002/hipo.22473.

**47. Brain-gut-brain endocannabinoid system control of food reward.**

**Camila Alvarez**

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Dysregulated neural and molecular pathways, including gut-brain endocannabinoid (eCB) signaling, contribute to obesity and overeating behaviors. It is not fully understood, however, if gut-brain eCB signaling engages brain reward pathways controlling motivated behavior through dopamine activity. Our lab has showed that mice strongly prefer WD over standard chow (SD, low fat/no sucrose), and this preference is blocked by both global CB1R inhibition using AM251 and mice that conditionally lack CB1Rs selectively in the intestinal epithelium. To investigate afferent and efferent vagus contributions during WD preference, mice underwent a 2-hour test while dopamine activity in the nucleus accumbens core was recorded with a virally mediated genetically encoded fluorescent dopamine sensor. Vehicle-treated controls displayed strong WD preference with sustained dopamine activity, while the peripherally restricted CB1R antagonist AM6545 significantly reduced both WD preference and dopamine activity. To determine whether CCK signaling mediates these effects, four groups—vehicle, AM6545, Devazepide (CCKA receptor antagonist), and AM6545+Devazepide—were run under a 12-hour preference test. AM6545 reduced WD preference, Devazepide increased preference, and co-administration still reduced preference, indicating CCKA signaling is not required. For efferent vagus involvement, atropine methyl nitrate (peripheral muscarinic antagonist) reduced WD preference. Immunohistochemistry revealed higher cFos/ChAT+ (cholinergic activity) expression in dorsal motor nucleus of mice exposed to SD/WD preference compared to SD/No Diet-preference tests. Collectively, these findings demonstrate that preferences for high-energy palatable foods are regulated by a mechanism involving peripheral eCB and acetylcholine signaling, with both afferent and efferent vagus feedback loops likely playing a critical role.

**48. Human neural stem cell-derived extracellular vesicles ameliorate breast cancer chemobrain.**

**Casey Hudson**

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About 75% of 3.8 million breast cancer survivors in the U.S. are suffering from chemobrain or cancer-related cognitive impairments (CRCI) that significantly impact survivors' quality of life. Chemobrain is characterized by memory loss, impaired recall, executive function deficits, and decreased processing speed and attention. We previously tested the efficacy of human neural stem cell-derived extracellular vesicles (hNSC-EVs) to alleviate radiation therapy-induced CRCI. In this study, we aimed to test the neuroprotective capabilities of hNSC-EVs in a syngeneic, immunocompetent female mouse breast cancer chemobrain model and demonstrated its mechanism of action. We performed behavioral testing and fluorescent IHC analyses to evaluate the impact of chemotherapy and the benefit of a systemic EV treatment on cognitive function, neuroinflammation, neuronal activity, and synaptic integrity. Breast cancer-bearing mice exposed to adjuvant chemotherapy (Adriamycin and cyclophosphamide) showed impaired learning and memory, memory consolidation, and executive function compared to chemotherapy-treated mice that received the EVs. IHC showed a significant increase in microglial activation, and significant decreases in synaptic density and neuronal plasticity-related IEG in breast cancer-bearing mice receiving chemotherapy. Conversely, EV-treated mice brains showed improvements in synaptic integrity and neuron function, and reductions in gliosis. MicroRNA sequencing identified three major miRNA candidates, Let-7, miR-9, and miR-21, with potential target pathways in chemobrain. We plan to elucidate the mechanism of action of functional EV cargo (miRNA)-mediated neurocognitive recovery through intra-cranial AAV-PHP.eB vector expressing miRNA. These results present a regenerative strategy to ameliorate chemobrain that could improve the QOL of millions of cancer survivors.

## 49. Targeted Organ Therapy with a Biodegradable Intra-Arterial Drug Delivery Platform: Sustained Release with Reduced Systemic Exposure.

**Manas Kinra**

University of California, Riverside

"Systemic drug delivery often results in sub-therapeutic drug levels at target organs and dose-limiting systemic toxicity. To address this challenge, we developed a biodegradable intra-arterial drug delivery (IADD) device capable of providing sustained, focal drug release directly to downstream organs. The IADD devices were engineered using a magnesium (Mg) micro-scaffold encased within poly(glycerol sebacate) (PGS), a biocompatible, biodegradable elastomer designed for controllable surface erosion. Devices were loaded with dexamethasone (DEX) or cisplatin (CIS) as model drugs. Structural, morphological, and chemical characterization was performed using SEM/EDS, TGA, and FTIR. In vitro release profiles were quantified over 30 days, alongside $Mg^{2+}$ ion release to evaluate device degradation. Cytocompatibility was assessed using HUVECs, and therapeutic efficacy of CIS-IADD release media was tested on F98 glioma cells. For in vivo validation, DEX-loaded IADD devices were surgically implanted in the carotid artery of rats to target the brain, with oral dosing as control. Drug levels were quantified using LC-MS/MS; histology and explant SEM assessed arterial tissue response and device integrity. IADD devices demonstrated sustained 30-day drug release without abrupt Mg degradation. HUVEC viability remained >94% across all test groups. CIS-IADD media induced ~38% glioma growth inhibition, confirming preserved pharmacological activity. Carotid implantation resulted in markedly enhanced focal drug delivery, achieving an ~11-fold increase in brain-to-serum DEX levels vs. oral dosing and ~20-fold higher brain drug levels overall. Histological analysis showed preserved arterial architecture with no thrombus or luminal obstruction. Explanted devices retained structural integrity with controlled PGS surface erosion. This first-generation IADD platform enables minimally invasive, biodegradable, and sustained focal drug delivery."

**50. Circadian regulation of astrocytic adenosine kinase after cranial radiation therapy.**

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Cranial radiation therapy (CRT) remains a frontline treatment modality for brain cancer. However, its clinical effectiveness is frequently accompanied by debilitating side effects of cognitive decline and circadian dysfunction, which significantly impair patient quality of life. Emerging evidence suggests that CRT-induced circadian disruption may be a byproduct of astrocyte-mediated dysregulation and altered adenosine metabolism. Adenosine kinase (ADK) is a key regulator of adenosine (ADO) homeostasis, providing neuroprotection to the brain. Previous studies have demonstrated that CRT induces ADK overexpression, leading to excessive influx of ADO into astrocytes, circadian dysrhythmia, and cognitive impairments. However, the mechanisms underlying such circadian dysregulation remain unclear. We hypothesized that CRT impairs a circadian gene, Bmal1-mediated sleep dysfunction through astrocyte-specific, ADK-dependent mechanisms. Utilizing a murine astrocytoma (CT2a) mouse model exposed to a clinically relevant fractionated irradiation schedule (8.67 Gy x 3 doses, 26.01 Gy total), we determined circadian-dependent molecular changes within astrocytes. Triple-fluorescence immunohistochemistry was performed to assess astrocytic ADK co-expressed with Bmal1 in the paraventricular nucleus (PVN), hippocampus, and tumor sites. Qualitative analysis of the tumor site revealed minimal presence of astrocytic ADK and Bmal1 expression, suggesting that tumors do not contribute to alterations in the brain's microenvironment after CRT. Additional analysis showed downregulation of Bmal1 within the PVN and hippocampus following CRT, accompanied by a concurrent upregulation of astrocytic ADK. These alterations were significant when animals were irradiated during their inactive (ZT4) phase and perfused during their active (ZT16) phase. These data suggest the Bmal1-mediated transcriptional regulation of ADK as a novel mechanistic pathway underlying CRT-induced circadian dysregulation.

Center for Glial Neuronal Interactions

19th Annual Symposium Center for Glial-Neuronal Interactions
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