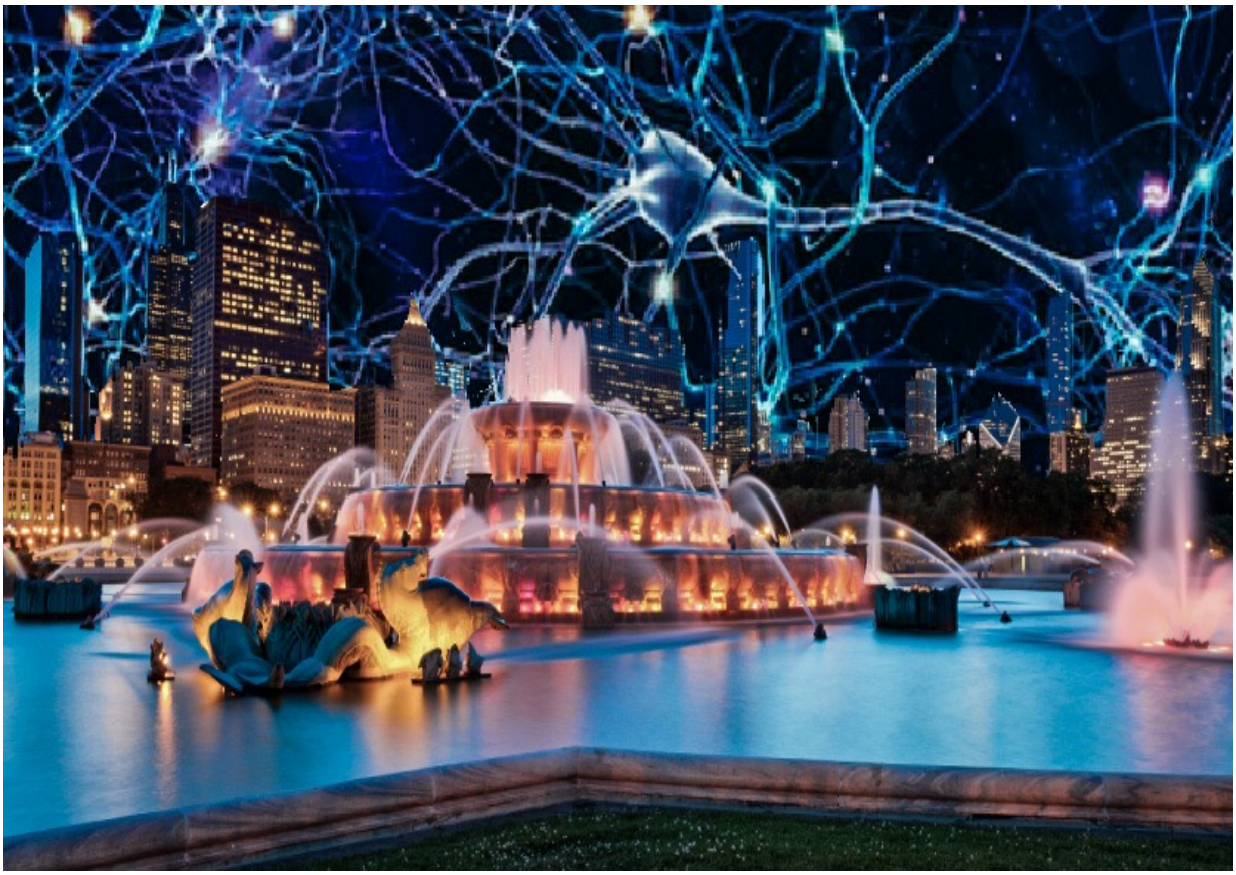
# The Chicago Chapter of the Society for Neuroscience Scientific Meeting 2019



## Friday, April 19th, 2019

## Northwestern Memorial Hospital

# 2019 Annual Scientific Meeting

**Northwestern University - Memorial Hospital**
**April 19th, 2019**

## MEETING OVERVIEW

| | | |
|---|---|---|
| **7:30-10:00 AM** | **Registration/Continental Breakfast** | ***3rd Floor*** |
| **8:00-8:45 AM** | **Mentoring Panel & Breakfast (with Conference Speakers)**<br>Moderator: Alexandra "Sasha" Prokuda | ***Pritzker Aud.*** |
| **8:00-4:00 PM** | **Poster Viewing and Vendor Display** | ***Atrium, 3rd Floor*** |
| **9:00-10:30 AM** | **PRESIDENTIAL SYMPOSIUM**<br>***New Developments in Neuroscience***<br>Chaired by Anna Lysakowski, Ph.D.<br>**Nitric-oxide-mediated plasticity helps us make sense of what we hear**<br>**Donata Oertel, Ph.D.** University of Wisconsin-Madison<br>**Neural mechanisms underlying robust sensory coding in the retina**<br>**Wei Wei, Ph.D.** University of Chicago | ***Room A*** |
| **10:30-11:30 AM** | **KEYNOTE SPEAKER**<br>**Lipids and the demise of neurons**<br>**Hugo Bellen, PhD, DVM,** Howard Hughes Medical Institute, Baylor College of Medicine | ***Room A*** |
| **11:30-1:45 PM** | **POSTER COMPETITIONS AND LUNCH BREAK**<br>Graduate, Undergraduate and Postdoctoral Poster Competitions | ***Atrium, 3rd Floor*** |
| **12:00-1:45 PM** | "Diversity in Careers" Lunch Tables | ***Room A*** |
| **12:15-1:15 PM** | Dr. Bellen and Graduate Student Symposium participants lunch | |
| **1:45-2:00 PM** | **Career Achievement Award Winner Peggy Mason, Ph.D.** | ***Room A*** |
| **2:00-3:30 PM** | **GRADUATE STUDENT SYMPOSIUM**<br>Selected Graduate Student Talks from six of the Chicago area Ph.D. granting medical schools | ***Room A*** |

**3:45-5:40 PM** **AFTERNOON SYMPOSIA** (*Concurrent Sessions*)

| | **Room A** | **Pritzker Auditorium** |
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| **3:45-3:50 PM** | ***Neuroinflammation and Brain Disorders***<br>Chaired by Joanne O'Keefe | ***Sensorimotor Circuit Development and Plasticity***<br>Chaired by Kaiwen Kam |
| **3:50-4:15 PM** | ***The fun and sometimes dangerous dance of neurons and astrocytes in ALS***<br>Hande Ozdinler (NWU) | ***Use of brain activity imaging to identify a novel memory mechanism***<br>Bill Frost (RFUMS) |
| **4:15-4:40 PM** | ***Inflammation and astrocytes: Wnt you like to know?***<br>Lena Al-Harthi (Rush) | ***Excitatory drive to STOP movement***<br>Kamal Sharma (UIC) |
| **4:40-5:05 PM** | ***Role of the microbiome in modulation of Ab amyloidosis and microglial physiology in mouse models***<br>Sangram "Sam" Sisodia (UC) | ***Precocious perisomatic inhibition coordinates high-speed locomotion in zebrafish***<br>Dave McLean (NWU) |
| **5:05-5:30 PM** | ***Therapeutic potential of targeting Neuregulin1-mediated neuroinflammation in neurodegenerative diseases***<br>Fei Song (UIC) | ***Mechanisms that promote and limit the ability to learn across development***<br>Sarah London (UC) |

| | |
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| **5:45-7:00PM** | **RECEPTION AND BUSINESS MEETING**<br>Social and announcement of awards, recognition, election results |

Map of Northwestern University downtown campus and
Feinberg Pavilion, 3rd Floor Conference Center, 251 E. Huron St., Chicago, IL 60611

## Meeting site for Chicago Chapter of SfN


Atrium, 3rd floor

- Take the escalators or elevators to Conference Center on 3rd Floor.
- Please visit the corporate exhibitor tables in the Atrium on the 3rd floor.
- Posters should be removed by 4:00 PM today.

Vote for next year's Chicago Chapter SfN Officers and Councilors
https://chicagosfn.org/annual-meeting/chicago-chapter-2019-annual-meeting/voting

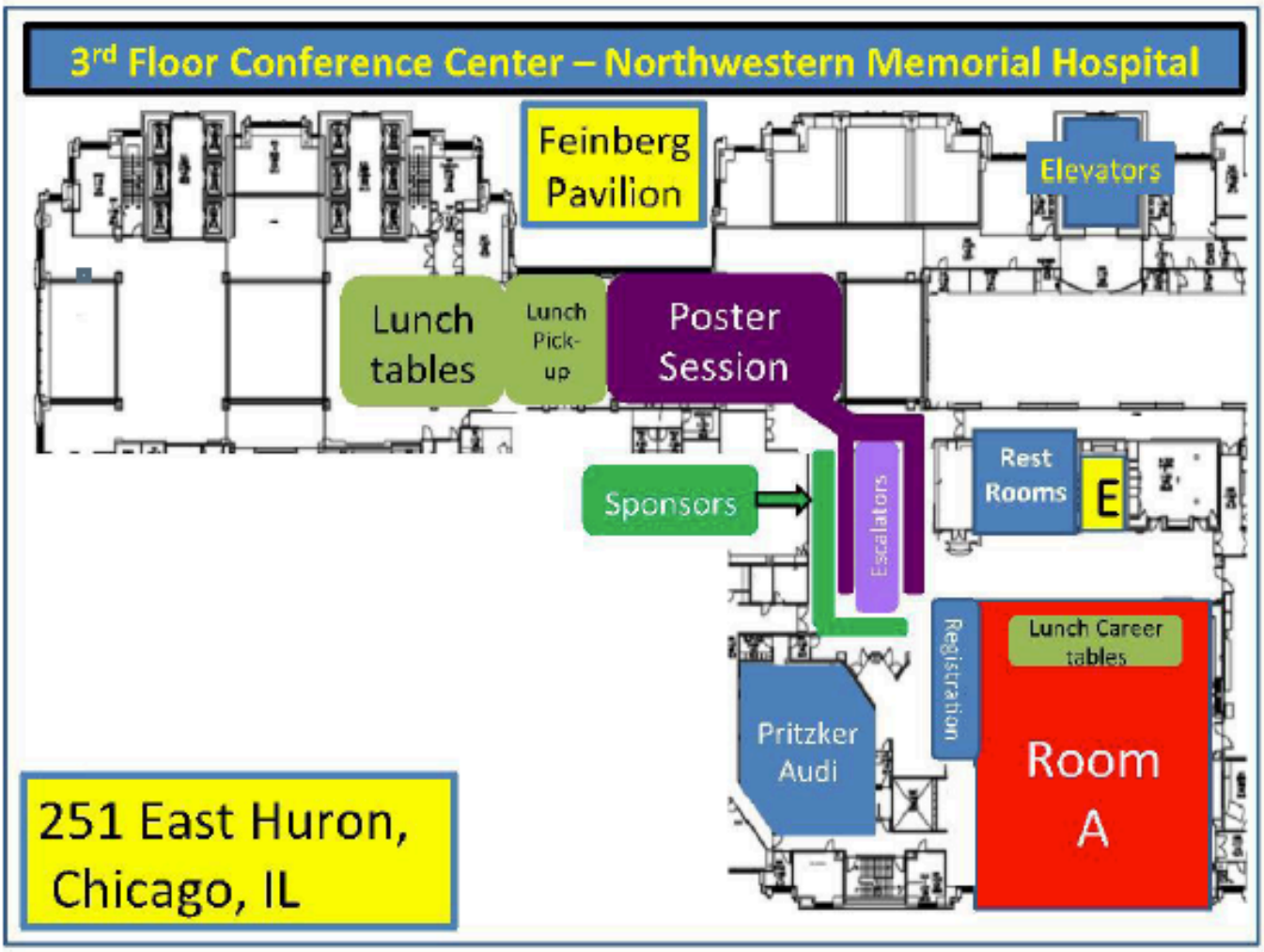
Please give us your opinion by answering our online survey.
https://docs.google.com/forms/d/1-XB8MRWS13-fiP436dhnlKFBx0eVNarWn4mUyTyQxEY/edit

- By answering the survey, you will be included in a drawing for a $25 gift card. Must be present at the awards ceremony to win. Your input is critical for a better meeting next year.

Parking

- When exiting Northwestern Hospital's parking garage, please show your validated parking voucher for a parking discount (validation provides up to 7 hours for $11, and 8 hours or more for $24).

**Cover Art:** Phoenix Toboz, Master's degree student from Northeastern Illinois University. Ms. Toboz is a member of Dr. Cindy Voisine's lab.



RUSH UNIVERSITY MEDICAL CENTER
Microbial Pathogens and Immunity

Wheaton College
For Christ and His Kingdom

The **Department of Microbial Pathogens and Immunity** is a multidisciplinary research department at the interface of neuroimmunology, neuro virology, and pathogen-host interactions.

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*Preparing people to lead extraordinary lives*

nuin Northwestern University Interdepartmental Neuroscience

UIC **Laboratory of Integrative Neuroscience**

RUSH UNIVERSITY
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CHICAGO 1972

## Department of Cell & Molecular Medicine at Rush University

Our research mission is to advance translational research by paying attention to underlying mechanisms. The objective is to identify therapeutic targets and biomarkers which, after appropriate clinical investigation, will improve human health. Thus, projects run the spectrum from fundamental molecular biology and genetics to cell signaling to tissue, organ, and organismal level responses. Studies are conducted using cell culture, model organisms, and human subjects. There are four current areas of emphasis: **cancer biology**, **musculoskeletal tissue injury and regeneration**, **movement disorders**, and **medical education research**.

DEPAUL UNIVERSITY
COLLEGE OF SCIENCE AND HEALTH
*Neuroscience Program*

Center for Cognitive & Social Neuroscience
THE UNIVERSITY OF CHICAGO

THE UNIVERSITY OF ILLINOIS AT CHICAGO
UIC

Northwestern
Neurobiology

## TABLE OF CONTENTS

## Chicago Society for Neuroscience
## Career Achievement Award 2019

**Peggy Mason, Ph.D.**

Dr. Mason is a Professor in the Department of Neurobiology at the University of Chicago. She has dedicated her academic career to making outstanding contributions to neuroscience research, innovative approaches to neuroscience education, and advancing public outreach in the greater Chicago community and beyond. First, Dr. Mason's groundbreaking research has attracted consistent extramural funding in multiple fields of neuroscience spanning the gamut of pain processing, anesthetic mechanisms, and somatosensation. Recently, her work has led to new insights into the source of pro-social behavior and empathy in mammals when they showed that such behavior is quantitatively evident in lower mammals such as rats.

Dr. Mason has shown a consistent drive to bring neuroscience to anyone who wants to learn it. Within the university setting she has served on multiple thesis committees and has inspired scores of students. She won several teaching awards including the Pritzker Favorite Faculty award two years in a row. She has also authored a lauded textbook, Medical Neurobiology, now in its second edition.

Finally, outside the university setting Dr. Mason has also hosted massive open online courses that have reached nearly 200,000 students from around the world. In addition, Dr. Mason inspires people as she co-hosts the podcase Chicago Brain Buddies with Aaron Freeman and appears on shows like Chicago Tonight.

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Social and announcement of awards, recognition, election results

# MORNING PROGRAM

## Mentoring Panel

8:00-8:45 AM — With Keynote Speaker and Presidential Symposium Speakers
Moderated by: Alexandra "Sasha" Prokuda — ***Pritzker Auditorium***

## PRESIDENTIAL SYMPOSIUM

**"*New Developments in Sensory Neuroscience*"**

9:00-10:30 AM — Chaired by Anna Lysakowski, Ph.D. — ***Room A***

9:00-9:10 AM *Welcoming Remarks*

9:10-9:50 AM **Nitric-oxide-mediated plasticity helps us makes sense of what we hear** *(Abstract p.19)*

**PSA** Donata Oertel, Ph.D.
*Mary Herman and Lucien Rubinstein Distinguished Chair of Neuroscience*
*University of Wisconsin- Madison*

9:50-10:30 AM **Neural mechanisms underlying robust sensory coding in the retina** *(Abstract p. 19)*

**PSB** Wei Wei, Ph.D.
*Department of Neurobiology*
*University of Chicago*

## KEYNOTE SPEAKER

10:30-11:30 AM — ***"*Lipids and demise of neurons"** *(Abstract p. 19)* — ***Room A***

Hugo Bellen, Ph.D.
Howard Hughes Medical Institute
Baylor College of Medicine

# LUNCH BREAK

11:30-1:45 PM **Poster Viewing & Vendor Tables** ***Atrium, 3rd Floor***

**Poster Competitions**

12:00-12:45 PM Authors in group A present for competition

12:45-1:30 PM Authors in group B present for competition

**Post-doctoral Poster Competition**
Chaired by Drs. Margaret Bell, Doug Wallace, Antonio Sanz-Clemente, Kaiwen Kam

**Graduate Student Poster Competition**
Chaired by Drs. Latha Malaiyandi, Angel Alvarez, Meagan Bailey, Nate Thom

**Undergraduate Student Poster Competition**
Chaired by Drs. Bill Rochlin, Naomi Wentworth, Denise Cook-Snyder, Maggie Gill

***For poster titles and abstracts, go to pages 24 and 36, respectively.***

12:00 -1:45 PM **Themed Lunch Tables (open to all Trainees)**
Chaired by Drs. Aaron Schirmer, Denise Cook-Snyder, Chaitanya Gavini

***"Diversity in Careers"*** ***Room A***

***Know more about your professional options***

**Table 1** ***Research and Teaching in Academia***
Dr. Denise Cook-Snyder, Assistant Professor, Carthage College
Dr. Aaron Schirmer, Associate Professor, Northeastern Illinois University
Dr. Chaitanya Gavini, Research Associate, Loyola University of Chicago

**Table 2** ***Science and Industry***
Dr. Simon Kaja, Chief Scientific Officer, Experimentica Ltd.
Ms. Alycia F. Tipton, Technical Sales and Support Specialist, Stoelting

**Table 3** ***Science and Entrepreneurship***
Dr. Garry Cooper, Co-founder/CEO, Rheaply, Inc.

**Table 4** ***Science Advocacy, Policy, and Law***
Dr. Krisztina Elek, Executive Director, The Chicago Council on Science and Technology ($C^2ST$)
Mr. Paul Rogerson, Associate, IP litigation, Sidley Austin

**12:15-1:15 PM** **Dr. Bellen and Graduate Student Symposium participants lunch** ***Room E***

2:00- 3:35 PM **GRADUATE STUDENT SYMPOSIUM** ***Room A***

*(For abstracts see p. 22)*

**Introduction**
Kelly Langert, Ph.D., Illinois Institute of Technology

2:05-2:20 PM **Reduced anti-inflammatory capacity: an early event in binge alcohol-induced neurodegeneration**
**GS1** Jennifer Schreiber
*Departments of Cellular and Molecular Pharmacology and Neuroscience, Loyola University*
**Advisor:** Michael Collins

2:20-2:35 PM **LY6K Promotes Glioblastoma Tumorigenesis Via Caveolin-Activated Erk Signaling**
**GS2** Namratha Sastry
*Department of Neurology, Northwestern Brain Tumor Institute, The Robert H. Lurie Comprehensive Cancer Center, Northwestern University*
**Advisor**: Shi-Yuan Cheng

2:35-2:50 PM **Endocannabinoid modulation of prefrontal afferent transmission and associated extinction of fear memory**
**GS3** Hanna Molla
*Dept of Cellular & Molecular Pharmacology, Rosalind Franklin University*
**Advisor**: Kuei-Yuan Tseng

2:50-3:05 PM **Ultrastructural underpinnings and functional consequences of white matter disruption during Alzheimer's pathogenesis**
**GS4** Matt Russo
*Department of Neurological Sciences, Rush University*
**Advisor**: Daniel Nicholson

3:05-3:20 PM **Cytoarchitectural changes induced by migraine are reversed by hdac6 inhibition**
**GS5** Zachariah Bertels
*Department of Psychiatry, University of Illinois at Chicago*
**Advisor**: Amynah Pradhan

3:20-3:35 PM **Interhemispheric Functional Connectivity in the Zebra Finch Brain, Absent the Corpus Callosum in Normal Ontogeny**
**GS6** Elliot Layden
*Department of Psychology, University of Chicago*
**Advisors:** Marc Berman and Sarah London

## AFTERNOON SYMPOSIUM-A

*(for abstracts, see p. 20)* ***Room A***

3:45-5:30 PM ***"NEUROINFLAMMATION AND BRAIN DISORDERS"***
Chaired by **Drs. Joanne O'Keefe and Maureen Rutherford**

3:45-3:50 PM **Introduction**
Dr. Joanne O'Keefe
*Department of Cell & Molecular Medicine, Rush University*

3:50-4:15 PM **The fun and sometimes dangerous dance of neurons and astrocytes in ALS**
**PASA1** Dr. Hande Ozdinler
*Department of Neurology, Northwestern University*

4:15-4:40 PM **Inflammation and astrocytes: Wnt you like to know?**

**PASA2** Dr. Lena Al-Harthi
*Department of Microbial Pathogens and Immunity, Rush University*

4:40-5:05 PM **Role of the microbiome in modulation of Ab amyloidosis and microglial physiology in mouse models**

**PASA3** Dr. Sangram "Sam" Sisodia
*Department of Neurobiology, University of Chicago*

5:05-5:30 PM **Therapeutic potential of targeting Neuregulin1-mediated neuroinflammation in neurodegenerative diseases**

**PASA4** Dr. Fei Song
*Department of Neurology and Rehabilitation, University of Illinois at Chicago*

## AFTERNOON SYMPOSIUM-B

*(for abstracts, see p. 21)* ***Pritzker Auditorium***

3:45-5:30 PM ***"SENSORIMOTOR CIRCUIT DEVELOPMENT AND PLASTICITY"***
Chaired by **Dr. Kaiwen Kam**

3:45-3:50 PM **Introduction**
Dr. Kaiwen Kam
*Department of Cell Biology and Anatomy*
*Rosalind Franklin University of Medicine and Science*

3:50-4:15 PM **Use of brain activity imaging to identify a novel memory mechanism**

**PASB1** Dr. William Frost
*Department of Cell Biology and Anatomy, Rosalind Franklin University of Medicine and Science*

4:15-4:40 PM **Excitatory drive to STOP movement**

**PASB2** Dr. Kamal Sharma
*Department of Anatomy and Cell Biology, University of Illinois at Chicago*

4:40-5:05 PM **Precocious perisomatic inhibition coordinates high-speed locomotion in zebrafish**

**PASB3** Dr. David McLean
*Department of Neurobiology, Northwestern University*

5:05-5:30 PM **Mechanisms that promote and limit the ability to learn across development**

**PASB4** Dr. Sarah E. London
*Department of Psychology, University of Chicago*

## EVENING PROGRAM

## AWARD CEREMONY, BUSINESS MEETING AND SOCIAL

***Atrium, Room A***

5:40-7:00 PM **Wine and Cheese Social ("EtOH Receptor Binding Study")**

**Election Results**
**Recognition of Councilors**

**Recognition of Chicago area students and student organizations for excellence in neuroscience education and outreach**

2019 Chicago Brain Bee winners
2019 Lake Forest College student members of the Nu Rho Psi Chapter
2019 Northwestern University Brain Awareness Organization (NUBAO)

**Announcement of prize winners**

**Undergraduate Student Poster Competition**
Presented by Bill Rochlin, Ph.D., Loyola University of Chicago

**Graduate Student Poster Competition**
Presented by Latha Malaiyandi, Ph.D., Midwestern University

**Post-doctoral Fellow Poster Competition**
Presented by Doug Wallace, Ph.D., Northern Illinois University

**Graduate Student Symposium**
Presented by Kelly Langert, Ph.D., Illinois Institute of Technology

# ABSTRACTS

## KEYNOTE LECTURE

### LIPIDS AND THE DEMISE OF NEURONS

Hugo Bellen, Ph.D.

Howard Hughes Medical Institute, Department of Molecular and Human Genetics, Neurological Research Institute, Department of Neuroscience, Baylor College of Medicine, Houston, TX

We are interested in unraveling the molecular mechanisms that underlie the loss of neurons in some neurological diseases. By studying loss of function mutations in homologues of genes that cause severe and early onset pediatric neurological diseases, we discovered that selective defects in lipid metabolism play critical roles in numerous neurological diseases including late onset neurodegenerative diseases. For example, loss of some proteins associated with very early neuronal loss in infants can cause very elevated levels of reactive oxygen species (ROS) leading to the production of high levels of peroxidated lipids. These peroxidated lipids are transferred to glia where they are sequestered in lipid droplets to prevent membrane damage. The transport of lipids and their accumulation in glial cells is evolutionarily conserved and relies on proteins that play a role in Alzheimer Disease (AD). Our data suggest that peroxidated lipids synergize with other insults to cause the demise of neurons in AD. In other experiments designed to assess the molecular mechanism related to Parkinsonism (PD), we discovered that ceramide levels are elevated. The elevation of ceramide levels is due to a dysfunction of the retromer. This organelle recycles lipids and proteins that are endocytosed. In various PD models we detect a defect in retromer function that leads to increased trafficking from endosomes to lysosomes. This leads to lysosomal stress, a further increase in ceramides and a further deterioration of retromer function, eventually leading to neuronal death. These examples underscore the importance of lipids in the progression of neurodegenerative diseases in infants and adults.

## PRESIDENTIAL SYMPOSIUM

**PSA**

### NITRIC-OXIDE-MEDIATED PLASTICITY HELPS US MAKE SENSE OF WHAT WE HEAR

Donata Oertel, Ph.D.
Professor and Mary Herman and Lucien Rubinstein Distinguished Chair of Neuroscience, School of Medicine and Public Health, University of Wisconsin-Madison

The cochlea converts sound to electrical signals that propagate to the brain through the auditory nerve. Auditory nerve fibers transmit information about the physical attributes of sound, its frequency content and its intensity. It is up to the brain to extract biologically useful features from auditory nerve fiber input. Mammals need to know where sounds arise what those sounds mean. At the first stage of the auditory pathway, four groups of principal cells extract differing features of sounds. One of those, the T stellate cells, individually track intensity over a narrow frequency range and as a population encodes spectral peaks and valleys. We have discovered a new form of plasticity that modulates excitatory inputs to T stellate cells. Recordings in slices show that when pairs of neighboring T stellate cells are coactivated, they excite one another through a polysynaptic pathway. That potentiation of interconnections requires signaling by nitric oxide, a retrograde messenger. Mutual excitation generates positive feedback among neurons that are similarly tuned and that therefore presumably often fire together. Positive feedback between cells that are similarly tuned can enhance the encoding of spectral peaks in normal listeners. Evidence from other investigators suggests that the strength of the positive feedback might increase after hearing loss and thus could contribute to hyperexcitability and tinnitus.

**PSB**

### NEURAL MECHANISMS UNDERLYING ROBUST SENSORY CODING IN THE RETINA

Wei Wei, Ph.D.
Associate Professor, Department of Neurobiology, University of Chicago, Chicago, IL

A critical function of sensory systems is to reliably extract ethologically relevant features from the complex natural environment. A classic model to study feature detection is the direction-selective circuit of the mammalian retina that computes the direction of visual motion. In this talk, I will discuss our recent work on the neural basis of the robustness of retinal direction selectivity. Using a combination of genetic manipulations, multiphoton imaging, electrophysiology and computational modeling, we dissected the inhibitory circuitry that preserves motion detection in the presence of background noise, and discovered an unexpected algorithmic function of a canonical disinhibition microcircuit.

## AFTERNOON SYMPOSIUM A

## NEUROINFLAMMATION AND BRAIN DISORDERS

### PASA1
### ASTROCYTES, MICROGLIA AND MOTOR NEURONS IN THE CORTEX OF ALS

Hande Ozdinler, PhD

*Department of Neurology, Northwestern University, Chicago IL*

Amyotrophic lateral sclerosis (ALS) is one of the most complex and heterogeneous neurodegenerative diseases, affecting both the cortical and the spinal component of the motor neuron circuitry, and with the involvement of both neuronal and non-neuronal cells. Even though the disease manifests itself with the progressive degeneration of the motor neurons, the role and the impact of the non-neuronal cells have always been an area of interest. Involvement of innate immunity, astogliosis, microgliosis, especially at the site of neurodegeneration, has been shown at different stages of disease initiation and progression. Early studies suggested that non-neuronal cells contribute as scavengers with a mission of clearing up the dead cells from the tissue towards the end-stage of the diseases, and recent studies find evidence for their early involvement. However, none of the studies were able to detect cells in action and determine the exact timing and the extent of their involvement in neuronal vulnerability and progressive degeneration. By using reporter lines that fluorescently label the upper moto neurons and cells that express MCP1 and CCR2, we began to reveal cell-cell interactions of vulnerable upper motor neurons and non-neuronal cells, particularly cells involved in innate immunity. Our studies reveal increased astrogliosis and microgliosis especially in the diseased motor cortex of at a stage when upper motor neuron degeneration becomes evident, suggesting a dynamic interplay between the motor neurons and the non-neuronal cells during early stages of the disease. Especially in the motor cortex with TDP-43 pathology, there is an imminent increase of CCR2+ cells infiltrating from the blood stream and moving towards the vulnerable upper motor neurons located in layer V of the motor cortex. Our studies bring cellular clarity and enable visualization of direct cellular interaction, revealing many details of their dynamic communication and how that contributes to neurodegeneration.

### PASA2
### INFLAMMATION AND ASTROCYTES: WNT YOU LIKE TO KNOW?

Lena Al-Harthi, PhD

*Rush University Medical Center, Chicago, IL.*

Wnt/b-catenin signaling is a ubiquitous pathway critical for organogenesis, cell communication and cell survival. In the CNS, Wnt signaling mediates neurogenesis and neuronal synapse formation and maturation. Little is known about Wnt/b-catenin integrity and role in astrocytes in health and disease. Astrocytes are the most abundant cell type in the brain, performing vital functions to maintain neuronal homeostasis, blood-brain barrier, and immune regulation. Disruption of astrocytes has a profound impact on a number of neurodegenerative diseases. We demonstrated that astrocytes have robust expression of Wnt ligands initiating Wnt signaling and particularly mediating canonical Wnt/b-catenin signaling. Under inflammation (modeled via human astrocyte exposure to inflammatory signals such as IFNg, toll-like receptors (TLRs), HIV, or Methamphetamine), Wnt/b-catenin signaling is diminished in astrocytes via multiple pathways. For example, IFNg mediates inhibition of Wnt/b-catenin by inducing an antagonist of the pathway (DKK-1) in a Stat-3-dependent manner while HIV inhibits Wnt/b-catenin via accessory protein Tat, which sequesters away a b-catenin transcription factor partner. In vitro and in vivo loss of b-catenin function resulted in profound biologic consequences, the most notable of which are: 1) disruption of the glutamate/ glutamine cycle through transcriptional down regulation of glutamate transporter excitatory amino acid transporter 2 (EAAT2 in humans or GLT-1 in rodents) and glutamine synthetase (GS) genes. 2) Induction of an astrocyte inflammatory (A1) phenotype characterized by gene profiling and enhanced IL-6 and IL-8 expression at the transcription level. 3) Induction of astrocyte senescence. These astrocyte alterations led to neuronal injury, characterized by significant reduction in microtubule associated protein 2 (MAP2) expression. Collectively, these studies demonstrate that inflammatory signals which disrupt Wnt/b-catenin signaling in astrocytes will both perturb their function and disrupt their communication with neurons, leading to neuronal injury.

*This study was funded by R01 NS060632; R01 MH113425; and R01 DA033966*

### PASA3
### MODULATION OF AMYLOID DEPOSITION AND NEUROINFLAMMATION BY THE MICROBIOME

Sangram Sisodia, PhD

[1]Hemraj Dodiya, [1]Shabana Shaik, [1]Myles Minter, [3]Rudolph Tanzi, [3]Martin Zhang, [2]Eugene Chang, [3]Jeff Leibowitz, [3]Oleg Butovsky, [1]Sangram Sisodia

*[1]Department of Neurobiology and [2]Medicine, University of Chicago, Chicago Il USA, [3]Harvard Medical School, Boston, MA USA*

**Objectives:** Animal models of Alzheimer's disease (AD) recapitulate the severe amyloidosis and neuroinflammation that is evident in the human disease. It is now well established that inflammation associated with amyloid deposition reflects the activation of astrocytes and microglia in response to injury, but the role of peripheral tissues and more importantly, the microbiota in regulating innate immunity that in turn leads to CNS dysfunction has not, to date been defined. We have tested the hypothesis that the composition of the intestinal microbiome plays a key role in modulating neuro-inflammation that will ultimately influence amyloid deposition in two established mouse models of b-amyloidosis.
**Methods:** We orally administered a combination of antibiotics to induce rapid and sustained alterations in gut microbial populations. The antibiotic cocktail was administered either postnatally or throughout the lifetime of the animal prior to cull and we employed IHC, biochemical and molecular assays to evaluate amyloid deposition and neuroinflammation in the mouse models.
**Results:** Our studies indicate that alterations in the microbiome parallel changes in plasma cytokines and chemokines, reductions in

amyloid deposition and modulation of morphological and transcriptional landscapes of microglia.
**Conclusions:** Our studies reveal an unexpected, but significant alteration in amyloid deposition and microglial phenotypes in the brains of transgenic mice upon treatment with orally administered antibiotics.

***Acknowledgments*** *This work was supported by Cure Alzheimer's Fund (CAF) the Edward H. Levi Fund and the Adler Foundation. SSS is a paid Consultant of AZTherapies Inc.*

**PASA4**
**THERAPEUTIC POTENTIAL OF TARGETING NEUREGULIN1-MEDIATED NEUROINFLAMMATION IN NEURODEGENERATIVE DISEASES**

Fei Song, PhD

*Department of Neurology and Rehabilitation, The University of Illinois at Chicago, Chicago IL*

Accumulating evidence suggests that neuroinflammation mediated by microglia is a common feature in the onset and progression of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). However, treatments have not been clinically effective as the disease pathogenesis of neuroinflammation-mediated neurodegeneration is not yet clearly understood. Therefore, new approaches and new mechanisms are desperately needed to stall the insidious and progressive neurodegeneration. Our group has been studying the neuronally-produced growth and differentiation factor neuregulin-1 (NRG1) that is a critical axoglial communication signal. We have found that NRG1 receptors are present and constitutively activated on activated microglia in ALS patients, ALS-SOD1 animal models, and in a nerve-injury mediated model of chronic pain**.** We have shown that this same peripheral nerve injury that produces a pathological inflammatory response in the pain model is greatly augmented in genetically predisposed ALS-SOD1 rats and produces significant synaptic stripping of the injured motor neurons. Blocking NRG1 signaling in both pain and ALS models prevents microglial activation, thereby preventing the development of chronic pain and reducing motor neuron loss in the ALS-SOD1 animal model. These results in other fields are the basis for our hypothesis that enhanced neuroinflammation leads to synaptic loss as a precursor to neuronal degeneration. We also ask whether this same pathway we discovered in ALS and chronic pain is pathogenic and contributes to neuronal and synaptic loss in the degenerative process of AD. We consistently found that human cerebrospinal fluid from AD patients has increased NRG1 activity. We found that NRG1 receptors are present and activated on microglia in AD and that blocking NRG1 receptor activation with a targeted NRG1 antagonist prevents and reverses microglial activation and amyloid beta plaque formation. Our study will have strong translational ramifications in understanding and characterizing a potential new therapeutic that targets the neuroglia axis in neurodegeneration.

## AFTERNOON SYMPOSIUM B

## SENSORIMOTOR CIRCUIT DEVELOPMENT AND PLASTICITY

**PASB1**
**USE OF BRAIN ACTIVITY IMAGING TO IDENTIFY A NOVEL MEMORY MECHANISM**

William Frost, PhD

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A current frontier in research on the neurobiology of learning concerns how neurons are chosen to join memory traces, a process called neuronal allocation. Large-scale imaging of a neural population with voltage sensitive dyes allowed us to watch a memory engram as it formed and then dissipated with the rise and fall of short-term sensitization, a form of non-associative learning, in the nudibranch mollusk *Tritonia*. In the absence of learning, the animal's naïve rhythmic escape swim network was found to consist of a core group of neurons that burst reliably on all cycles of the motor program, and a second group of variably-participating neurons that burst on some, but not all cycles. We found that with sensitization, the reliably bursting group increased its numbers by 38%, reflecting network strengthening with learning. Further analysis revealed that the sensitization memory involved more than simple recruitment of neurons to the core network – one specific type of neuron was at the same time selectively ejected from the reliably-bursting group. This bidirectional restructuring of the network with learning suggests that engram formation involves an orchestrated reorganization of the network to store specific information. Further work identified modulatory neurons that direct this process, confirmed by the finding that driving them in the absence of training implanted a false memory for sensitization. Our findings thus identify a novel mechanism for neuronal allocation in memory, involving networks operating at rest with mixtures of reliably and variably participating neurons, with memory formation occurring via neuromodulatory enhancement of the degree of commitment of neurons to the motor program.

**PASB2**
**EXCITATORY DRIVE TO STOP MOVEMENT**

Kamal Sharma, PhD

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A century ago Sherrington wrote, "*The role of muscle as an executant of movements is so striking that its office in preventing movement and displacement is somewhat overlooked"* (Sherrington, 1915). We are probing the roles of pontine glutamatergic neurons in preventing/stopping movement. Optogenetic interrogation of neurons in the subpeduncular tegmentum shows their role in promoting wakefulness at the expense of sleep. Rapid firing of these neurons induces slow oscillation in the prefrontal cortex and simultaneously freezes ongoing motor activity. Whether these pontine neurons are the common substrate for fear induced freezing and long-term

disturbances in sleep as observed in PTSD remains an intriguing possibility. In a separate study, optogenetic activation of glutamatergic neurons in the interpeduncular nucleus produces strong place aversion behavior. Together these findings indicate that in addition to initiating movement (mesencephalic locomotor region), glutamatergic drive from pontine neurons also plays an important role in coordinating cessation of movement.

**PASB3**
**PRECOCIOUS PERISOMATIC INHIBITION COORDINATES HIGH-SPEED LOCOMOTRION IN ZEBRAFISH**

David McLean

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Inhibitory circuits in the spinal cord ensure alternating movements during locomotion. In both limbed and limbless vertebrates, increases in locomotor speed require increases in the cyclical frequency of rhythmic movements and the number and size of active motoneurons. Consequently, the burden to maintain alternation increases with speed, as inhibition must contend with faster oscillations in a larger population of neurons. Currently, it is unclear how spinal inhibitory circuits orchestrate this fundamental process, given the challenge in linking synaptic connectivity to neuronal identity and recruitment. Here, I will discuss our recent work exploring how *Dmrt3*-labeled dI6 spinal interneurons, a source of commissural glycinergic inhibition implicated in gait control during limbed locomotion, ensure left-right alternation at different frequencies of swimming in larval zebrafish.

**PASB4**
**MECHANISMS THAT PROMOTE AND LIMIT THE ABILITY TO LEARN ACROSS DEVELOPMENT**

Sarah E. London, PhD

*Department of Psychology, University of Chicago*

Learned behavior pervades daily life in little and small ways. Some behaviors, language acquisition is a striking example, are most efficient when sensory learning occurs from social situations during development. What are the properties of the brain that promote and limit the ability to learn from others? We use the zebra finch songbird model to dissect how changes in genomic function relate to the ability to form sensory memories that are the basis of vocal communication. Male zebra finches (*Taeniopygia guttata*) learn to sing; females cannot sing. The basis of each male's song structure is the memory he forms of a "tutor" male's song during a developmental Critical Period, a restricted phase when experience has profound and permanent influence on brain and behavior. Combining molecular, genomic, and epigenetic levels of analysis, we leverage the "on" and "off" switches of the Critical Period, the ability to manipulate brain function and tutor experience, and the natural sex difference in singing behavior to reveal properties of the brain that distinguish individuals who can and cannot memorize tutor song. With this approach, we discover how mechanisms of maturational and experience-dependent neural plasticity intersect to promote and limit the ability to learn complex natural behavior.

## GRADUATE STUDENT SYMPOSIUM

**GS1**
**REDUCED ANTI-INFLAMMATORY CAPACITY: AN EARLY EVENT IN BINGE ALCOHOL-INDUCED NEURODEGENERATION**

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Selective degeneration of dentate granule cells in hippocampus (HC), pyramidal cells in entorhinal cortex (EC), and olfactory bulb neurons occurs in adult male rats subjected to severe alcohol (ethanol) binges over 4 days that generate maximal blood alcohol levels of 350-450 mg/dl. Concurrent with brain damage specifically in these brain regions, significant alterations are elicited by alcohol in the levels of phospholipase A2 (PLA2) enzymes, i.e., (1) increases in $Ca^{2+}$-dependent cytosolic cPLA2 and secreted sPLA2, two membrane phospholipid-metabolizing enzymes causing neuroinflammation *via* mobilization of omega-6 arachidonic acid, a largely pro-oxidative neurocellular mediator; and (2) reductions in $Ca^{2+}$-independent iPLA2, known to selectively regulate membrane release and turnover of anti-inflammatory, anti-oxidative omega-3 docosahexaenoic acid (DHA). Furthermore, these neurodegenerative and neuroinflammatory changes are replicated *in vitro,* along with a loss in DHA content itself, in rat organotypic adult-age HC-EC slice cultures binge-treated with 100 mM (~460 mg/dl) alcohol. The objective of this study was to determine if phospholipid-mediated neuroinflammatory changes exist from alcohol in the absence of neurodegeneration. Here we report that rats subjected to less severe binges - and thus lower blood alcohol levels of ~150 mg/dl, which are insufficient to cause detectable brain damage and/or neuroinflammatory cPLA2 and sPLA2 elevations - nevertheless cause significantly reduced iPLA2 levels that are largely reversed by DHA supplementation. The results imply that iPLA2 depletion and, loss of cellular DHA (that iPLA2 regulates), are critical, previously unappreciated first indicators or markers of brain neuroinflammation due to binge alcohol. Similar changes in iPLA2, potentially due to its sensitivity, may have a bearing on other forms of brain insults causing neuroinflammation and ultimately neurodamage.
*This study is supported by: NIAAA T32 (AA013527-Loyola) and NIAAA U01 (AA0182790-MAC/HYK).*

**GS2**
**LY6K PROMOTES GLIOBLASTOMA TUMORIGENESIS VIA CAVEOLIN-ACTIVATED ERK SIGNALING**

Namratha G. Sastry[1], Tianzhi Huang[1], Angel A. Alvarez[1], Rajendra P. Pangeni[1], Xiao Song[1], Xuechao Wan[1], John Kessler[1], Cameron W. Brenann[2], Erik P. Sulman[3], Ichiro Nakano[4], Bo Hu[1], and Shi-Yuan Cheng[1]

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Glioblastoma (GBM) is the most malignant brain cancer, with extremely poor prognosis in patients. GBM tumors are characterized by distinct molecular subtypes, known as proneural (PN), classical, and mesenchymal (MES). Inherited heterogeneity and aberrant aggressiveness contribute to therapy resistance and frequent recurrence of malignant GBM tumors. In addition, GBM tumors also contain a small subpopulation of tumor-initiating or stem-like cancer cells (GSCs). Gene expression profiling studies from our laboratory showed that patient-derived GSCs can also be classified into two subtypes, PN and MES, that are phenotypically similar to clinical GBM. Among three thousand genes that are differentially expressed between PN and MES-like GSCs, *Lymphocyte Antigen 6 Complex, Locus K (LY6K)* was identified as a top differentially expressed gene. LY6K is a GPI-anchored protein from the LY6 family. Several members of the LY6 family have been implicated in human cancers, including breast, esophageal, and lung cancers. Moreover, the role of LY6K in GBM has not been reported. Here, we examined how LY6K upregulation affects GBM tumorigenesis and investigated the underlying mechanism of LY6K action. We hypothesized that high levels of *LY6K* promotes GBM tumorigenesis. Based our other preliminary data, we further hypothesized that LY6K functions by enhancing ERK activation. We first examined the role of *LY6K* in advancing GBM tumorigenic behaviors of GSCs. Tumorigenicity assays showed that the presence of *LY6K* significantly increases cell growth and glioma sphere forming ability in vitro and promotes tumor formation in orthotopic brain xenograft mouse models. The underlying mechanism governing *LY6K* expression was found to be DNA promoter methylation. Moreover, preliminary data indicate that irradiation strongly induces *LY6K* expression in GSCs with otherwise undetectable levels. Furthermore, we observed that there is a strong relationship between LY6K and ERK signaling in GSCs and U87 glioma cells. The presence of LY6K stimulates ERK activation and subsequently augments cell proliferation, likely through caveolin-mediated signaling. Lastly, we identified the GPI-anchor domain of LY6K as a key region in enhancing ERK activation and are currently examining the mechanistic properties of this domain. The information gained from our studies will advance current knowledge of aberrantly upregulated LY6K and ERK signaling enhancement in promoting GBM tumorigenicity. Given that LY6K is a cancer/testis antigen, elucidating this pathway can have therapeutic implications for GBM patients.

*This study is funded by the Fishel Award from Northwestern University, Robert H Lurie Comprehensive Cancer Center and F31 National Research Service Award (NRSA) from the National Institutes of Health (NIH), National Cancer Institute (F31 CA232630).*

## GS3
## ENDOCANNABINOID MODULATION OF PREFRONTAL AFFERENT TRANSMISSION AND ASSOCIATED EXTINCTION OF FEAR MEMORY

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Prefrontal cortex (PFC) maturation during adolescence involves remodeling of glutamatergic and GABAergic transmission in the PFC, and is partly dependent upon proper modulation of afferent drive. Previous studies have also implicated changes in signaling components of the endocannabinoid system (CB1 receptor and endocannabinoids such as 2-AG and anandamide) in the PFC during adolescence. However, the manner by which endocannabinoid signaling impacts PFC synaptic transmission during the transition to adulthood remains unknown. Here we conducted *in vivo* local field potential recordings in rats and examined how pharmacological manipulations of prefrontal endocannabinoid signaling affects transmission originating from the basolateral amygdala (BLA) and ventral hippocampus (vHIP). We found the recruitment of endocannabinoid-CB1R signaling in the PFC is developmentally regulated, which emerges to exert a powerful inhibitory control of BLA and vHIP inputs after P45. Our data indicate both 2-AG and anandamide contribute to limit vHIP-to-PFC transmission, yet only 2-AG was recruited to modulate BLA inputs. At the behavioral level, PFC elevation of endocannabinoids delays the extinction of fear memory, an effect that cannot be mimicked by prefrontal activation of CB1Rs. Together, these results show that endocannabinoid-CB1R signaling in the PFC emerges to control the gain of afferent transmission in an age-dependent and input-specific manner.for anxiety and AUD susceptibility in both humans and rodents.

*Funding support: NIH grants R01MH086507 and R01MH105488 to KY Tseng*

## GS4
## ULTRASTRUCTURAL UNDERPINNINGS AND FUNCTIONAL CONSEQUENCES OF WHITE MATTER DISRUPTION DURING ALZHEIMER'S PATHOGENESIS

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Alzheimer's disease (AD) is a devastating disorder marked by substantial cognitive decline, and it is becoming an increasingly prominent problem as the world's aged population grows. A well-known characteristic of AD patients is cortical thinning and grey matter atrophy commonly seen via magnetic resonance imaging, which is likely attributable to synapse and cell loss. Interestingly, diffusion tensor imaging (DTI) studies have consistently shown that measures of white matter integrity, such as fractional anisotropy and volume, are also significantly compromised in patients with early and pre-clinical AD. However, the cellular basis of these white matter changes remains poorly understood. Potential insights to this question have come from *in vitro* studies and histological examination of the grey matter. Specifically, amyloid beta, the major constituent of amyloid plaques in AD, exhibits cytotoxic effects on cultured oligodendrocytes, the myelinating cells of the central nervous system. In addition, it has been observed that myelin basic protein staining is substantially attenuated or completely absent from the periphery and cores of amyloid plaques. Therefore, the characteristic pathology of AD may drive damage to white matter by decreasing the integrity of the myelin sheath. In an effort to assess this possibility, the present study employed a combination of high-resolution microscopy and electrophysiology. We specifically examined the alveus, a major output pathway of the hippocampus that extends from CA1 to various target regions. Our observations indicate that aged transgenic AD mice (5xFAD) and human AD patients exhibit a substantially higher occurrence of myelin abnormalities relative to respective controls. Further, physiological assessment shows an increased degree of heterogeneity among CA1

pyramidal neurons of 5xFAD mice in their ability to propagate action potentials relative to control neurons. Our current findings suggest that decreased myelin integrity likely contributes to the white matter changes observed with DTI, and that these deficits translate to changes that can affect neuronal communication. Further experiments are currently underway to assess potential proteomic effects of myelination changes with AD pathology.

*This work is supported by the Northwestern University Mechanisms of Aging and Dementia Training Grant (AG020506) and a research award from the NIH (AG017139).*

**GS5**

## CYTOARCHITECTURAL CHANGES INDUCED BY MIGRAINE ARE REVERSED BY HDAC6 INHIBITION

Zachariah Bertels[1], Harinder Singh[2], Isaac Dripps[1], Pal Shah[1], Justyna Chmura [2], Serapio Baca[3], Mark M Rasenick[2,1], Amynah A. Pradhan[1]

*1 Department of Psychiatry, University of Illinois at Chicago; 2 Department of Physiology & Biophysics, University of Illinois at Chicago; 3 Department of Pharmaceutical Science, University of Colorado*

Migraine is one of the most common neurological disorders and is estimated to affect 14% of the world population, making it the third most prevalent disease worldwide. About 50% of patients say they are dissatisfied with their current medication demonstrating a need for greater understanding of migraine pathophysiology and development of novel therapeutics. One particularly debilitating subset of migraine is chronic migraine, which is defined by having 15 or more headache days a month. A variety of chronic disease states have been found to result in shifts in neuroplasticity and altered dendritic morphology including a variety of chronic pain states. Microtubule dynamics are a key factor in cytoarchitecture. Microtubules are formed by heterodimers of α and β tubulin and may undergo a variety of post translation modifications including α-tubulin acetylation. Acetylated tubulin is associated with stable microtubules that are more resistant to damage or breakage. α-tubulin is acetylated by α -tubulin N-acetyltransferase I (αTAT1) and deacetylated through histone deacetylase 6 (HDAC6). Here we reveal a yet undiscovered cytoarchitectural basis for migraine pathophysiology and show that inhibition of HDAC6 could be an effective treatment for this disorder. In the nitroglycerin (NTG) model of chronic migraine we find altered cytoarchitecture such that neurons in key migraine processing regions have decreased neurite growth, which can be reversed by inhibition of HDAC6. In addition, in a model of migraine aura - cortical spreading depression (CSD) – we also observed decreased neurite growth in the cortex and administration of HDAC6 inhibitor not only decreased CSD susceptibility, but also reversed cytoarchitectural deficits. Our results demonstrate that migraine pathophysiology is associated with disruption of neuronal cytoarchitecture and that HDAC6 could serve as an effective therapeutic target.

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**GS6**

## INTERHEMISPHERIC FUNCTIONAL CONNECTIVITY IN THE ZEBRA FINCH BRAIN, ABSENT THE CORPUS CALLOSUM IN NORMAL ONTOGENY

Elliot Layden, Marc Berman, Ph.D. and Sarah London, Ph.D.

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Bilaterally symmetric intrinsic brain activity (homotopic functional connectivity; FC) is a fundamental feature of the mammalian brain's functional architecture. In mammals, homotopic FC is primarily mediated by the corpus callosum (CC), a large interhemispheric white matter tract thought to balance the bilateral coordination and hemispheric specialization critical for many complex brain functions, including human language. The CC first emerged with the Eutherian (placental) mammals ~160 MYA and is not found among other vertebrates. Despite this, other vertebrates also exhibit complex brain functions requiring hemispheric specialization and coordination. For example, the zebra finch (*Taeniopygia guttata*) songbird learns to sing from tutors much as humans acquire speech and must balance hemispheric specialization and coordination to successfully learn and produce song. We therefore tested whether the zebra finch also exhibits homotopic FC, despite lacking the CC. Resting-state fMRI analyses demonstrated widespread homotopic FC throughout the zebra finch brain across development, including within a network required for learned song that lacks direct interhemispheric structural connectivity. The presence of homotopic FC in a non-Eutherian suggests that ancestral pathways, potentially including indirect connectivity via the anterior commissure, are sufficient for maintaining a homotopic functional architecture, an insight with broad implications for understanding interhemispheric coordination across phylogeny.

**G- GRADUATE STUDENT COMPETETION**
**PD- POSTODOCTORAL STUDENT COMPETITION**
**UG- UNDERGRADUATE STUDENT COMPETITION**
**A/B- JUDGING GROUP A OR JUDGING GROUP B**

## POSTER ABSTRACT TITLES

### *THEME A. COGNITION AND BEHAVIOR*

**A1**
**THE BEHAVIORAL AND CARDIOVASCULAR EFFECTS OF A HIGH FATTY ACID DIET ON TRAUMATIC STRESS**
Cole Brashaw, Max Harlan, Carissa Bowie, Ryan Merideth, Malaz Kreiker, Josie Martin, Dr. Brian Sanders
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**A2-PDA**
**THE HDAC INHIBITOR SAHA ALLEVIATES DEPRESSION-LIKE BEHAVIOR AND NORMALIZES HDAC2 AND ACETYLATED HISTONE H3 LEVELS IN THE HIPPOCAMPUS DURING ALCOHOL WITHDRAWAL**
WY Chen[1], H Zhang[1], E Gatta[1], H Chen, SC Pandey[1,2], & AW Lasek[1]
*[1]University of Illinois at Chicago, Center for Alcohol Research in Epigenetics and Department of Psychiatry & [2]Jesse Brown VA Medical Center, Chicago, IL 60612 USA*

**A3 -UGA**
**CHRONIC ADMINISTRATION OF NICOTINE DOES NOT IMPROVE COGNITIVE FLEXIBILITY IN AN ATTENTIONAL SET-SHIFTING PARADIGM**
A. King[1], Maddux, J.M.[1]
*Department of Psychology and Neuroscience Program, Lake Forest College*

**A4-GA**
**MEDIAL ORBITOFRONTAL CORTEX TO NUCLEUS ACCUMBENS INTERACTIONS PERMIT RISK-ASSESSMENT BEHAVIORS**
M.K. Loh[1,2,3], N.C. Ferrara[1,2,3] and J.A. Rosenkranz[2,3]
*[1]School of Graduate and Postdoctoral Studies; [2]Center for the Neurobiology of Stress Resilience and Psychiatric Disorders, [3]Discipline of Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science*

**A5-UGB**
**BASAL AND STRESS-INDUCED CORTISOL AND ANXIETY-LIKE BEHAVIOR AFTER CANNABIDIOL (CBD) INJECTION IN ZEBRAFISH (*DANIO RERIO*)**
N. A. Opiola and M. L. Petrunich-Rutherford
*Department of Psychology, Indiana University Northwest*

**A6**
**ADOLESCENT STRESS SEX-SPECIFICALLY ALTERS PASSIVE BEHAVIORS IN X-LINKED CONGENIC RAT STRAIN OF PASSIVE COPING**
M. M. Mocchi[1,2], E. E. Redei[1]
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**A7-UGA**
**Effects of Prolonged Social Isolation: Sex Differences in Anxiety, Depression, and Sociability Behavior in Male and Female Adolescent Rats**
Eliska Mrackova, J. Amiel Rosenkranz, Ph.D.
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*Neuroscience Program, Lake Forest College, Lake Forest, IL 60045*

**A8-UGB**
**DISRUPTED SPATIAL LEARNING AND MEMORY IS AFFECTED BY TRAINING PRIOR TO INTERMITTENT HYPOXIA EXPOSURE**
Chinwendu U. Nwakudu, Alejandra Arias-Cavieres, Maggie A. Khuu, Alfredo J. Garcia III
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*2The Committee on Neurobiology, The University of Chicago, Chicago, IL.*

**A9 -UGA**
**SYSTEMIC ADMINISTRATION OF THE CANNABINOID CB1 RECEPTOR AGONIST WIN DURING ADOLESCENCE DISRUPTS THE MATURATION OF TRACE FEAR EXTINCTION BEHAVIOR**
A. Orozco[1], H. Molla[1-2], A. M. M. Miguelez Fernandez[1], A. Caballero[1], K. Y. Tseng[1]
*[1]Department of Anatomy & Cell Biology, University of Illinois at Chicago;[2] Department of Cellular and Molecular Pharmacology, Rosalind Franklin University*

**A10 -PDB**

**DEPRESSION DURING PREGNANCY IS ASSOCIATED WITH ALTERED GUT MICROBIOME AND IMMUNE SYSTEM**

Beatriz Penalver Bernabe[1], Shannon Dowty[2], Lacey Pezley[3], Zainab Shah[2], Elle Hill[1], Neil Gottel[1], Robert Gibbons[4], Lisa Tussing-Humphreys[3], Pauline M. Maki[2,5,6], Jack A. Gilbert[1,7]

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**A11 -UGB**

**A NOVEL FORM OF ALTRUISM: *AMPHIPRION OCELLARIS* NON-BREEDERS STEP-FATHER UNRELATED EGGS WHEN LEFT UNATTENDED**

E. Phillips[1, 2, 3], J.S. Rhodes[1, 2, 3]

*[1]University of Illinois at Urbana-Champaign [2]Beckman Institute for Advanced Science and Technology [3]Department of Psychology*

**A12**

**OBSERVING COGNITIVE CONTROL DURING IMPLICIT ASSOCIATION TEST**

Spencer Huynh[1]*, Austin Li[1]*, Grace Liu[1]*, Nguyen Tran[1]*, Jerrick Tran[1]*, Valentin Torres[1], Kristen Warren[2]

*[1]Walter Payton College Prep, [2]Northwestern University*

**A13-GB**

**Fear Reduces Food Consumption via Locus Coeruleus induced Heterosynaptic Plasticity.**

Ben Yang[1], Javier Sanchez-Pallida[1], Jyothisri Kondapalli[1], Yu Chen[1], Danielle R Schowalter[1], Eric Delpire[2], D. James Surmeier[1]

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## *THEME B. DEVELOPMENT*

**B1**

**Ephrin-A3 and -B2 Forward Signaling in Tonotopic Map Formation in the Mouse Cochlear Nucleus**

Amali M. Fernando, Natalia Hoshino, M. William Rochlin, Wei-Ming Yu

*Department of Biology, Loyola University Chicago*

**B2**

**Spiral Ganglion Neurons with Distinct Preferred Frequency Response Employ Different Strategies to Innervate the Cochlear Nucleus**

Samiha S. Mohammed, Darwin A. Gutierrez, Chloe K. Borcean, Annie J. Parng, Hyun-Ju Yoon, Wei-Ming Yu

*Department of Biology, Loyola University Chicago*

**B3**

**Relationships between neuronal birthdates and tonotopic position in the mouse cochlear nucleus**

Jennifer L. Scheffel, Austin R. Shepard, and Wei-Ming Yu

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**B4-UGA**

**Your face and my emotions: An adolescent perspective**

Uliana Solovieva, Alessandra Passarotti, Ph.D.

*Department of Psychology | Institute for Health and Research Policy (IHRP) | University of Illinois at Chicago Honors College*

**B5-UGB**

**DIFFERENTIAL EFFECT OF NATURAL VERSUS ARTIFICIAL VITAMIN E ON BRAIN GENE EXPRESSION OF DEVELOPING MICE**

Pragya Thaman, Catarina Rendeiro, Amanda Snyder, Heinrich Pinardo, Jonathan G. Mun[1,2,4], Kristy Du[1,2,4], Jennifer Zadeh, Sriram Chandrasekaran, Matthew Kuchan, Chron-Si Lai, Karen Schimpf , and Justin S. Rhodes[1,2,3,4]

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**B6**

**LIMITED NG2 GLIAL TROPISM OF RECOMBINANT ADENO-ASSOCIATED VIRAL (rAAV)-MEDIATED GENE DELIVERY FOR IN VIVO NEURONAL REPROGRAMMING**

Mentor Thaqi, Emily Reisenbigler, Renae Greene, and Daniel A. Peterson

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## *THEME C. DISORDERS OF THE NERVOUS SYSTEM*

**C1**

***APOE4* IMPAIRS ANGIOGENESIS *IN VITRO***

Sami Alahmadi[1], Felecia M Marottoli[1], Leon M Tai[1]
[1]*Department of Anatomy and Cell Biology, University of Illinois at Chicago, Chicago, IL 60612*

**C2-GA**

**Using Multimodal Serotonergic Drugs as Adjunct Treatments for Parkinson's Disease**

Feras Altwal, Alex Ritger, Nivea Falcao Voelkner, Janhavi Dhargalkar, Rabia Malik, Valentina Olivera, Anthony R. West
*Rosalind Franklin University, Department of Neuroscience, North Chicago, IL*

**C3-PDA**

**DISRUPTION OF NEONATAL NEUROGENESIS LEADS TO ANATOMICAL, CELLULAR & COGNITIVE IMPAIRMENTS THAT PERSIST INTO ADULTHOOD: IMPLICATIONS FOR NEURODEVELOPMENTAL DISORDERS**

Meagan L. Auger[1,2], Maric Tse[2], Shaina Cahill[2], Patrick T. Piantadosi[2], John Darby Cole[2], Olivia Li[2], Stephanie Miflores[2], Justin Jao[2], Jason Snyder[-2] & Stan B. Floresco[2]
[1]*Department of Anatomy & Cell Biology, University of Illinois-Chicago,* [2] *Department of Psychology & Brain Research Centre, University of British Columbia*

**C4-GB**

**CONTRIBUTING FACTORS TO REACHING DYSFUNCTION IN INDIVIDUALS WITH CHRONIC MODERATE TO SEVERE HEMIPARETIC STROKE**

Grace C. Bellinger and Michael D. Ellis
*Interdepartmental Neuroscience; Department of Physical Therapy and Human Movement Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL*

**C5-GA**

**DETERMINING THE NOVEL ROLE OF GALECTINS IN MEDIATING THE UNCONVENTIONAL SECRETION OF ALPHA-SYNUCLEIN**

Kevin Burbidge[1], Luc Bousset[2], Ronald Melki[2], Jeffrey H. Kordower[3,4], Edward Campbell[1]
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**C6-PDB**

**Parkinson's disease related LRRK2 regulates striatal intracellular signaling cascades**

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**C7-PDA**

**COMBINED ANTIRETROVIRAL THERAPY (TRIUMEQ) INCREASES FIRING AND $CA^{2+}$ INFLUX VIA VOLTAGE-GATED $CA^{2+}$ CHANNELS AMONG PYRAMIDAL NEURONS IN THE MEDIAL PREFRONTAL CORTEX OF RATS**

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**C8-PDB**

**SEX-SPECIFIC EFFECTS OF MICROBIOME PERTURBATIONS ON CEREBRAL AMYLOIDOSIS AND MICROGLIA PHENOTYPES**

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**C9**

**Sovateltide and its Neuro-regenerative Effects on Spinal Cord Injury**

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**C10-UGA**

**Insight into Parkinson's Disease from Yeasts: Combined impact of covalent modifications & familial mutations on α-synuclein**

Yoan Ganev, Rosemary Thomas, Estella Tcaturian, Chisomo Mwale, Joseph Mountain, Ariane Balaram, Alexandra Roman, Morgan Marshall, & Shubhik DebBurman
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**C11-PDA**

**GABAergic inhibitory interneurons as therapeutic target for Spinocerebellar Ataxia Type1**

Jimmy George, Chandrakanth Edamakanti, Marco Martina and Puneet Opal
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**C12**

**EFFECTS OF SWI1 PRION DOMAIN MUTANTS ON [SWI$^+$] MAINTENANCE AND FORMATION**

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**C13-GB**

**REGULATION OF BINGE ALCOHOL DRINKING BY ANAPLASTIC LYMPHOMA KINASE (ALK) AND SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3)**

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**C14-GA**

**XANTHOHUMOL PROTECTS CORNEAL EPITHELIAL CELLS AGAINST OXIDATIVE STRESS *IN VITRO***

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**C15**

**METERGOLINE MICROINJECTION INTO THE BASOLATERAL AMYGDALA IS SUFFICIENT TO MODEL PANIC DISORDER AS EVIDENCED BY SODIUM LACTATE-INDUCED TACHYCARDIA**

B. A. Heidenreich[1,2], D. R. Schuweiler[2], J. L. Butler[2], D. A. Snell[1], Y. Cam[1] and A. R. Adams[1]
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**C16-UGB**

**INVESTIGATING AGGREGATION OF BAF COMPLEX PROTEINS IN YEAST**

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**C17**

**STRAIN SPECIFIC ZIKA MEDIATED ASTROCYTE CELL DEATH**

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**C18**

**LRRK2 IS A CRITICAL REGULATOR OF DOPAMINE-DEPENDENT STRIATAL LONG TERM DEPRESSION AND STRIATAL MOTOR LEARNING**

Shuo Kang, Chuyu Chen, Bharanidharan Shanmugasundaram, Guoxiang Liu, Loukia Parisiadou
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**C19-GB**

**THE EFFECTS OF MYELINATING GLIAL CONNEXIN DEFICIENCY WITHIN THE CENTRAL NERVOUS SYSTEM**

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**C20-GA**

**DUSP4: an endogenous MAPK inhibitor and potential target for epilepsy therapy**

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**C21-GB**

**EVIDENCE FOR ATTENUATION OF BBB-DYSFUNCTION VIA CALPAIN-CATHEPSIN INHIBITION STRATEGIES RELEVANT TO TBI AND ADRD**

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**C22**

**OPTIMIZATION AND CHARACTERIZATION OF SELECTIVE ABCA1 INDUCERS AS POTENTIAL ALZHEIMER'S DISEASE THERAPEUTICS**

Cutler T. Lewandowski[1], Md. Wasim Khan[2], Manel Ben Aissa[1], Oleksii Dubrovskyi[1], Bhargava Karumudi[1], Mary Jo LaDu[3], Brian T. Layden[2], Gregory R.J. Thatcher[1]
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**C23-UGA**

**The Effect of Age, Sex and *APOE* Genotype on ApoE Lipidation and Ab Aggregation in an AD Transgenic Mouse Model**

Lumnie Lika, Allison Hansen, Naomi Faulk, Christine Pham, Deebika Balu, Ana Valencia-Olevara, and Mary Jo LaDu
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**C24-PDB**

**MODELING HEREDITARY SPASTIC PARAPLEGIA TYPE 3A USING ISOGENIC IPSCs**

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**C25-UGB**

**AD SYMPTOMATIC PROFILES THAT PREDICT THE DOMINANCE OF SEX OR *APOE* GENOTYPE IN EFAD MICE**

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**C26-GA**

**VOLTAGE INCREASES PROSACCADE ERROR RATE IN BILATERAL DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE**

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**C27-UGA**

**IH-DEPENDENT HIF1A SIGNALING IS IMPORTANT FOR NEURONAL GENERATION IN ADULT HIPPOCAMPAL NEUROGENESIS**

Thara Nallamothu[1], Maggie A. Khuu[1], Alfredo J. Garcia III[1]
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**C28**

**DIFFERENTIAL MODULATION OF DORSOLATERAL AND DORSOMEDIAL STRIATUM BY PARTIAL M1 MUSCARINIC RECEPTOR AGONIST ATTENUATES REPETITIVE BEHAVIORS IN THE BTBR MOUSE MODEL OF AUTISM**

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**C29-UGB**

**PRAZOSIN EFFECTIVENESS IN THE ALLEVIATION OF PTSD IS ELICITED BY MECHANISTIC PATHWAYS SEPARATE FROM STRESS AXIS ELEMENTS POMC, CRH, GR, AND CORTISOL**

Michael P. O'Daniel[1], Harold E. Olivey[2], Maureen L. Petrunich-Rutherford[1]
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**C30**

**CINNAMON AND ITS METABOLITE MITIGATES PARKINSONIAN PATHOLOGY IN A MPTP MOUSE MODEL OF PD VIA ASTROCYTIC GDNF**

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**C31-PDA**

**ELEVATED GLUTAMATE TRANSPORTER EXPRESSION IN FEMALES WITH DEPRESSION.**

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**C32**

**THE EFFECTS OF DUAL-TASK COGNITIVE INTERFERENCE ON GAIT AND TURNING IN HUNTINGTON'S DISEASE**

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**C33**

**NON-INVASIVE DETECTION OF SOLUBLE AMYLOID-β OLIGOMERS USING MRI IN THE NEW ZEALAND WHITE RABBIT**

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**C34-GB**

**TESTOSTERONE RECOVERS CHRONIC VESTIBULAR IMPAIRMENT FOLLOWING REPEAT MILD TRAUMATIC BRAIN INJURY**

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**C35**

**NEUROLOGICAL DEFICITS FOLLOWING SUBARACHNOID HEMORRHAGE MAY RESULT FROM DIFFERENTIAL EFFECTS OF BLOOD PRODUCTS ON CENTRAL NERVOUS SYSTEM CELL POPULATIONS**

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**C36**

**Heparan Sulfate Analog SPGG- a Potent Inhibitor of Human Cytomegalovirus Infection**

Dominik D. Kaltenbach[1, 2, 3], James Elste[2], Harsh Sharthiya[3], Michele Fornaro[3], Umesh R. Desai[2], and Vaibhav Tiwari[2]
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**C37**

**CELL TO CELL SPREADING OF TDP-43 C-TERMINAL FRAGMENTS MAY LEAD TO TOXICITY IN *CAENORHABDITIS ELEGANS***

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**C38**

**The Effect of Binge Alcohol and Traumatic Brain Injury on Hippocampal Neural Precursor Cell Proliferation and Survival**

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*Department of Neuroscience, Hines VA Hospital*

**C39-UGA**

**ROLE OF UNC5C, AN ALZHEIMER'S RISK GENE IN LATE-ONSET ALZHEIMER'S DISEASE IN A NOVEL MOUSE MODEL**

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**C40**

**ROLE OF MICROGLIA IN A MOUSE MODEL OF NEURONAL CEROID LIPOFUSCINOSES**

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**C41-UGB**

**Creating a Tool Kit for the Structural Characterization of Neurotoxic Amyloid Beta Oligomers in Alzheimer's disease**

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**C42-PDB**

**REGULATION OF BACE1 TRAFFICKING THROUGH C-TERMINAL MOTIFS**

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**C43**

**Exosomes secreted by diseased ALS cerebral cortex include messages to modulate disease progression**

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**C44**

**HORMONAL CONTRACEPTIVE USERS EXHIBIT BLUNTED REWARDING EFFECTS OF ALCOHOL**

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**C45-GA**

**INERTIAL SENSOR-BASED TREMOR AND BRADYKINESIA QUANTIFICATION AND POTENTIAL FOR EARLY DISEASE IDENTIFICATION IN FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME (FXTAS)**

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**C46**

**EFFICACY OF LONG TERM INTRATHECAL 2-HYDROXYPROPRL-ß-CYCLODEXTRIN TREATMENT ON BALANCE AND GAIT DEFICITS IN NIEMANN-PICK TYPE C1**

Jessica Joyce[1], Kathryn Wrobel[4], Nicollette Purcell[1], Medha Parulekar[4], Elizabeth Berry-Kravis[2,3], Joan A. O'Keefe[1,2]
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**C47**

**DEVELOPMENT OF A CRE-DEPENDENT TRANS-SYNAPTIC TRACER TO ANALAYZE THE OUTPUTS OF NEURONS CARRYING MUTATIONS**

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**C48**

**ABCA1 ACTIVATION IN THE CNS AS A THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE-LIKE PATHOLOGY IN A NOVEL TRANSGENIC MOUSE MODEL**

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**C49**

**THE AGE-DEPENDENT EFFECT OF *APOE* AND SEX ON ALZHEIMER'S DISEASE PATHOLOGY IN A NOVEL TRANSGENIC MOUSE MODEL**

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**C50**

**EFFECTS OF AGE, *APOE* GENOTYPE, AND SEX ON THE PLASMA LIPOPROTEIN PROFILE OF A NOVEL ALZHEIMERS DISEASE TRANSGENIC MOUSE MODEL**

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**C51**

**TOLL-LIKE RECEPTOR-4 ANTAGONISM AS A THERAPEUTIC FOR AD-ASSOCIATED NEUROINFLAMMATION**

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**C52**

**THE EFFECTS OF SEX AND *APOE* GENOTYPE ON THE GUT MICROBIOME IN EFAD TRANSGENIC MICE**

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**C53**

**THE EFFECT OF AGE, SEX, AND *APOE* GENOTYPE ON Aβ PATHOLOGY IN AN ALZHEIMERS DISEASE TRANSGENIC MOUSE MODEL**

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**C54**

**OAb IN HUMAN PLASMA AS A MECHANISTIC BIOMARKER FOR ALZHEIMER'S DISEASE IN HUMAN PLASMA**

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**C55-GB**

**BINGE ALCOHOL DRINKING ALTERS THE EXPRESSION OF THE TRANSCRIPTION FACTOR ORTHODENTICLE HOMEOBOX 2 (OTX2) IN THE VENTRAL TEGEMENTAL AREA.**

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**C56**

**SEIZURE SUSCEPTIBILITY IN A PCDH19 EPILEPSY MOUSE MODEL**

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**C57-GA**

**DEVELOPMENT OF A NOVEL NAMPT ACTIVATOR AS A POTENTIAL ALZHEIMER'S DISEASE THERAPEUTIC**

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## *THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS*

**E1 -UGA**

**FEMINIZATION OF BEHAVIOR, PLASMA SEX HORMONE PROFILE, AND GONADAL HISTOLOGY FROM ENDOCRINE DISRUPTION IN SEXUALLY LABILE ANEMONEFISH**

Rhodes JS (1), Gonzalez JA (1), Lange DA(1), Bhuvanagiri SA (1), Kaur A (1), Parker CG (1), Rosenfeld CS (2), Martyniuk CJ (3), Denslow ND (3)
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(3) Department of Physiological Sciences, University of Florida, Gainesville, FL, USA

**E2-PDA**

**THE SUBFORNICAL ORGAN RECRUITS PHASIC DOPAMINE SIGNALLING TO WATER AVAILABILITY VIA MULTI-ORDER PATHWAYS**

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**E3-UGB**

**GENETIC DISSECTION OF THE CONTRIBUTION OF CENTRAL AND PERIPHERAL CIRCADIAN CLOCKS TO *DROSOPHILA* FEEDING RHYTHMS**

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**E4-GB**

**CENTRAL EXENDIN-4 SELECTIVELY SUPPRESSES CUE-EVOKED PHASIC DOPAMINE SPIKES AND RESULTANT BEHAVIOR**

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**E5-UGA**

**GESTATIONAL EXPOSURE TO POLYCHLORINATED BIPHENYLS SHOW SEX AND BRAIN REGION SPECIFIC EFFECTS ON DOPAMINE MODULATING SYSTEMS IN ADOLESCENT RATS**

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**E6-GA**

**ACTIVE FEMINIZATION OF THE PREOPTIC AREA OCCURS INDEPENDENTLY OF THE GONADS IN *AMPHIPRION OCELLARIS***

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**E7-UGB**

**Elevated cortisol and alpha-amylase levels in behaviorally inhibited individuals exposed to physiologic stress: Implications for enhanced associative plasticity with anxiety vulnerability**

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**E8**

**DEVELOPMENTAL EFFECTS OF POLYCHLORINATED BIPHENYLS (PCBS) ON ACTIVATIONAL MORPHOLOGY OF MICROGLIA IN THE ADULT BRAIN**

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## *THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA*

**F1-GB**

**NMDAR-ACTIVATED PP1 DEPHOSPHORYLATES GLUN2B TO MODULATE NMDAR-PLASTICITY**

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**F2-PDB**

**THE ROLE OF POTASSIUM IN THE SYNAPTIC TRANSMISSION BETWEEN TYPE I HAIR CELL AND CALYX IN VESTIBULAR SYSTEM OF TURTLES**

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**F3-GA**

**ANTIOXIDANTS PROTECT AGAINST REACTIVE ASTROCYTOSIS-INDUCED SENSITIZATION TO OXIDATIVE STRESS**

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**F4**

**THE REGULATION OF NMDA RECEPTORS SYNAPTIC AND EXTRASYNAPTIC DISTRIBUTION**

Pavla Hubalkova[1], Andrew M. Chiu[1], John A. Gray[2], Levi Barse[1], and Antonio Sanz-Clemente[1]
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**F5-GB**

**EXTRACELLULAR AND INTRACELLULAR SPHINGOSINE-1-PHOSPHATE DISTINCTLY REGULATES EXOCYTOSIS IN CHROMAFFIN CELLS**

Zhongjiao Jiang, Taylor L. Delaney, Liang-Wei Gong.
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**F6-GA**

**Understanding the molecular mechanisms involved in the intercellular transport of the Activity-Regulated Cytoskeleton-associated (Arc) protein**

Michael Long and Edward Campbell
*Loyola University of Chicago*

**F7**

**CHARACTERIZATION OF DE-IDENTIFIED HUMAN BRAIN CULTURE BY IMMUNOFLUORESCENCE**

Tina Moazezi[1], Zylfi Memedovski[1], Laura Phelps[2], Alice Meyer[3], Ellen Andrews[3], Zachary Jaffa[4], Donald Schleicher[4], Diane Sierens[4], and Alejandro M. S. Mayer[2]
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**F8-GB**

**Matrix Metalloproteinase-9 Release From Ultrapure *Porphyromonas gingivalis* Lipopolysaccharide (LPS) Treated Rat Brain Microglia *in vitro***

Zylfi Memedovski[1], Evan Czerwonka[1], Shiting Liao[2], Jin Han[2], Joshua Mayer[2], Mary L. Hall[3], and Alejandro M.S. Mayer[1,3]
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**F9**

**V-ATPase dysfunctions contribute to lysosome-autophagosome mediated proteinopathy in early stages of Alzheimer's disease pathogenesis.**

Sarah Mustaly[1], Nicolas Kapecki, Kenneth D. Beaman[2], Alice Gilman-Sachs[2], John McDaid[1], Sean Schrank[1], Robert Marr,[1] Grace Stutzmann[1]
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**F10-GA**

**THE ROLE OF ASTROCYTE CALCIUM SIGNALS IN THE PRODUCTION OF INFLAMMATORY FACTORS AND MODULATION OF SYNAPTIC FUNCTION**

Michaela Novakovic[1], Murali Prakriya[1]
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**F11**

**β-CATENIN NEGATIVELY REGULATES IL-6 AND IL-8 EXPRESSION AT TRANSCRIPTIONAL LEVEL AND INDUCES REACTIVITY IN HUMAN ASTROCYTES**

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**F12-PDA**

**IMPAIRED M-CURRENT IN KCNQ2 EPILEPTIC ENCEPHALOPATHY EVOKES DYSHOMEOSTATIC MODULATION OF EXCITABILITY IN PATIENT-DERIVED NEURONS**

D. Simkin[1,2], T. J. Searl[2], B. N. Piyevsky[1], M. Forrest[3], M. Schwake[1], G. L. Robertson[1], P. Penzes[3], J. J. Millichap[4], A. L. George, Jr.[2] and E. Kiskinis[1]
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**F13-GB**

**ESTRADIOL ENHANCES ETHANOL-STIMULATED FIRING OF VTA NEURONS THROUGH AN ERα AND MGLUR1-DEPENDENT MECHANISM**

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**F14-GA**

**THE ROLE OF STORE OPERATED CALCIUM ENTRY IN ASTROCYTE GENE EXPRESSION**

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## *THEME G. NOVEL METHODS AND TECHNOLOGY DEVELOPMENT*

**G1**

**Astrocyte-derived HIV evolution in humanized mice**

Hannah J. Barbian, Victoria Lutgen, Srinivas D. Narasipura, Lena Al-Harthi
*Rush University Medical Center*

**G2**

**THE INFLUENCE OF THE VAL66MET POLYMORPHISM OF THE BRAIN DERIVED NEUROTROPHIC FACTOR GENE ON PATHOLOGY IN AN ISOGENIC HUMAN IN VITRO MODEL OF NEUROTRAUMA**

Franz Colin K.[1], Phillips Jack K.[2], Cotton Kristen Y.[1], Valladeres Maria J. Q.[1], Finan John D.[2]
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**G3**

**ILLUMINATING THE MOLECULAR LANDSCAPE OF INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELLS: A MULTIFACETED APPROACH**

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**G4-GB**

**QUANTIFYING THE ABILITY OF A LINEAR CLASSIFIER TO DISCRIMINATE BETWEEN SHOULDER TASKS IN PARETIC AND NON-PARETIC ARMS OF INDIVIDUALS WITH CHRONIC HEMIPARETIC STROKE**

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**G5-GA**

**CEREBRAL ORGANOIDS AS A MODEL TO STUDY FOCAL CORTICAL DYSPLASIA**

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**G6**

**A NETWORK ANALYSIS OF SNPS IN MULTIPLE GENES REVEALS POLYGENIC EFFECT ON PAIN IN SICKLE CELL DISEASE**

Nilanjana Sadhu[1], Ying He[1,2], Yingwei Yao[3], Diana J. Wilkie[3], Robert E. Molokie[1,2,4,5], Zaijie Jim Wang[1,2]
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**G7-UGA**

**ACCURACY OF DEEPLABCUT MACHINE LEARNING TO MARKERLESSLY TRACK FOOT POSITION DURING SKILLED WALKING.**

Lake R[1], Adamczyk N[1], Blackwell AA[1], Osterlund J[1], Segismundo A[2], Foecking E[2,3], Hastings P[4], Wallace DG[1]
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## *THEME H. SENSORY AND MOTOR SYSTEMS*

**H1**

**RESPONSES OF NEURONS IN SPINAL TRIGEMINAL NUCLEUS INTERPOLARIS (SpVi) TO STIMULATION OF THE WHISKERS IN DIFFERENT DIRECTIONS AND AT DIFFERENT SPEEDS**

Trevor J. Alston[1], Chris S. Breese[2†], Kevin J. Kleczka[1,3], Admir Resulaj[2] and Mitra J.Z. Hartmann[1,3]
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**H2-UGB**

**STRUCTURAL DIFFERENCES IN MITOCHONDRIA ADJACENT TO THE CUTICULAR PLATE IN TYPE 2 HAIR CELLS**

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**H3**

**FUNCTIONAL IMPACT OF DIVERSE SODIUM CURRENTS ON VESTIBULAR AFFERENT NEURON FIRING PATTERNS**

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**H4-GB**

**SINGLE LOW DOSE OF SIMULATED SPACE RADIATION DISRUPTS FINE MOTOR CONTROL**

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**H5-UGA**

**INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELL LOSS IN THE 5xFAD MOUSE MODEL FOR ALZHEIMER'S DISEASE**

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**H6-UGB**

**MTK Analysis of Interactions Between Crista Junctions in Subcuticular Mitochondria**

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**H7 -UGA**

**THERMOSENSORY EFFECTS ON DROSOPHILA CIRCADIAN BEHAVIOR**

Evan Kaspi, Michael H. Alpert, Dominic D. Frank, Ravi Allada, Marco Gallio
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**H8**

**Juxtaposing Energy Models to Describe Inner Ear Hair Cell Mitochondria**

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**H9-GA**

**NOTCH SIGNALING IN ZEBRAFISH OLFACTORY NEUROGENESIS**

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**H10-GB**

**Functional divergence at the mouse type 6 retinal bipolar cell terminal**

David Swygart, Greg Schwartz, Rachel Wong, Wan-Qing Yu, Sharm Knecht
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**H11-GA**

**IMPLICATION OF DOPAMINERGIC SYSTEM ON MOTOR PERFORMANCE DURING HABITUATION TO FORCED EXERCISE**

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**H12-UGB**

**FREQUENCY-DEPENDENT EFFECTS OF BACKPROPAGATING ACTION POTENTIALS ON SENSORY ENCODING**

Maisam Yousef, Wolfgang Stein, Margaret L. DeMaegd
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**H13**

**CHANGES IN SPINAL EXCITABILITY FOLLOWING STROKE**

T. Zuleger[1, 3], M. Lamberti[3], Y. Moon[3], K. McKenzie[3], L. Yingling[3], A. Jayaraman[1,2,3]
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**H14-UGA**

**EXPLORING A RAT MODEL OF THE BYSTANDER EFFECT**

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# POSTER ABSTRACTS

## *THEME A. COGNITION AND BEHAVIOR*

**A1**

### THE BEHAVIORAL AND CARDIOVASCULAR EFFECTS OF A HIGH FATTY ACID DIET ON TRAUMATIC STRESS

Cole Brashaw, Max Harlan, Carissa Bowie, Ryan Merideth, Malaz Kreiker, Josie Martin, Dr. Brian Sanders

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Post Traumatic Stress Disorder (PTSD) is a mental illness known to develop in some individuals following periods of trauma. Symptoms can include flattened affect, negative thoughts and feelings, angry outbursts, etc. Additionally, traumatic stress is associated with a higher risk of cardiovascular disease. Given the prevalence of these disorders, it's important to investigate factors that may affect these disease outcomes. Previous studies have shown that there is a significant, cross-sectional relationship between unhealthy dietary patterns and poorer mental health in adolescents. Fatty Acids (Omega-3s), have been suspected to produce effects including modulation of neurotransmitters, anti-inflammation and manipulation of cardiac myocytes. The purpose of this study was to explore whether a high fatty acid diet has a protective effect against negative behavioral and cardiovascular effects following exposure to a traumatic event. In rodents, a common way to induce PTSD-like symptoms is a single prolonged stress (SPS). The four treatment groups in this study consisted of rodents that were maintained on a high fatty acid or control diet, with animals in each condition exposed to SPS or not. One week following the SPS, a battery of tests for anxiety- and depressive-like behaviors were performed. In addition, cardiovascular measurements were collected during conditions of rest and stress. Data indicate that animals exposed to the SPS exhibited greater locomotion and that a diet high in fish oil exerted a cardio-protective effect. Studies such as this can provide insight into the role of diet and fatty acids in modulating harmful psychological outcomes following traumatic stress.

*This work was supported by the College of Arts and Sciences and The Department of Psychology and Neuroscience at Drake University*

**A2-PD**

### THE HDAC INHIBITOR SAHA ALLEVIATES DEPRESSION-LIKE BEHAVIOR AND NORMALIZES HDAC2 AND ACETYLATED HISTONE H3 LEVELS IN THE HIPPOCAMPUS DURING ALCOHOL WITHDRAWAL

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Withdrawal from chronic alcohol drinking leads to a negative affective state defined by depression, anxiety and anhedonia. This negative affective state can contribute to relapse to alcohol abuse, thus continuing the cycle of addiction. Alcohol withdrawal causes changes in acetylation of the N-terminal tails of histone proteins in the brain, leading to alterations in the expression of key genes involved in depression. These epigenetic neuroadaptations are also observed in stress-induced models of depression. Notably, treatment with histone deacetylase (HDAC) inhibitors reduces depression-like behavior in rodents. The purpose of this study was to examine the levels of acetylation of histone H3 lysine 9 (H3K9ac) and expression of 10 HDAC genes in the hippocampus, an alcohol-sensitive region of the brain involved in depression, and to determine if treatment with a pan-histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA) can alter H3K9ac and alleviate depression-like behavior during withdrawal from chronic alcohol drinking. Male Sprague-Dawley rats were treated with the Lieber-DeCarli ethanol liquid diet for 15 days and then underwent alcohol withdrawal for 24 hours. Total H3K9ac levels were decreased in the hippocampal CA3 region during withdrawal as measured by immunogold labeling. Corresponding increases in HDAC2 (mRNA and protein) and HDAC6 (mRNA) also occurred during withdrawal. Treatment with SAHA during withdrawal normalized levels of both H3K9ac and HDAC2 protein. We next examined depression-like behavior during withdrawal using the sucrose splash and sucrose preference tests. Withdrawal from chronic alcohol drinking decreased grooming time and sucrose preference, indicative of depression. Treatment with SAHA during withdrawal alleviated depression-like behavior. These results demonstrate that withdrawal from chronic alcohol drinking causes epigenetic alterations in the hippocampus and depression-like behavior that can be normalized by treatment with an HDAC inhibitor. This investigation provides a novel epigenetic-based target for the treatment of alcohol withdrawal-related depression.

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**A3 -UG**

### CHRONIC ADMINISTRATION OF NICOTINE DOES NOT IMPROVE COGNITIVE FLEXIBILITY IN AN ATTENTIONAL SET-SHIFTING PARADIGM

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A common way to measure cognitive flexibility is through an attentional set-shifting task (ASST). Studies demonstrate that administering nicotine before the task improves performance; however, no studies have examined the effect of chronic administration when rats are tested drug-free. To assess the effect of prior chronic nicotine administration, daily nicotine (0.4 mg/kg) or saline injections were given to rats across 14 days, and tests were conducted drug-free. Due to reports of neuroplastic changes in brain reward circuits induced by repeated nicotine administration, this regimen was predicted to improve performance in the ASST. However, this treatment did not influence performance. A locomotor activity control experiment was then conducted to determine if nicotine had an effect in a validated behavioral paradigm known to be sensitive to nicotine exposure. A subset of the saline and nicotine pre-treated rats were given an acute nicotine injection and observed for locomotor activity. In agreement with previous studies, nicotine naïve rats demonstrated less locomotor activity than nicotine pre-treated rats in response to this single nicotine injection. This demonstrates the

nicotine had a behavioral effect in a paradigm separate from the ASST, which shows that the nicotine pre-treatment regimen was functionally effective. Considered together with previous work, our findings suggest that nicotine must be present at test in the ASST to enhance behavior.

**A4-G**
**MEDIAL ORBITOFRONTAL CORTEX TO NUCLEUS ACCUMBENS INTERACTIONS PERMIT RISK-ASSESSMENT BEHAVIORS**

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The ability to assess risk and predict potential negative consequences heavily biases the decision-making process and is evolutionarily important for survival. The nucleus accumbens (NAc) supports reward-directed actions, and its activity is reflective of risky behavior and reward-seeking. These behaviors are influenced by the input from several brain regions to the NAc. Namely, the medial orbitofrontal cortex (MO) contributes to behavior guided by reward probability and sends direct projections to the NAc, suggesting MO input to the NAc may play a key role in evaluating risk. Therefore, a clearer understanding of MO-NAc interactions is essential to elucidate the neural mechanisms underlying risk assessment. In this study, we investigated the interactions between the MO and NAc in gating risk assessment behaviors. Using a disconnection approach, we found that MO-NAc interactions may be necessary for risk assessment behaviors in rats, such as stretch and attend postures (SAP) measured on the elevated plus maze (EPM). In line with these findings, we found that adolescent subjects, who characteristically have delayed frontal lobe maturation and potentially less cortical input influence, also demonstrated less risk assessment behaviors on the EPM. A balance between reward versus risk elements is weighed during decision-making, perhaps reflected by the interactive nature of cortical and limbic inputs into the NAc. Therefore, we investigated if MO input to NAc interactions influence circuits that underlie reward-seeking using *in vivo* extracellular single-unit electrophysiology. To investigate the nature of MO influence on NAc activity, we stimulated basolateral amygdala (BLA) input to the NAc to evoke NAc firing, as these projections facilitate reward-seeking behaviors and have been shown to attenuate cortical-NAc interactions. We hypothesized that MO stimulation will diminish BLA-evoked NAc spiking. To accomplish this, single pulses at increasing interstimulus intervals (ISI; 1-, 6-, 11-, and 21-ms) and frequency-varying trains (5, 10, 20, 40, and 60 Hz) were delivered to the MO to assess its effects on BLA-evoked NAc spiking. We found that MO single-pulse stimulation enhanced BLA-evoked NAc spiking in a time-dependent manner that was optimal at the11-ms ISI. Shifts to BLA-evoked NAc spike probability by MO train stimulation were also frequency-dependent. Further, MO train stimulations resulted in a bimodal distribution of BLA-evoked NAc activity, where half of BLA-responsive NAc neurons showed diminished spike probability to MO train stimulation while the remainder showed an increase. This suggests that the timing and frequency of MO activity are important in modulating NAc activity. Due to the behavioral role of both MO and BLA-NAc projections, these interactions may contribute to the neurobiological mechanism in the incorporation of risk information to influence reward-directed actions.

**A5-UG**
**BASAL AND STRESS-INDUCED CORTISOL AND ANXIETY-LIKE BEHAVIOR AFTER CANNABIDIOL (CBD) INJECTION IN ZEBRAFISH (*DANIO RERIO*)**

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Cannabidiol (CBD) has recently gained popularity for treatment of various disorders, including stress-induced conditions like anxiety. CBD is the one of the main psychoactive ingredients found in the *Cannabis sativa* plant, and acts on the endogenous cannabinoid (eCB) system in the body. The eCB system plays a role in many brain and behavioral functions, including the stress response. Anxiety disorders are often associated with dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, leading to unpredictable stress responses. Although CBD elicits anxiolytic effects, more studies are needed to determine whether the clinical effects are mediated by HPA normalization. Vertebrates such as zebrafish (*Danio rerio*) share a high degree of functional and genetic homology with humans, and therefore make excellent research subjects when studying the eCB system. Thus, we set up a paradigm involving exposure of zebrafish to either CBD or a vehicle. Intraperitoneal (IP) injection was chosen for the procedure due to the lipid nature of CBD. After an hour of habituation following the injections, we subjected the fish to a nine-minute stress test or a control condition and measured their behavior in a light/dark assay. Upon observing their behavior in the light/dark tank for fifteen minutes, the fish were euthanized and their cortisol levels measured via ELISA assay. We predicted that the stress exposure would increase cortisol and increase anxiety-like behavior, and that injection with CBD would attenuate these effects. The results from this study may further the understanding of the mechanisms mediating clinical efficacy of CBD.

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**A6**
**ADOLESCENT STRESS SEX-SPECIFICALLY ALTERS PASSIVE BEHAVIORS IN X-LINKED CONGENIC RAT STRAIN OF PASSIVE COPING**

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Stress during adolescence is thought have lasting negative behavioral effects and increase risk for developing numerous mood disorders, but it is also shown to promote resilience to stress in adulthood. The individual differences that cause these paradoxical effects of susceptibility and resilience is currently unknown. One potential mechanism is the beneficial effects of active coping and the detrimental effects of passive coping in the management of stress, with the differing consequences of stress on the individual. The current study employs a congenic rat strain predisposed to passive coping behaviors and increased anxiety that was generated by transferring an X- chromosomal region of a rat exhibiting anxiety and passive coping

strategies into a background strain with active coping strategies. We investigated the interaction of genetic predisposition to anxiety and passive coping and acute stress (6-minute forced swim stress) during adolescence (31-33 days of age) on adult anxious, social, and coping behaviors. Our results indicate that contextual fear memory increased and anxiety decreased for stressed males and females compared to controls. Furthermore, stressed males tended to show increased social recognition memory while stressed females demonstrated increased passive coping seen as immobility behavior in the forced swim test. Thus, adolescent stress alters genetic predisposition to passive coping by worsening it in females, but decreases anxiety-like behaviors in both males and females. Future transcriptional analyses of genes within the congenic locus with sequence variations between the parental strains will help to identify molecular pathways underlying this sex-specific reactivity to stress.

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**A7-UG**

**Effects of Prolonged Social Isolation: Sex Differences in Anxiety, Depression, and Sociability Behavior in Male and Female Adolescent Rats**

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Clinically, early life stress such as prolonged social isolation is regarded as a risk factor for the development of depression and anxiety. Extensive research has found that sex differences in depressive-like behaviors emerge during adolescence, with females more at risk than males. Despite the rising social isolation and loneliness across the world, the causes and effects of social isolation in adolescence remain still poorly understood. Therefore, the purpose of this research project was to determine whether the timing or duration of social isolation, sex of the animal or the housing condition would affect the development of depressive-like behaviors. Overall, the Open Field test (OF) revealed significant differences due to the social isolation (SI) condition after 4 weeks of SI. Furthermore, the duration of social isolation (1-week vs 4-week), condition (group housed (GH) versus socially isolated (SI)) and sex (male vs female) had significant effects on social behavior both in the Social Interaction test as well as the Conditioned Place Preference test (CPP). Appetitive conditioning with anxiogenic bright light showed that after 4 weeks of social isolation both males and females' number of active nose pokes significantly dropped due to the presence of the bright light stressor and returned to the baseline when a bright light was turned off. Overall, this research adds a new insight into the understanding of sex differences associated with prolonged social isolation and subsequent depressive-like behaviors. Moreover, future research will focus on determining the differences between socially isolated males and females using the deltaFosB staining as an indicator of neuronal activation in response to chronic stress in the Basolateral Amygdala (BLA).

**A8-UG**

**DISRUPTED SPATIAL LEARNING AND MEMORY IS AFFECTED BY TRAINING PRIOR TO INTERMITTENT HYPOXIA EXPOSURE**

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The working theory for memories is that they are encoded in the hippocampus as working memory before they are consolidated into long-term memory and stored in the neocortex. Intermittent hypoxia (IH) is a common event occurring with untreated sleep apnea, a clinical condition commonly associated with cognitive deficits in learning and memory. Rodents exposed to IH, as a model for sleep apnea, exhibit impairments in spatial learning and memory. However, it is unclear if IH impairs encoding or consolidation. The objective of this ongoing study is to determine whether training prior to IH exposure influences performance on spatial learning tasks following IH. We hypothesize that while IH impairs spatial learning and memory, training prior to exposure will improve performance on spatial memory tasks following IH. To test this, we developed a Barnes maze protocol to assess spatial learning and memory in mice preceding and succeeding exposure to 10 days of IH (IH10). Before IH10, variance between control and IH10 mice was not evident during the probe trial in the latency to initial entry into the exit zone. Variance was also not evident when performance in the probe trial of the second session was compared to the performance in the probe trial of the first session for both mice. However, during the first training trial of the second maze session, IH10 treated mice (n=4) took longer to find the exit compared to the probe trial of the previous session. Conversely, mice naive to IH10 exhibited similar performance between sessions (n=5). LTP measured in area CA1 was suppressed in hippocampal brain slices from mice exposed to IH (control 162%±12% (n=7) vs. IH 122±7% (n=11)). These results indicate that IH disrupts consolidation, not encoding, despite suppressed LTP following IH indicating an impairment in the hippocampus.

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**A9 -UG**

**SYSTEMIC ADMINISTRATION OF THE CANNABINOID CB1 RECEPTOR AGONIST WIN DURING ADOLESCENCE DISRUPTS THE MATURATION OF TRACE FEAR EXTINCTION BEHAVIOR**

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During the transition from adolescence to adulthood, the prefrontal cortex (PFC) undergoes marked development accompanied by increased risk for developing psychiatric disorders which display prefrontal dysfunction. In preclinical studies, administration of synthetic cannabinoids during adolescence has been shown to disrupt the functional connectivity between the ventral hippocampus and PFC when tested in adulthood (Cass et al., *Molecular Psychiatry* 2014). Accordingly, a disruption of PFC-mediated extinction of trace fear memory emerged. What remains unknown is whether the effect of

adolescent cannabinoid exposure on the PFC can be observed immediately or it is manifested only when reaching adulthood. To fill this gap in knowledge, i.p. injection of the synthetic CB1 receptor agonist WIN was delivered once daily for 5 days to adolescent (postnatal days P35-40) rats at 2 mg/kg. Behavioral assessment of ventral hippocampal-PFC function was determined using the trace fear conditioning and extinction paradigm at 24 hours or 10 days post-last injection of WIN or vehicle. Results show that the rate of extinction was significantly decreased in WIN-treated rats when compared to vehicle controls. Moreover, rats exposed to WIN had extinction rates equivalent to those observed in P30-35 juveniles. Collectively, the results show that exposure to CB1 receptor cannabinoids during adolescence is sufficient to elicit behavioral deficits which can be detected shortly after administration. However, the disruption endures and becomes more apparent in adulthood as ventral hippocampal-PFC functional connectivity is recruited to regulate behavior.
*This study is supported by NIH grants R01-MH086507 and R01-MH105488 to KYT.*

**A10-PD**
**DEPRESSION DURING PREGNANCY IS ASSOCIATED WITH ALTERED GUT MICROBIOME AND IMMUNE SYSTEM**

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One in ten women experience depression during their pregnancy or antenatal depression (AND). AND confers significant risks to mother (e.g., suicide) and child (e.g., preterm birth, low birth weight, infant neurodevelopmental disorders), yet only 5% of women with AND receive adequate care. Despite increasing evidence linking depression to the gut microbiome, this research has not been extended to the perinatal period. Our aim was to examine gut microbial structure and composition and the activity of the immune system in pregnant women with and without AND. Sixty-four pregnant women provided fecal and blood samples at their first (<16 gestational weeks) and second trimesters (24-28 gestational weeks) and completed the Computerized Adaptive Diagnostic Test for Major Depression Disorder (MDD) diagnostic screening tool (CAD-MDD). Using DADA2, 16S rRNA amplicon sequence analysis of fecal DNA, DADA2 identified exact sequence variants (ESVs) that were correlated against AND using Generalized Linear Models (GLM). GLM were adjusted by age, gestational weeks and BMI and all multiple comparisons were corrected for false discovery rate. AND rates were 15.6% (T1) and 10.6% (T2). While Shannon index was not associated with AND, the average Bray-Curtis distance was inversely associated with AND (p=0.02). Several ESV were significantly different in women with AND compared with those without. For instance, *Paraprevotella* and *Faecalibacterium* were enriched and depleted respectively in women with AND overall, while *Lactobacillus* was only depleted at their first trimester. Additionally, TNF-alpha was negatively associated with AND during the first trimester (p-value<0.1), and IL-6 and IL-12(p70) were increased in mothers with AND in the second trimester (p-value<0.05). In summary, we provide new evidence that AND is associated with altered gut microbial and immune systems that vary with gestational age and could serve as a future assay to detect AND in clinical settings.
*The current work is funded by the Arnold O. Beckman Postdoctoral Fellowship Award and the NIH R03HD095056*.

**A11-UG**
**A NOVEL FORM OF ALTRUISM: *AMPHIPRION OCELLARIS* NON-BREEDERS STEP-FATHER UNRELATED EGGS WHEN LEFT UNATTENDED**

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Darwinian theory predicts that individuals will display energetically costly parental care behaviors towards genetically related offspring rather than unrelated offspring. Curiously, after removing the breeding male, *Amphiprion* non-breeders have been observed step-fathering unrelated offspring. This was assumed to be due to coercion by the breeding female. The purpose of this study was to eliminate the external motivation by the female to provide parental care and determine if non-breeders would step-father when both the male and female are removed, providing an example of internally motivated altruism. Groups of three individuals (male, female, and non-breeder) were videotaped daily for three spawn cycles. During the first spawn cycle, groups remained undisturbed, and in the second spawn cycle, the male was removed. In the third spawn cycle, the male and the female were removed leaving the non-breeder alone with the unrelated eggs. The non-breeder began to care for the eggs after the male was removed and further increased parental care after removal of the male and female. Higher rates of egg loss were observed after removal of the male, but these rates were comparable to the performance of first-time fathers. Our results show that when left alone, non-breeders will step-father unrelated eggs, providing a novel example of altruism potentially due to the highly stereotyped instinct for parental care in this species.
*This study was supported from indirect costs recovered from NIH grants and private funding to J.S.R., and the Janssen Family Undergraduate Award.*

**A12**
**OBSERVING COGNITIVE CONTROL DURING IMPLICIT ASSOCIATION TEST**

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Implicit biases have a large impact on the decision-making process. The Implicit Association Test (IAT) measures a test subject's implicit bias towards dark and light skin tones. Recent research indicates that test subjects with higher implicit biases use more cognitive control during the IAT than test subjects with less implicit biases. Additional research indicates that cognitive control and decision making are associated with increased high beta power (freq. 22-38 Hz), and fMRI activity in

the prefrontal cortex. We aim to test the hypothesis that high beta power increases in the prefrontal cortex during this task relative to rest in individuals with higher implicit bias. In order to test this theory, we use an Emotiv EPOC+ Electroencephalograph (EEG) to compare the percent change in high Beta power during a participant's resting state and while they take the IAT. Results show that test subjects who have higher implicit bias tended to have a greater percent change of prefrontal high beta power from rest than those who had less implicit bias. This supports the research that individuals with greater implicit bias may need more cognitive control to make unbiased decisions. Future studies should expand on this preliminary data by including a larger, more diverse population and better control over the testing environment.

*This study is funded through Northwestern University Brain Awareness Outreach, the Northwestern University Interdepartmental Neuroscience Program, and the Chicago chapter of the Society for Neuroscience*

**A13-G**

**Fear Reduces Food Consumption via Locus Coeruleus induced Heterosynaptic Plasticity**

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How emotional states (such as fear and stress) affect need states (such as feeding) is not well understood. Loss of weight and appetite has been reported in patients with posttraumatic and other stress disorders as well as in animals that are fear conditioned or treated with other stressors. The brainstem locus coeruleus (LC) nucleus and its neighboring pontine parabrachial nucleus (PBN) are both known to mediate stress responses and threat signals, as well as to regulate feeding. They also both receive inputs from the central nucleus of amygdala (CeA), which play pivotal roles in fear and stress. In this study, we used fear conditioning as an animal model to explore how the intrinsic activities of LC and PBN and synaptic inputs from CeA to them changed under fear and contributed to feeding.

We first found that fear conditioning reduced consumption of regular food but not palatable food. We found no change of intrinsic activities of LC and PBN after fear conditioning. We then found that CeA has inhibitory inputs to PBN but not LC and CeA-PBN synapses were depressed after fear conditioning. Furthermore, we found LC has both glutamatergic and noradrenergic inputs to PBN, and activation of α1-adrenoceptors in PBN induced endocannabinoid-mediated long-term depression (eCB-LTD) at CeA-PBN synapses. Knocking-out type 1 cannabinoid receptors (CB1Rs) specifically in CeA diminished both reduction of food consumption after fear conditioning and loss of weight after α1-adrenoceptor agonist injection. Collectively, we found a heterosynaptic mechanism of plasticity at CeA-PBN synapses induced by LC that mediates fear-induced reduction of feeding.

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## *THEME B. DEVELOPMENT*

**B1**

**Ephrin-A3 and -B2 Forward Signaling in Tonotopic Map Formation in the Mouse Cochlear Nucleus**

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Sound information is transmitted to the central nervous system via spiral ganglion neurons (SGNs) in the cochlea. SGNs innervate the cochlear nucleus in the brainstem in a tonotopic fashion, meaning the neurons are organized by their responses to different sound frequencies. Ephs and ephrins signaling molecules are known to be involved in axon guidance and have been shown to play a role in development of topographic gradients in other sensory systems. In an initial screening, we found that ephrin-A3 and –B2 molecules are expressed in a gradient along the tonotopic axis of the cochlear nucleus during development. To test whether ephrin-A3 or -B2 forward signaling guides SGN fibers to find their targets and thus plays a role in tonotopic map formation within the cochlear nucleus, we conducted ephrin-A3 and ephrin-B2 stripe assays using SGN explants from different portions of the cochlea. We found that a subset of auditory nerve fibers were differentially repelled by stripes containing ephrin-A3 or -B2-Fc. In future studies, we will conduct stripe assays with solutions containing varying concentrations of ephrins to determine whether ephrin-A3 or -B2 have a concentration-dependent effect on the outgrowth of SGN. This will allow us to determine whether ephrin-A3 and -B2 forward signaling serves as a molecular guidance mechanism in tonotopic map formation.

**B2**

**Spiral Ganglion Neurons with Distinct Preferred Frequency Response Employ Different Strategies to Innervate the Cochlear Nucleus**

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To allow animals to separate a complex sound into its frequency components, the auditory system is organized in tonotopy; neurons at various levels of the auditory pathway are topographically arranged by their responses to different sound frequencies. Disruption of tonotopy often results in auditory processing disorders and language learning disabilities. Despite its importance in auditory functions and clinical implications, almost nothing is known about how the tonotopic map is established during development. In this study, we use genetic approaches to label spiral ganglion neurons (SGNs) and their auditory nerve fibers with different characteristic frequencies respectively. We found that functionally distinct SGN populations employ different cellular strategies to target and innervate neurons in the cochlear nucleus during tonotopic map formation. Auditory nerve fibers with high characteristic frequencies (high-CF fibers) initially overshoot and sample a large area of different targets before refining their connections to correct targets, while fibers with low characteristic frequencies (low-CF fibers) are more accurate in initial targeting and undergo minimal target sampling. Additionally, most high-CF fibers

terminate on bushy cells unbranchedly as a single large Endbulb of Held, while low-CF fibers form multiple terminal branching and small endbulb endings. These observations reveal the diversity of cellular mechanisms that functionally distinct auditory neurons use to pick their targets during tonotopic map formation.

**B3**

**Relationships between neuronal birthdates and tonotopic position in the mouse cochlear nucleus**

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Tonotopy is a key anatomical feature of the vertebrate auditory system, but little is known about the mechanisms underlying its development. Since date of birth of a neuron correlates with tonotopic position in the cochlea, we investigated if it also correlates with tonotopic position in the cochlear nucleus. In the cochlea, spiral ganglion neurons are organized in a basal to apical progression along the length of the cochlea based on birthdates, with neurons in the base (responding to high-frequency sounds) born early around mouse embryonic day (E) 9.5-10.5, and those in the apex (responding to low-frequency sounds) born late around E12.5 to 13.5. Using a low-dose thymidine analog incorporation assay, we examine whether cochlear nucleus neurons are arranged in a spatial gradient according to their birthdates. Most cochlear nucleus neurons are born between E10.5 to E13.5, with a peak at E12.5. A second wave of neuron birth was observed in the dorsal cochlear nucleus beginning on E14.5 and lasts until E18.5. Large excitatory neurons were born in the first wave and small local circuit neurons were born in the second. No spatial gradient of cell birth was observed in the dorsal cochlear nucleus. In contrast, neurons in the anteroventral cochlear nucleus (AVCN) were found to be arranged in a dorsal to ventral progression according to their birthdates, which is aligned with the tonotopic axis. Most of these AVCN neurons are endbulb-innervated bushy cells. The correlation between birthdate and tonotopic position suggests testable mechanisms for specification of tonotopic position.

**B4-UG**

**Your face and my emotions: An adolescent perspective.**

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Previous research has indicated that emotional regulation and face emotion recognition are strongly related and are key to emotional intelligence. Moreover, development of these skills continues until late adolescence. We examined the relation between emotional regulation and facial emotion recognition in adolescents. Fifteen adolescents, ages 14-18 (M=15.4; SD=1.6) completed the BRIEF Emotion Regulation Questionnaire and the Facial Emotion Recognition Test (PenER40) - a computerized test of emotion perception. We posited that adolescents would be less accurate and slower when identifying neutral and mild face emotions compared to negative and extreme emotions. We also predicted that false positives for negative expressions will correlate with emotional dysregulation. T-test and correlation results are summarized below. Adolescents were significantly less accurate when detecting anger (M=64%; SD=16) as compared to neutral (M=94%; SD=6) and the rest of emotions (All Ps < .05). Further, adolescents had the fastest RT for happy faces (M=1700.97; SD=279.97) relative to neutral faces (M=2042.33; SD=408.4), and the other emotions (all Ps < .05). We also found greater accuracy for extreme expressions (M=90%; SD=7) than for mild expressions (M=81%; SD=10). Lastly, we found a positive correlation between percent of "neutral" false positives in the actual presence of negative emotions (anger, fear, sadness) and impairment on the Behavior Regulation subscale of the BRIEF (M=33.2; SD=5.35), p<.05. The present findings suggest that during a face emotion task adolescents find it more difficult to correctly recognize mild as compared to extreme facial expressions, and angry faces compared to neutral faces. Our correlation results suggest that inaccurate misattribution of negative expressions is correlated with impaired emotional regulation. Further research on the causal relationship between emotional regulation and emotional recognition is needed in developmental studies.

**B5-UG**

**DIFFERENTIAL EFFECT OF NATURAL VERSUS ARTIFICIAL VITAMIN E ON BRAIN GENE EXPRESSION OF DEVELOPING MICE**

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Vitamin E is an essential nutrient, required for female fertility. Alpha tocopherol (the bioactive form of vitamin E) has 8 different stereoisomers, only one of which, RRR, is found in nature. The artificial variety, standardly put in baby formula, nutritional supplements, and other food products, is a racemic mixture that includes equal proportions of all 8 stereoisomers, henceforth referred to as "all rac". Although all-rac is known to be less potent than RRR (i.e., the minimum concentration needed to support fertility is approximately 40% higher for all-rac than RRR), whether stereoisomer composition affects biological functions outside of fertility, especially development of the nervous system in the offspring, is not known. The goal of this experiment was to determine the extent to which gene expression in the developing mouse hippocampus is influenced by stereoisomer composition. Adult male and female C57BL/6J mice were paired together and fed either all-rac or RRR at a moderately low (37.5 IU) or standard (75 IU) dose, resulting in 4 groups (n=10 per group). When their pups were 21 days old, they were euthanized, brain extracted, hippocampus dissected, and processed for RNA-sequencing. Approximately 800 genes were found significantly different between groups, most between doses, but some between RRR and all-rac. Network analysis indicated transcription regulation was the major biochemical process targeted by the treatments. Further analysis revealed significant correlations between known vitamin E interacting proteins and gene expression profiles. Results suggest alpha tocopherol dose and stereoisomer composition impact gene expression in the developing hippocampus.

**B6**

**LIMITED NG2 GLIAL TROPISM OF RECOMBINANT ADENO-ASSOCIATED VIRAL (rAAV)-MEDIATED GENE DELIVERY FOR IN VIVO NEURONAL REPROGRAMMING**

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Direct reprogramming of cell identity from a glial to neuronal phenotype has been demonstrated both in vitro and in vivo. The induction of phenotypic neurons from glial cell populations follows forced expression of pioneering transcription factors, such as Ngn2, NeuroD1, and Ascl1, that are normally expressed during development to specify neuronal fate. Viral vectors can be used to deliver reprogramming transcription factors to glial cells. The efficiency of vector tropism has a major impact on the feasibility to reprogram a sufficient number of new neurons to achieve a meaningful functional integration. NG2 glia, also known as oligodendrocyte progenitor cells (OPCs), represent one cellular population that could be an ideal target for neuronal induction for repair. NG2 glia, understood to represent a reserve cell population to replace oligodendrocytes, are actively dividing in the mature CNS, perform no known critical neural activity and respond to injury by proliferation and subsequent population homeostasis. Previously, we have successfully targeted and reprogrammed NG2 glia to neurons in vitro and in vivo using retroviral vectors to target the actively proliferating NG2 cell population. rAAV vectors are an alternative delivery platform frequently used to achieve efficient and widespread in vivo gene delivery. However, no systematic assessment of AAV serotype efficiency in targeting NG2 glia has been reported. We delivered CMV-eGFP constructs into rat cortex and striatum (n=3 animals per site) using the following AAV serotypes: 1, 2, 4, 5, 6, 6.2, 8, 9, rh10, DJ, PHP.s, PHP.B, PHP.eB. Analysis of infected cell types, three weeks post-injection, revealed most serotypes were substantially neurotropic with tropism for astrocytes also observed with AAV5 and AAV8. However, cultured adult-derived OPCs were infected by AAV 6.2, and the AAV PHP variants s, B, and eB, suggesting that these serotypes may be suitable for in vivo gene delivery to OPC populations in the CNS.

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## *THEME C. DISORDERS OF THE NERVOUS SYSTEM*

**C1**

***APOE4* IMPAIRS ANGIOGENESIS *IN VITRO***

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Cerebrovascular (CV) dysfunction is emerging as a significant component of various neurodegenerative diseases. Growing evidence has shown that genetic risk factors, such as *APOE* genotype, contribute to cognitive decline through CV dysfunction. *APOE4* is associated with greater cognitive decline and increased CV dysfunction in aging compared to *APOE3* is the greatest genetic risk factor for Alzheimer's disease (AD). Decreased vessel coverage is one marker of CV dysfunction and is associated with *APOE4* in aging and AD. Lower vessel coverage contributes to cognitive decline through disruption of the physical and metabolic interface between the CNS and periphery. Brain endothelial cells (BEC) at the level of the capillary are a key component of this interface and are crucial for controlling the function of the CV. However, the mechanisms by which *APOE4* affects BEC and CV dysfunction are severely understudied. We hypothesize that *APOE* genotype differentially regulates BEC function. To test this hypothesis, we isolated primary BECs from EFAD mice, which express human *APOE3* or *APOE4,* and analyzed BEC angiogenesis, an *in vitro* surrogate for vessel coverage. Compared to *APOE3*, *APOE4* BECs demonstrated lower angiogenesis as indicated by fewer meshes and lower total vessel length. Previous research in our lab found that epidermal growth factor (EGF) prevented *APOE4*-induced cognitive dysfunction and vessel coverage deficits. Given these findings, we treated *APOE4* BECs with another EGF receptor ligand, TGF-α, and found that angiogenesis in these BECs drastically recovered. The next logical step is to elucidate the mechanism by which *APOE4* and EGF ligands influence these deficits in BEC angiogenesis (e.g. migration, proliferation). Our data suggest that *APOE4* genotype in BECs regulates BEC function as evidenced by lower vessel coverage relative to *APOE3* and may represent a novel mechanism by which *APOE4* genotype contributes to CV deficits.

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**C2-G**

**Using Multimodal Serotonergic Drugs as Adjunct Treatments for Parkinson's Disease**

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Parkinson's disease (PD) is a devastating neurodegenerative disorder affecting over one million Americans. The gold standard treatment for PD is levodopa (L-DOPA), which is effective for increasing dopamine (DA) tone and improving motor dysfunction, but unfortunately produces debilitating motor side-effects termed L-DOPA-induced dyskinesias (LIDs). Recent studies in dyskinetic parkinsonian models have implicated serotonergic raphe-striatal terminals in the uptake and conversion of L-DOPA to DA, as well as the non-physiological release of DA and serotonin (5-HT) which may underlie the pathophysiological mechanisms of LIDs. Indeed, the utility of co-treatments with either selective 5-HT reuptake inhibitors (SSRIs) which block the 5-HT transporter (SERT), or selective 5-$HT_{1A/B}$ receptor (5-$HT_{1A/Br}$) ligands which stimulate 5-HT autoreceptors to potentially suppress DA release from 5-HT terminals, has been assessed in pre-clinical models and clinical trials. Many of the drugs tested were found to reduce LIDs, but unfortunately also reduced the prokinetic effects of L-DOPA. The goal of the current study was to identify a multimodal 5-HT drug which can act to attenuate the expression and severity of LIDs, without interfering with the antiparkinsonian efficacy of L-DOPA. Vilazodone is of interest in this regard as it is known to exhibit a potent SSRI-like action, along with 5-$HT_{1Ar}$ partial agonism property. Unilateral 6-OHDA-lesioned rats modeling PD were treated with either vehicle and L-DOPA

(5.0 mg/kg), vilazodone (10.0 mg/kg) and L-DOPA, or escitalopram (12.5 mg/kg) and L-DOPA. Rats were treated for 5 consecutive days/week, for 2 weeks. On the second day of each week, stepping tests were performed prior to drug administration, and 60 minutes post L-DOPA treatment. Behavioral assessment of LIDs was performed (30-180 min) at the end of each week. Vilazodone pretreatment (30 min) significantly reduced LIDs in 6-OHDA lesioned rats, but had no effects on forelimb akinesia or L-DOPA-induced prokinetic effects. Escitalopram pretreatment also induced a significant reduction in total LIDs score but interfered with the therapeutic efficacy of L-DOPA. Electrophysiological studies were conducted to assess the impact of these treatments on corticostriatal transmission and striatal neuronal activity. The current results indicate that together with L-DOPA, multimodal 5-HT drugs such as vilazodone may be safe and efficacious co-therapies for reducing side-effects such as hyperkinesia and dystonia in PD patients, potentially allowing for more flexibility in L-DOPA dose ranges and protracted chronic treatment.

**C3 -PD**

**DISRUPTION OF NEONATAL NEUROGENESIS LEADS TO ANATOMICAL, CELLULAR & COGNITIVE IMPAIRMENTS THAT PERSIST INTO ADULTHOOD: IMPLICATIONS FOR NEURODEVELOPMENTAL DISORDERS**

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Changes in neuronal proliferation and survival during gestation and the early postnatal period have been proposed as a mechanism in several neuropsychiatric disorders with developmental origins. In the present study, we examined the long-lasting effects of reduced neurogenesis during a developmental period in rats that corresponds to the third trimester in humans on anatomical, cellular and behavioral phenotypes in adulthood. Transgenic rats that express herpes simplex virus-thymidine kinase under the promotor for glial fibrillary-associated protein (GFAP) were treated with the antiviral drug valganciclovir (TK-Valg) in order to ablate dividing neural progenitors on post-natal day 5, 7 and 9. TK-Valg rats and controls were tested with a battery of cognitive tests starting at two months of age, and histological assessment of brains for markers of proliferation was conducted after sacrifice. The brains of a separate cohort of adult animals underwent microCT imaging. Ablation of neonatal neurogenesis was associated with developmental delay, motor impairments and craniofacial abnormalities. TK-Valg rats showed a broad learning impairment that was observed during acquisition of Pavlovian fear conditioning and a spatial radial maze task, and the initial discrimination phase of an operant attentional set-shifting task. Although fear conditioning was deficient, TK-Valg rats showed an increase in anxiety-like behavior. Brain imaging studies revealed severe cerebellar hypoplasia, and enlargement of ventricles. In the cerebellum, there was a profound reduction in granule layer neurons, while GABAergic Purkinje cell numbers were unaffected. Reductions in granule layer neurons and GFAP-positive cells born immediately after Valg treatment were observed in the dentate gyrus of the hippocampus. Furthermore, TK-Valg rats had reduced expression of doublecortin in the dentate gyrus suggesting that elimination of proliferation during the neonatal period also disrupts neural progenitors necessary for adult neurogenesis. Collectively, these findings indicate that perturbations in neurogenesis during the late prenatal and/or early postnatal phase have profound effects on cerebellar and hippocampal development that lead to pervasive learning and motor impairments. Further, they support the hypothesis that impairments in neurogenesis and neuronal survival during this period may be implicated in phenotypes observed in neurodevelopmental disorders, such as fetal alcohol syndrome, and also the outcomes of prenatal Zika virus infection.

**C4-G**

**CONTRIBUTING FACTORS TO REACHING DYSFUNCTION IN INDIVIDUALS WITH CHRONIC MODERATE TO SEVERE HEMIPARETIC STROKE**

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Chronic stroke survivors demonstrate a myriad of impairments impacting reaching function including flexion synergy, passive range of motion limitations, spasticity (i.e., hyperactive stretch reflexes), and weakness. The relative and concurrent contributions of each of these underlying factors has not yet been quantitatively explored in depth. 34 individuals (23 males, 58.3 ± 10.8 years old) with chronic stroke (11.8 ± 8.3 years post-stroke) participated in the study. The Fugl-Meyer Motor Assessment scores ranged from 15 to 49 indicating moderate to severe impairment. Reaching function was quantified with a robotic device and defined as maximum reaching distance against gravity. A multiple regression model was implemented to investigate the constitutive elements of reaching function. The regressors included: 1) maximal shoulder abduction and elbow extension strength that were normalized to the unaffected side, 2) spasticity-related biceps activation measured as the increase in EMG occurring after elbow extension onset during reaching, 3) flexion synergy that was measured as the highest abduction load at which the participant could successfully lift the arm and reach standardized targets, and 4) passive range of motion at the elbow. A significant regression equation was found ($F(6,18) = 3.724$, $p = 0.014$) with an $R^2$ of 0.554. Reaching function (Mean ± SD; 0.608 ± 0.358) was significantly correlated with flexion synergy emergence (0.310 ± 0.244, $r = 0.634$, $p = 0.001$), shoulder abduction strength (0.557 ± 0.193, $r = 0.390$, $p = 0.023$), and elbow extension strength (0.437 ± 0.186, $r = 0.407$, $p = 0.017$). Passive range of motion, active flexor spasticity, and flexion synergy takeover did not significantly correlate with reaching function. A subsequent model dropping non-correlated regressors found a significant regression equation ($F(3,22) = 6.858$, $p = 0.002$) with an $R^2$ of 0.483. Flexion synergy emergence was the only significant regressor in both the complete (standardized beta = 0.594, $p = 0.007$) and reduced (standardized beta = 0.521, $p = 0.005$) models. The results indicate that impairments such as strength, flexor spasticity, and passive range of motion limitations may not contribute to reaching dysfunction to the same extent as flexion synergy. The significant standardized beta coefficient can be interpreted as a one unit increase in the flexion synergy emergence threshold (less synergy impairment) being associated with a 0.521 unit increase in reaching function. The findings of this study suggest that prioritizing flexion synergy impairment is

likely to have the greatest impact when attempting to restore reaching function in chronic moderate to severe stroke.
*This study is funded by Northwestern University Department of Physical Therapy and Human Movement Sciences.*

**C5-G**
**DETERMINING THE NOVEL ROLE OF GALECTINS IN MEDIATING THE UNCONVENTIONAL SECRETION OF ALPHA-SYNUCLEIN**

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The misfolding and subsequent accumulation of alpha-synuclein (α-syn) is central to the pathogenesis of Parkinson's disease (PD). It is believed that α-syn induces pathology in a prion-like manner in which pathological α-syn acts as a template to "seed" the misfolding of native α-syn and spreads from cell-to-cell; thus propagating pathology.
Previous works from our group and others have demonstrated that when exogenous α-syn fibrils enter cells through endocytosis they can damage and rupture the membranes of their endocytic vesicles in which they are trafficked. It is known that damaging these vesicles leads to the recruitment of galectin and autophagic proteins and introduction into the autophagic-lysosomal pathway.
In this current study, we followed the fate of exogenous fibrils and endogenous α-syn expressed in target cells following vesicle rupture. We hypothesize that the cellular response to ruptured vesicles may promote subsequent steps in α-syn's cycle of propagation and spreading. We observe the co-localization of exogenous and endogenous α-syn within the autophagic-lysosomal compartments (ALC) which are positive for galectin proteins as well as in the extracellular vesicles released from these cells. Collectively, this suggests that seeding may occur in the ALC compartment and that the release of α-syn occurs via secretory autophagy.
To determine the mechanistic role of these proteins in the release of α-syn, we used SH-SY5Y and iPSC derived dopaminergic neurons to determine if depletion of autophagic proteins or galectin proteins affected the release of α-syn from these cells. We observe that depletion of ATG-7, galectin-3 and other proteins associated with the secretory autophagy pathway reduce α-syn release from cells. These studies suggest a model in which damage to the ALC by α-syn creates an intracellular environment which promotes seeding and subsequent release of pathological α-syn species from cells, promoting the propagation of α-syn pathology in PD.

**C6-PD**
**Parkinson's disease related LRRK2 regulates striatal intracellular signaling cascades**

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Mutations in LRRK2 represent a strong genetic risk for both hereditary and sporadic forms of Parkinson's disease. Therefore, knowledge on LRRK2 function might be leveraged for therapeutic benefit. LRRK2 is significantly enriched in spiny projection neurons (SPN) in the dorsal striatum. This cellular expression pattern argues that *LRRK2* mutations contribute to striatal pathophysiology in PD. Our previous findings demonstrate that LRRK2 regulates glutamatergic synaptic functions by directing PKA signaling in SPNs, whereas the $LRRK2^{R1441C}$ pathogenic mutation results in increased synaptic PKA activities. As PKA pathway is the critical effector of dopamine receptors, we showed that this aberrant PKA activity in $LRRK2^{R1441C}$ SPNs leads to perturbations in dopaminergic and corticostriatal signaling. We propose that altered subcellular compartmentalization of PKA imposed by the $LRRK2^{R1441C}$ mutation is the central mechanism for aberrant PKA signaling in SPNs. In the present study, using a series of super-resolution, structured illumination microscopy (SIM) imaging and PKA sensors we show how PKA localization shapes PKA activity in pathway-specific (direct and indirect) mutant *LRRK2* SPNs. Specifically, we determine whether the effect of LRRK2 on PKA localization results in increased PKA availability to synaptic A-kinase anchoring protein 5 (AKAP5), suggesting a direct contribution of AKAP5 to LRRK2-related phenotypes. Overall, our study provides mechanistic insights of LRRK2-mediated cellular deficits in the striatum that in turn contributes to PD symptomatology.

**C7 -PD**
**COMBINED ANTIRETROVIRAL THERAPY (TRIUMEQ) INCREASES FIRING AND $CA^{2+}$ INFLUX VIA VOLTAGE-GATED $CA^{2+}$ CHANNELS AMONG PYRAMIDAL NEURONS IN THE MEDIAL PREFRONTAL CORTEX OF RATS**

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Combined antiretroviral therapy (cART) suppresses HIV replication, improves immune function, and prolongs life of $HIV^+$ patients. Despite cART, the prevalence of HIV-associated neurocognitive disorders (HAND) occurs in ~50% of $HIV^+$ patients. The side effects of cART are found to be neurotoxic; but it is unknown if cART worsen HIV dysregulation of the medial prefrontal cortex (mPFC), a key regulator of cognition. Triumeq is a first-line cART regimen for treating HIV/AIDS, which is formulated by abacavir (ABC, a NRTI), dolutegravir (DTG, an integrase inhibitor), and lamivudine (3TC, a NRTI). Here we assessed the acute (*in vitro*) and chronic (*in vivo*) effects of Triumeq on the activity of mPFC pyramidal neurons in rat brain slices using whole-cell patch-clamp recording. We found that, at a concentration comparable to that detected in the cerebrospinal fluid (CSF) of $HIV^+$ patients, acute Triumeq *in vitro* did not affect firing. But at 10-fold (x) or 100x higher concentrations, Triumeq significantly increased firing. Further, a 4-week (4wk, but not 2wk) Triumeq treatment significantly increased firing of mPFC neurons; and that was associated with significantly-enhanced $Ca^{2+}$ influx *via* VGCCs. In contrast, chronic treatment of individual ABC, DTG, or 3TC *in vivo* for 4wk did not alter firing. These novel findings demonstrate that chronic cART/Triumeq abnormally increases mPFC neuronal activity by enhancing $Ca^{2+}$ influx *via* over-activated VGCCs; and suggest that such side effects of cART could exacerbate HIV-induced neurotoxicity in the mPFC, especially during aging.
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**C8-PD**

**SEX-SPECIFIC EFFECTS OF MICROBIOME PERTURBATIONS ON CEREBRAL AMYLOIDOSIS AND MICROGLIA PHENOTYPES**

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In prior efforts, our group demonstrated that antibiotic (ABX) perturbated gut microbiome reduces amyloid-β (Aβ) plaque pathology and gliosis in male mice of Aβ amyloidosis, termed $APP_{SWE}/PS1_{\Delta E9}$, wherein the co-integrated transgenes are driven by the mouse prion protein promoter. To extend these findings, we employed the highly aggressive (Aβ plaque and gliosis develops as early as 6-7 weeks of age) APPPS1-21 mouse model wherein the Thy1.2 promoter drives co-integrated APPSwe and PS1L166P.

ABX treatment (4mg/ml Kanamycin, 0.35mg/ml Gentamicin, 8500U/ml Colistin, 2.15mg/ml Metronidazole, 0.45mg/ml Vancomycin: in autoclaved water from post-natal day 14 to day 21 followed by an ad-libitum access to freshly prepared 1:50 diluted ABX water until the time of cull) was performed to evaluate the role of gut microbiota employing both sexes in APPPS1-21 line. To establish a causal relationship, we performed fecal microbiota transplantation experiments in ABX-treated male APPPS1-21 mice. Histopathology, microglia phenotypic characteristics, brain transcriptome, peripheral cytokines and gut microbiota profiles were evaluated.

Similar to our previous reports, ABX perturbed microbiome was associated with a reduction in Aβ pathology and altered microglia phenotypes only in male mice. We observed reduced species diversity and similar microbiome profiles in both male and female mice immediately after postnatal ABX, but interestingly, the microbiota exhibited sex-specific differences by 7 weeks of age. While ABX treatment had a significant impact on microglial morphology in male mice at 7 weeks compared with vehicle-treated mice, we did not observe these microglial morphological alterations in female mice. Furthermore, ABX treatment led to pronounced alterations in inflammation-related transcripts in the male cortex compared with female mice. Finally, we demonstrate that fecal microbiota from age-matched APPPS1-21 male mice transplanted into ABX-treated male mice partially restored Aβ plaque pathology and microglial morphological phenotypes. We conclude that the ABX-perturbed gut microbiome lead to sex-specific influences on cerebral Aβ amyloidosis and microglial phenotypes in current model. Additionally, fecal transfer experiments using ABX-male and ABX-female fecal samples were transplanted into female APPPS1-21 mice to investigate if female mice exhibit similar beneficial effects from ABX-treated male fecal microbiota. The data from the later experiment is currently being evaluated and will be presented at the conference.

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**C9**

**Sovateltide and its Neuro-regenerative Effects on Spinal Cord Injury**

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**Introduction**: Spinal cord injury (SCI) is a traumatic injury to the spinal column with no cure for the damage incurred at this time. SCI causes neuronal cell death, astrocyte proliferation and scar formation, and inflammation associated with microglial activation. With neuronal apoptosis being the most prominent event described in both acute and chronic SCI, an intervention targeting both neuronal protection and neurorestoration could lead to improved functional recovery. Previous studies demonstrated that Sovateltide, an agonist of ETB receptor, successfully induce angiogenesis and neurogenesis in different neurodegenerative diseases like stroke and Alzheimer`s disease. This study has focused on the neurogenic role of Sovateltide in an ex vivo model of SCI, specifically investigating morphological changes occurring at the side of lesion after 60 days of recovery and gene expression associated with treatment.

**Methods**: A contusion injury was performed on adult male rat at the spinal cord level T10-L1. The animals were equally divided into three experimental groups: 1. Treated with Sovateltide (1nM three treatment after 1, 3 and 5 hr post lesion on day 1); 2. treated with a vehicle (control); 3. Sham animals (no injury). At day 60 post-SCI, IRL-1620-treated rats and vehicle-treated rats were sacrificed. In addition, a 6-hour group of rats injured and treated with or without Sovateltide were observed to confirm spinal cord injury. The spinal cords were harvested, fixed in 4% formaldehyde, and cryopreserved. Samples were dehydrated in ethanol and embedded in paraffin. Spinal cords were cut into 10 µm sections using a microtome and stained with hematoxylin and eosin or processed for immunofluorescence imaging. Gene expression was validated via qPCR on genes of interested from gene array analysis.

**Results**: Rats treated with vehicle compared to the IRL-1620 treatment group showed significant morphological changes. The vehicle group had statistically significant decrease in MBP-positive myelinated fibers compared to the Solvateltide treatment group while the total spinal cord area comparison yielded no statistical difference. Moreover, The number of Neu-N positive neurons significantly decrease in the control group compared to the solvateltide -treated. Additional data shows qualitative data of microglia cells depicted by IBA-1 gathering near areas of lesion and repair. Gene array verification has shown varying results.

**Conclusions**: A low dose (1ug/KG) of Solvateltide significantly increases motor functions after 60 days post-SCI in animal treated compared to control. The morphology of the site of lesion suggest a neuroprotective role of Solvateltide in terms of preservation of both NeuN-positive neurons and myelinated fibers in our rat in vivo model of SCI.

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**C10-UG**

**Insight into Parkinson's Disease from Yeasts: Combined impact of covalent modifications & familial mutations on α-synuclein**

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Parkinson's disease (PD) is a neurodegenerative disorder linked to the loss of dopaminergic neurons in the midbrain. A key pathological marker of PD is the presence of Lewy bodies, which are mainly composed of misfolded alpha-synuclein protein. Alpha-synuclein is a highly post-translationally modified protein. While phosphorylation and nitration of alpha-synuclein are well-studied as contributors to PD pathology, less is known about sumoylation, which is proposed to be neuroprotective based on limited studies. The majority of sumoylation takes place on lysine-96 and lysine-102 of alpha-synuclein, and it increases the protein's solubility. The first goal of this research was to better understand the role of sumoylation in regulating alpha-synuclein toxicity, and we performed four studies towards it. We evaluated the effects of blocking sumoylation on alpha-synuclein in the well-established budding yeast model for PD and found that alpha-synuclein becomes more aggregated and toxic, losing its membrane localization. Second, we evaluated the effects altering sumoylation pathways by using yeast strains with reduced (*ulp1ts*) or excessive sumoylation (*smt3ts*), and found that alpha-synuclein aggregates more with reduced sumoylation, but becomes less toxic with increased sumoylation. Third, we asked how altering the phosphorylation of alpha-synuclein would alter sumoylation's protective role and found that blocking phosphorylation reduced alpha-synuclein toxicity in the absence of sumoylation. Finally, we evaluated whether blocking sumoylation on familial PD mutant versions of alpha-synuclein would exacerbate its toxicity, but we have found little evidence to that effect. We also began investigating two more-recently discovered modifications of alpha-synuclein – acetylation and glycation. We found preliminary evidence for the hypotheses that acetylation is protective, glycation is harmful, and both can interact with sumoylation and phosphorylation.

**C11-PD**

**GABAergic inhibitory interneurons as therapeutic target for Spinocerebellar Ataxia Type1**

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Spinocerebellar ataxia type1 (SCA1) is an adult-onset neurodegenerative movement disorder caused by a pathogenic polyglutamine expansion (CAG repeat) in the protein Ataxin-1 (ATXN1). SCA1 is a condition characterized by progressive problem with movement. People with this condition initially experience problems with coordination and balance (ataxia). Gradually patient suffers with muscle atrophy, cognitive impairment and succumb to death due to respiratory failure. Main pathological hallmark of the disease is Purkinje cell loss in cerebellum. Since ATXN1 is a transcriptional regulator it is not surprising that transcriptional misregulation appears as the initiating pathogenic event— indeed occurring as early as the first week of postnatal life. It is still unclear whether pathogenic changes occur only in Purkinje cells (PCs), the cells that are especially vulnerable in the disease, or whether other cell types contribute to pathogenesis. Given the importance of this postnatal period for cerebellar development, we asked whether this region might be developmentally altered by mutant ATXN1. Using SCA1 mice and Patients, we found that mutant ATXN1 —through transcriptionally upregulating the sonic hedgehog pathway—stimulates the proliferation of a relatively understudied cerebellar stem cell niche (defined by prominin-1; also, called CD133). Because these stem cells differentiate into GABAergic interneurons (basket cells and stellate cells) in molecular layer, there is an exaggerated inhibitory synapse formation with Purkinje cells. We have also confirmed the exaggerated GABAerigc interneuron connections in human SCA1 patients. This leads to significant increase in GABAergic interneuron inhibition of PCs, disrupting cerebellar Purkinje cell function in a non-cell autonomous manner. Mutant ATXN1 thus alters the neural circuitry of the developing cerebellum, setting the stage for the later vulnerability of Purkinje cells in SCA1. To interfere with the excessive GABAergic inhibition, we activated the endocannabinoid system (known to tamp down GABAergic inhibition in cerebellum by acting on presynaptic release of GABA) using endocannabinoid receptor agonist. We found that treated SCA1 mice performed significantly better on rotarod assay than untreated mice. This is the first drug that shows such a dramatic and prompt symptomatic improvement. Cannabinoid agonists are already FDA-approved for several disorders and we are optimistic that this might lead to a novel therapeutic treatment for SCA1.

Key words: Spinocerebellar ataxia-1, stem cells, GABAergic interneurons, basket cells, Purkinje neurons, endocannabinoids, cerebellum, therapy

**C12**

**EFFECTS OF SWI1 PRION DOMAIN MUTANTS ON [SWI$^+$] MAINTENANCE AND FORMATION**

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Prions are self-perpetuating, alternative protein conformations that are often amyloid. The collection of prion-forming or prion-like proteins include myriad proteins across the kingdoms of life – from plants to fungi to mammals – and can be disease-related or functional. The exact protein qualities and sequences that give rise to prions and support their propagation continues to be intensely studied. The budding yeast, *Saccharomyces cerevisiae* contains several endogenous prion-forming proteins that provide an avenue for the study of prions. One such protein, Swi1 – a component of the SWI/SNF chromatin remodeling complex – can form the prion [*SWI*$^+$], as discovered by our lab. Like most yeast prion proteins, Swi1 is rich in glutamine and asparagine residues. Previous research by our lab showed that the N-terminal domain of Swi1 contains the prion domain (i.e. the region necessary and sufficient for prion formation and propagation). Furthermore, the extreme N-terminal, Swi1$_{1\text{-}38}$ alone can recapitulate many aspects of [*SWI*$^+$]. To better understand the amino-acid residues that support Swi1 aggregation and propagation and formation of

[*SWI*$^+$], we have mutagenized Swi1$_{1\text{-}38}$. The resulting mutants have been assayed for aggregation frequency and pattern when expressed alongside full-length Swi1. Replacement of several polar, uncharged residues of Swi1$_{1\text{-}38}$ with hydrophobic residues proportionally disrupts aggregation. Meanwhile, replacement of the two aromatic residues within Swi1$_{1\text{-}38}$ leads to severe aggregation disruption. In addition, [*SWI*$^+$] maintenance by these Swi1$_{1\text{-}38}$ mutants was examined via dropout of full-length Swi1. The presence of the aromatic residues is key in promoting maintenance and propagation of [*SWI*$^+$]-linked aggregation by Swi1$_{1\text{-}38}$. Furthermore, examination of *de novo* prion formation by Swi1$_{1\text{-}38}$ mutants reveals the residues whose replacement provide the most sensitivity to prionogenesis. Indeed, we are examining the effects that these relatively small mutations in Swi1$_{1\text{-}38}$ have when brought back to larger Swi1 constructs, including the full-length protein. Understanding the contributions of various amino acids to the prion capabilities of Swi1 will allow for enhanced knowledge regarding the factors that contribute to the prionogenicity of proteins in general, including those involved in neurodegeneration.

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**C13-G**

**REGULATION OF BINGE ALCOHOL DRINKING BY ANAPLASTIC LYMPHOMA KINASE (ALK) AND SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 3 (STAT3)**

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Of the estimated $249 billion financial burden caused by alcohol use disorder (AUD), over $190 billion are related to binge drinking, highlighting the importance of research aimed at understanding and mitigating binge drinking. The contribution of the neuroimmune system to AUD has become a major focus of interest in recent years and robust immune activation has been found in individuals with AUD. Signal transducer and activator of transcription 3 (STAT3) plays a critical role in the regulation of the immune response and is activated by anaplastic lymphoma kinase (ALK) in response to alcohol exposure *in vitro*. The goals of this study were to determine if: 1) binge ethanol drinking activated ALK and STAT3 signaling in the brain, and 2) to determine if inhibition of their signaling could reduce binge drinking. The drinking in the dark test was used as a mouse model of binge ethanol consumption. Male and female C57BL/6J mice were given access to 20% ethanol in a single bottle on their home cages for 2 hours on days 1-3 and 4 hours on day 4. Brains were collected at 0 and 24 hours after the final drinking session on day 4 and specific brain regions, including the hippocampus, were dissected for analysis of gene expression by qPCR and protein levels and phosphorylation by western blotting. ALK and STAT3 activation, as measured by tyrosine phosphorylation, were dynamically altered in the hippocampus after binge alcohol drinking. In addition, the expression of STAT3 target genes, such as *Gfap* and *Socs3*, were also increased following binge drinking. To determine if inhibition of ALK and STAT3 can alter binge ethanol drinking, mice were treated with the ALK inhibitor, alectinib, or the STAT3 inhibitors, stattic or niclosamide, prior to drinking sessions in the drinking in the dark test. Systemic treatment with either ALK or STAT3 inhibitors decreased binge-like drinking. These results indicate that ethanol exposure activates ALK and STAT3 signaling and that these pathways play an important role in binge drinking. Pharmacological inhibitors targeting ALK and STAT3 may represent viable new therapeutic approaches to reducing excessive alcohol consumption.

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**C14-G**

**XANTHOHUMOL PROTECTS CORNEAL EPITHELIAL CELLS AGAINST OXIDATIVE STRESS *IN VITRO***

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Xanthohumol is a natural compound found in *Humulus Lupulus*, commonly known as hops, a species of flowering plant in the hemp family. Xanthohumol exerts potent cytoprotective effects against oxidative stress, which plays a major role in the causative etiology of many diseases, including neurodegenerative and ophthalmic conditions. Previous studies have reported the potent antioxidant properties of Xanthohumol *in vitro,* and potential therapeutic benefits in preclinical models for ischemia/reperfusion injury as well as neurodegenerative and proliferative disorders. Dry Eye Disease (DED) is a multifactorial disorder that affects the tear film and the ocular surface. Inflammation and oxidative stress are generally considered the primary contributors to disease progression. Currently approved drugs for DED, i.e. ophthalmic cyclosporine (Restasis® and Cequa™) and lifitegrast (Xiidra®) solely target the inflammatory component of the disease. However, topical administration of antioxidants has been shown to provide potential benefits for slowing and/or reversing disease progression by reducing corneal surface damage and inflammation and protecting the lacrimal gland against leukocyte infiltration. We here hypothesized that Xanthohumol may protect human corneal epithelial cells against oxidative stress *in vitro*. Human Corneal Epithelial cells (HCE-T; Riken; Japan) were exposed to concentrations from 1 nM to 100 μM Xanthohumol in order to determine possible cytotoxicity. Xanthohumol did not exert any cytotoxicity up to 10 μM in the MTT and the lactate dehydrogenase (LDH) release assay. We next exposed HCE-T cells to chemically-induced exogenously-applied oxidative stress by treating cells with *tert*-butyl hydroperoxide (tBHP) for 6 hr. Cells were pretreated for 24 hr. with 0.1 μM to 5 μM Xanthohumol, vehicle (0.1% DMSO) or remained untreated. Pre-treatment with Xanthohumol resulted in a statistically significant dose-dependent protection of HCE-T cells from tBHP-induced oxidative stress compared with vehicle-treated cells. Analysis of protein expression of enzymes of the endogenous antioxidant system revealed statistically significant increases in phase II antioxidant enzymes, including superoxide dismutase 2 and heme oxygenase 1. Our *in vitro* findings support future testing of Xanthohumol in preclinical models for DED, either as monotherapy or in combination with established anti-inflammatory treatment modalities.

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**C15**
**METERGOLINE MICROINJECTION INTO THE BASOLATERAL AMYGDALA IS SUFFICIENT TO MODEL PANIC DISORDER AS EVIDENCED BY SODIUM LACTATE-INDUCED TACHYCARDIA**

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Panic disorder (PD) is a common mental illness characterized by recurring, spontaneous panic attacks. Scientific investigation into PD has been accelerated by the development of rat models of PD. These models can be validated by responses, including tachycardia, to intravenous sodium lactate (NaLac) that are similar to PD patient responses. NaLac also induces hyperventilation in PD patients but respiratory measures are not usually collected in rat models. Previous work on established PD models has suggested that antagonism of serotonin (5-HT) receptors in the basolateral amygdala (BLA) may be sufficient to model PD. To test this hypothesis, the 5-HT receptor antagonist metergoline (MET, 10nmol in 0.2µl) or vehicle was microinjected into the BLA of rats anesthetized with urethane (1.5g/kg i.p.). 10min after the microinjection, NaLac (0.5M, 10ml/kg) or d-mannitol (0.5M, 10ml/kg) was infused intravenously over 15min. Heart and respiratory rates were recorded and analyzed for evidence of panic-like reactions. The results indicate that only the rats treated with MET and NaLac exhibited tachycardia, confirming the utility of these treatments for modeling panic. Hypoventilation was observed in all d-mannitol treated rats, and hyperventilation was observed in all NaLac treated rats. This suggests the respiratory effects of NaLac are dissociable from the cardiovascular effects. Currently, we are analyzing the distribution of c-fos, a marker of neuronal activation, in brainstem regions that regulate cardiorespiratory activity. The lateral parabrachial nuclei (LPBN) show numerous c-fos immunoreactive neurons in the urethane-anesthetized rat, regardless of treatment. Preliminary results do not suggest an effect of the MET and NaLac treatments on the number of c-fos expressing neurons in the LPBN in this model of PD.
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**C16 -UG**
**INVESTIGATING AGGREGATION OF BAF COMPLEX PROTEINS IN YEAST**

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Protein aggregation in a prion-like manner (conversion of a protein from its native confirmation to a group of self-propagating pathogenic confirmations) plays an important role in neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Recent research has indicated that this prion-like aggregation occurs in additional diseases, including cancer. The chromatin remodeling brahma-associated factor (BAF) complex is mutated in >20% of cancers, including several forms of brain cancers, and contains multiple protein subunits predicted to be aggregation-prone. To further understand whether these proteins may aggregate and act in a prion-like manner, we examined three protein subunits of the BAF complex – CREST, SS18, and BAF53B. Using a yeast model, we examined these proteins for aggregation ability and prionogenicity. Aggregation ability was examined via controlled expression in a yeast model system – both CREST and SS18 are able to aggregate in yeast. To investigate the ability of these proteins to act in a prion-like manner, we employed the Sup35 assay. For this assay, the proteins of interest – CREST, SS18, and BAF53B are fused to the MC regions of Sup35, a known yeast prion protein that acts as a translation terminator. If the fusion protein aggregates as a prion, a loss of translation termination function occurs as a result of sequestration of the MC domain. This set-up allows for phenotypic readouts including growth on particular selective media and changes in colony color. We have found that CREST, SS18, and BAF53B are unable to provide normal translation termination function when fused with MC due to three different issues. A toxicity assay using the quick and malleable yeast system will be conducted for CREST and SS18 and selected mutants of them. These methods tested the following hypotheses: 1. CREST and SS18 will act in a prion-like manner because they more closely share sequences with known prion/prion-like proteins, while BAF53B will only aggregate in a non-prion-like manner and 2. Mutants predicted to be aggregation-promoting will have enhanced aggregation and enhanced toxicity. Understanding the possible aggregation of BAF complex proteins and the effects of their mutations on this phenomenon serves as a viable path for treatments for cancers and other illnesses involving the BAF complex.
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**C17**
**STRAIN SPECIFIC ZIKA MEDIATED ASTROCYTE CELL DEATH**

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In the last decade there have been several large outbreaks of Zika Virus (ZIKV) in the Americas. In newborns ZIKV is associated with significant neurologic abnormalities including microcephaly. We initiated an investigation to address differences in CNS pathogenicity between various ZIKV strains on human astrocytes. We infected primary human fetal astrocytes (HFAs) with 0.1 MOI of five strains of ZIKV and measured cell viability at regular intervals over a period of 21 days. We found that all strains successfully infected HFAs and caused cell death after 21 days of infection. However, IBH30656 an African strain, caused significantly higher rate of cell mortality compared to all other strains. On day 21, IBH30656 caused more than 80% cell death while infection with other strains resulted approximately 10% cell death. Wnt/b-catenin signaling is a pro-survival pathway that maintains central nervous system function pre-and post-development. We show that all strains downregulate b-catenin. Further, overexpression of a transcriptionally active form of b-catenin through transfection protected astrocytes from ZIKV mediated cell death. Our findings suggest differences in cytotoxicity of ZIKV strains, and that b-catenin

protects astrocytes from Zika mediated cell death. ** OAJ is supported by Rush IMSD (R25 109421)*

**C18**

**LRRK2 IS A CRITICAL REGULATOR OF DOPAMINE-DEPENDENT STRIATAL LONG TERM DEPRESSION AND STRIATAL MOTOR LEARNING**

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Missense mutations in *LRRK2* represent the most common genetic cause of Parkinson's disease (PD) and *LRRK2* locus variations confer risk for the development of the most common non-genetic form of PD. Thus, leveraging new knowledge of LRRK2 function will increase our comprehension of fundamental disease-related processes. Our research team recently discovered that *LRRK2*$^{R1441C}$ mutation leads to aberrant synaptic protein kinase A (PKA) signaling in the striatal projection neurons (SPNs). Given that PKA is the prominent signaling pathway that underlies striatal motor learning, our data revealed an impairment in dopamine-dependent striatal motor learning in *LRRK2*$^{+/R1441C}$ knock-in mice, indicative of altered synaptic plasticity in the SPNs. Accumulating data emphasize the role of regulator of G protein signaling 4 (RGS4) in the control of striatal plasticity. Specifically, in indirect SPNs (iSPNs), RGS4 activation suppresses high frequency stimulation (HFS)-induced long-term depression (LTD) via inhibiting mGluR5-$G_q$ signaling. Importantly, RGS4 activity is regulated by dopamine D2 (D2R) and A2A (A2AR) receptors via PKA. Based on this and our preliminary findings, we hypothesized that the aberrant PKA signaling in the *LRRK2*$^{+/R1441C}$ mice inhibits mGluR5-$G_q$ signaling via RGS4, leading to the elimination of LTD that may underlie the impaired striatal motor learning. In the present study, we showed that striatal RGS4 expression levels and activity were increased in *LRRK2*$^{+/R1441C}$ striatal extracts leading to alterations of the mGluR5-Gq signaling in *LRRK2*$^{R1441C}$ indirect SPNs. Specifically, mGluR-$G_q$ signaling evaluated by fluorescent reporters was elevated in primary cultured *LRRK2*$^{+/R1441C}$ iSPNs compared to controls. In addition, the impairments of *LRRK2*$^{+/R1441C}$ mice in the striatal motor learning task were ameliorated by RGS4 inhibitor, emphasizing the centrality of RGS4 function in the *LRRK2*$^{R1441C}$ mediated striatal functions. Taken together, our findings support a new model outlining the linkage among LRRK2$^{R1441C}$, increased PKA activities, impaired striatal plasticity, and aberrant motor learning. Notably, clinically asymptomatic LRRK2 mutation carriers exhibit altered corticostriatal connectivity, similar to idiopathic PD patients. Thus, a precise understanding of the corticostriatal plasticity mechanisms in *LRRK2*$^{R1441C}$ mice and related interventions to LRRK2 enzymatic activity prior to neuronal death, may provide the basis for early neuroprotection practices in PD.

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**C19-G**

**THE EFFECTS OF MYELINATING GLIAL CONNEXIN DEFICIENCY WITHIN THE CENTRAL NERVOUS SYSTEM**

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Glial cells of the central nervous system (CNS) express several different connexins. These connexins are integral membrane proteins that form gap junction channels and provide a low resistance pathway for the diffusion of small molecules and ions between coupled cells. The mutation or deficiency of oligodendritic connexins 32 and 47 have been linked to the disease states X-linked Charcot-Marie-Tooth disease (CMT1X) and Pelizaeus-Merzbacher-Like disease 1 (PMLD1), respectively. The direct effect of these Cx mutations on the functionality of the myelinating oligodendrocytes results in myelin degeneration, malformation, and motor system impairment with heterogenous behavioral expression. In CMT1X patients, Cx32 deficiency expresses predominantly peripheral nervous system impairment and mutation dependent transient CNS symptoms. Conversely, the Cx47 deficiency found in PMLD1 patients, causes progressive leukodystrophy with profound motor impairment of both the peripheral and central nervous systems. In both disease models Cx deficiency has been shown to cause an increased immune response at baseline and an increased susceptibly to inflammatory attack.

This project focuses on how the knockout of either Cx32 or Cx47 affects the central nervous system (CNS), with a goal of elucidating evidence for inflammatory states at baseline. Glial cell type changes within the CNS of Cx32KO and Cx47KO pups were evaluated in mixed glial culture at baseline and after lipopolysaccharide (LPS) treatment, a well-known neuroinflammatory inducer. Utilizing immunolabeling, we examined presence of oligodendrocytes, astrocytes, and microglia in Cx32KO and Cx47KO, when compared to wild-type controls. These results continue to support and highlight the critical role connexins play in oligodendrocytes and implicates further investigation into the role of inflammation in these diseases.

**C20-G**

**DUSP4: an endogenous MAPK inhibitor and potential target for epilepsy therapy**

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Epilepsy is a disease of recurrent seizures due to abnormal synchronized firing. Approximately one third of all epileptic patients are resistant to current drug treatments, many of which produce significant side effects. In order to develop improved therapeutics, the molecular basis of epilepsy, needs to be better understood. Based on previous studies with human epileptic neocortical tissue that incorporated histology and transcriptomics, our lab identified the Mitogen Activated Protein Kinase (MAPK) pathway as highly upregulated in epileptic regions of the human brain. Our studies have also shown that pharmacological inhibition of the MAPK pathway reduced the development of epileptic spiking, marking this pathway as therapeutically significant. In hopes to better understand endogenous MAPK regulation, we then focused on one member of the MAPK family, Dual Specificity Phosphatase 4 (DUSP4). DUSP4 is a known, potent endogenous inhibitor of MAPK signaling. With recent studies using an integration of in vitro mechanistic studies in the human SH-SY5Y cell line paired with transcriptomic and histological analysis of human epileptic neocortical tissue samples, we have found that DUSP4 displays unique regulation in the epileptic brain. We find DUSP4 translation is activity dependent and MAPK signaling dependent. Additionally, in regions where DUSP4 is expressed, MAPK signaling is dramatically decreased suggesting that DUSP4 creates an activity

dependent feedback loop with MAPK signaling in the epileptic brain that may prevent the spread of epileptogenesis and thus may be a potential therapeutic target. Recently, we have found an FDA-approved drug increases DUPS4 expression in vitro and thus may be repurposed for the treatment of epilepsy.

**C21-G**
**EVIDENCE FOR ATTENUATION OF BBB-DYSFUNCTION VIA CALPAIN-CATHEPSIN INHIBITION STRATEGIES RELEVANT TO TBI AND ADRD**

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The calpain-cathepsin hypothesis (CCH) is an underlying mechanism implicated in the early pathogenesis of Alzheimer's disease and related dementia (ADRD). This hypothesis implicates two cysteine proteases, calpain-1 (CAPN1) and cathepsin B (CTSB), as key mediators of neurodegeneration and is supported by studies with small molecule inhibitors, such as NYC-438, that reduce cognitive deficits in AD mouse models. Though they display efficacy, NYC-438, a nonselective CAPN1/CTSB inhibitor, and selective CAPN1 inhibitors developed by Abbvie exhibit poor brain bioavailability. We hypothesized that the CCH could apply equally to the blood-brain barrier (BBB) and, in particular, brain endothelial cells (BECs). To test this theory and further characterize selective vs nonselective targeting of CAPN1 vs CTSB, we developed selective small molecule inhibitors, and characterized both their neuroprotective efficacy in *in vitro* ischemia-reperfusion injury and neuroinflammatory attenuation in an *in vivo* mTBI mouse model of oxidative-stress (OS). Various inhibition strategies provided the expected dose-dependent neuroprotection in primary neurons and mitigated the post-mTBI neuroinflammatory surge seen in the OS-mouse model. We then isolated BECs from WT and OS mice and saw enhanced susceptibility in the OS-BECs after ischemia-reperfusion injury, suggesting a role for oxidative stress and lipid peroxidation in exacerbating CAPN1/CTSB mediated BBB damage. We are currently testing our molecules on stressed WT and OS BECs, examining changes in cell viability, tight junction proteins, and transendothelial electrical resistance. Overall, this research provides support for targeting CAPN1/CTSB in protecting the BBB, either in early life trauma, such as mTBI, or in ADRD itself.
*This study is funded by the T32 ADRD award 1T32AG057468-01*

**C22**
**OPTIMIZATION AND CHARACTERIZATION OF SELECTIVE ABCA1 INDUCERS AS POTENTIAL ALZHEIMER'S DISEASE THERAPEUTICS**

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There are currently no disease-modifying therapies for Alzheimer's Disease (AD). Clinical trials with amyloid-targeting agents have consistently failed, indicating an urgent need to explore novel therapeutic avenues. The connection between AD and type 2 diabetes (T2D), underlined by shared deficits in lipid metabolism, insulin signaling, and inflammation, represents one such avenue. Literature reports show that increased expression of the cholesterol transporter ABCA1 corrects these deficits; elevated ABCA1 should also increase lipidation and function of apoE and therefore provide added benefit to *APOE* ε4 carriers. However, transcription factors controlling ABCA1 also promote hepatic triglyceride synthesis (via SREBP1c protein), so non-selective activity leads to fatty liver disease. Our objective is to develop novel, selective small molecule inducers of ABCA1 that possess multifunctional therapeutic effects without impacting peripheral lipogenesis. To that end, we first conducted a luciferase-based high-throughput screen to identify compounds that increased ABCA1, but not SREBP1c, expression. Following validation, structural analogs of a selected hit were synthesized to identify new compounds with enhanced potency. Through multiple synthetic iterations, we developed a lead compound that demonstrated sub-micromolar potency toward ABCA1 induction *in vitro* while maintaining minimal effect on SREBP1c. This optimized molecule was further validated in multiple phenotypic cell-based assays, in which we observed increased cholesterol transport and reduced inflammatory response to LPS stimulation following treatment. Finally, we tested this compound in high-fat diet (HFD) mice, demonstrating diminished weight gain and adipose tissue deposition along with heightened insulin sensitivity in probe- vs. vehicle-treated mice. Notably, probe treatment actually decreased plasma and liver triglycerides in these mice, showing the promise of our strategy to develop small molecules with multifactorial ABCA1-mediated therapeutic activity but minimal adverse effects. Additional work is ongoing to evaluate and optimize pharmacokinetic and metabolic properties, in preparation for long-term studies in AD mouse models to explore probe efficacy at correcting cognitive deficits and AD pathology associated with *APOE4*.
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**C23-UG**
**The Effect of Age, Sex and *APOE* Genotype on ApoE Lipidation and Ab Aggregation in an AD Transgenic Mouse Model**

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*APOE4*, the gene encoding apolipoprotein E4 (apoE4), is the greatest genetic risk factor for Alzheimer's disease (AD), compared to common *APOE3*, with *APOE2* protective but rare. In the brain, levels of apoE4 are lower than apoE2 and apoE3, likely the result of instability as apoE4 is poorly lipidated. AD is characterized by accelerated accumulation of amyloid-b (Ab) peptide, which aggregates to form both amyloid plaques and soluble oligomeric Ab (oAb), the latter a proximal neurotoxin. In humans, female (♀) *APOE4* carriers have a greater: risk for AD, rate of cognitive decline, and accumulation of Ab compared to male (♂) *APOE4* carriers. In EFAD transgenic mice (expressing human apoE isoforms and overexpressing Ab42), we demonstrated a significant decrease in lipidated-apoE and an increase in soluble oAb in 6-month (M) ♀and♂E4FAD compared to ♀and♂ E3FAD mice. **Thus, the goal of this project is to determine the interactive effects of age, *APOE* genotype and sex on apoE4 lipidation and soluble levels of Ab42 and oAb in EFAD mice.** The cortices of 4-18M ♂ and ♀EFAD mice were extracted via a 3-step sequential

method, producing soluble (TBS), detergent (TBSX/triton X-100) and insoluble (FA/formic acid) fractions, with lipidated-apoE extracting in the TBSX fraction. Total-, TBSX- and FA-Ab42 increased with age. Soluble oAb levels increased with age in all genotypes (♂E3FAD<♂E4FAD<♀E3FAD<♀E4FAD), while soluble Ab42 levels plateaued (♂E3FAD<♀E3FAD<♂E4FAD<♀E4FAD). This is critical as even in EFAD brain tissue, soluble oAb tracks disease progression. Total- and FA-apoE levels increase with age. Importantly TBS-X apoE increases with age and genotype (E3FAD> E4FAD), with the exception of ♀E4FADs, which show no age effect. This suggests an age-induced compensatory that is absent in the ♀E4FAD. This age-induced increase in AD pathology mirrors the increased AD risk in humans (♂E3FAD≤♂E4FAD≤♀E3FAD<♀E4FAD). Thus, the EFAD mice serves as a viable therapeutic pre-clinical mouse model.

**C24-PD**

**MODELING HEREDITARY SPASTIC PARAPLEGIA TYPE 3A USING ISOGENIC IPSCs**

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Hereditary spastic paraplegias (HSPs) are a heterogeneous group of neurogenetic disorders characterized by axonal degeneration of cortical motor neurons, a group of large projection neurons (PNs). How cortical PN axons specifically degenerate in HSP patients remain largely unknown. HSP type 3A (SPG3A), the most early-onset form of HSP, is caused by mutations in the *ATL-1* gene that encodes atlastin-1 proteins. Here, we examine the role of perturbed altlastin-1 in axonal defects by generating isogenic human pluripotent stem cell (hPSC) lines with *ATL*-1 mutations using CRISPR-cas9 mediated homologous recombination. We first differentiated these hPSCs into cortical PNs using the well-established protocol in our lab. The axonal length of cortical PNs with *ATL-1* mutations was significantly reduced as compared to that in normal iPSC-derived cortical PNs. We then examined the axonal transport of synaptophysin, an important synaptic vesicle protein, and found that atlastin-1 mutations impaired the synaptophysin transport including reduced axonal transport velocity and decreased moving synaptic vesicles. Finally, we examined the synaptic defects by co-culturing SPG3A cortical PNs with their target, spinal motor neurons; and compared with co-culture of normal cortical PNs and spinal motor neurons. The synaptic connections between cortical PNs and spinal MNs in different groups were evaluated using both immunostaining and electrophysiological analyses. The number of $Synapsin^{+}/EYFP^{+}/PSD95^{+}$ synaptic clusters in SPG3A co-culture models was significant reduced comparing to normal co-culture group. The impaired synaptic connections in SPG3A co-culture models were further supported by the dramatic decrease in the frequency of spontaneous excitatory postsynaptic currents (sEPSC) recorded in SPG3A spinal MNs after the activation of ChR2-expressing cortical PNs. Taken together, our data reveal that perturbed atlastin-1 in cortical PNs result in reduced axonal outgrowth, aberrant axonal transport, and impaired synaptic connections with their targets, providing a unique system to study the pathogenic mechanism and explore the treatment for HSPs.

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**C25-UG**

**AD SYMPTOMATIC PROFILES THAT PREDICT THE DOMINANCE OF SEX OR *APOE* GENOTYPE IN EFAD MICE**

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While age is the greatest risk factor for Alzheimer's disease (AD), *APOE4* is the greatest genetic risk factor for AD compared to the common *APOE3*, an effect exacerbated in female (♀) *APOE4* carriers. In the brain, levels of apoE4 are lower than apoE3, likely the result of instability as apoE4 is poorly lipidated. AD is caused by the accumulation of amyloid-β (Aβ) peptide, which aggregates to form both amyloid plaques and soluble oligomeric Aβ (oAβ), the latter considered a proximal neurotoxin. In the EFAD mouse model (expresses human *APOE* and overexpresses Aβ42), AD pathology includes cognitive impairments, amyloid deposition, neuroinflammation, neuronal loss, reduced lipidation of apoE4, and increased soluble Aβ42 and oAβ. Pathology develops: ♀E4FAD > ♂E4FAD ≥ ♀E3FAD > ♂E3FAD, and is exacerbated with age (4-18 months/M). However, when attempting to compare ♀E3FAD and ♂E4FAD carriers the results are inconclusive. If ♀E3FAD exhibit greater AD pathology than ♂E4FAD, then sex would be a dominant risk factor. If ♂E4FAD males exhibit greater AD pathology than ♀E3FAD, then *APOE* genotype would be the dominant risk factor. Thus, we are evaluating all our readouts for AD pathology from 4-18M ♀ and ♂E3FAD and E4FAD mice using advanced biostatistics to identify whether the ♀sex effect dominates the *APOE4* effect on AD pathology or whether *APOE4* effect dominates the ♀sex effect. Since ♀E3FAD and ♂E4FAD share neither the same sex or genotype, they cannot be directly compared statistically, requiring 2 controls: 1) ♂E3FAD as negative control and 2) ♀E4FAD as a positive control. These data will leverage extensive research results to address how age, *APOE* genotype and sex interact to affect AD pathology in ♀E3FAD vs. ♂E4FAD, with the goal of defining symptomatic profiles that predict the dominance of sex or genotype between these 2 cohorts.

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**C26-G**

**VOLTAGE INCREASES PROSACCADE ERROR RATE IN BILATERAL DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE**

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Voltage is the most commonly manipulated parameter during the initial stages of bilateral subthalamic nucleus deep brain stimulation (STN DBS) programming. However, few studies have systematically investigated how individuals with Parkinson's disease (PD) respond to voltage manipulations. These studies have reported maximal

improvement at 3 volts and plateauing thereafter in motor aspects like tremor, bradykinesia, rigidity, and overall movement but worsened cognitive aspects like speech intelligibility at 4 volts. To further understand the extent to which voltage can modulate performance, we studied the antisaccade task which has both motor and cognitive aspects of control. Six participants with PD and bilateral STN DBS performed the antisaccade task. The following 6 voltages (0, 1, 2, 3, 3.5, and 4 volts) were randomly tested following a 12-hour overnight withdrawal from anti-parkinsonian medication. Frequency, pulse width, and active contacts remained at clinical settings. Eye-tracking data was utilized to obtain primary saccade latency and gain, and prosaccade error rates during the antisaccade task. First, we found a significant quadratic relationship between the intensity of voltage and both the latencies for correct antisaccade trials and prosaccade error trials. The minimum latencies occurred while both stimulators were set to 2 or 3 volts. Second, we showed a significant quadratic relationship between voltage and primary saccade gain during correct antisaccade trials. The maximum gain occurred while both stimulators were set to 2 or 3 volts. Finally, we found a significant linear relationship between voltage and prosaccade error rate. As the voltage increased, the probability of making a prosaccade error also increased. Eye movement outcomes of latency and gain are improved until clinical voltages are attained during correct antisaccade trials. Further increase in voltage results in prolonging latency and reducing gain. With respect to prosaccade error rate, increasing voltage is linearly related to an increase in the probability of prosaccade errors. When movements are internally driven, increasing voltage is beneficial for motor aspects up to a critical voltage and beyond this point benefit declines as seen in latency and gain. In respect to cognitive aspects, increasing voltage is progressively detrimental as seen in the prosaccade error rate. Further research is required to investigate the network wide neurophysiology that underlies the voltage and behavioral effects of STN DBS.

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**C27-UG**

**IH-DEPENDENT HIF1A SIGNALING IS IMPORTANT FOR NEURONAL GENERATION IN ADULT HIPPOCAMPAL NEUROGENESIS**

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Intermittent hypoxia (IH), is a consequence of sleep apnea, a common disorder associated with impaired neurological health, including hippocampal structure and function. We have recently demonstrated that thirty days of IH impairs hippocampal long term potentiation and reduces the number of immature granule cells generated during hippocampal adult neurogenesis. Hypoxia Inducible Factor 1a (HIF1a) is a transcription factor important to stem cell development that is normally stimulated by hypoxia. The objective of this on-going study is to determine the role of IH-induced HIF1a signaling in the generation of adult-born neurons in the hippocampus. We hypothesize that IH suppresses hippocampal neurogenesis through a mechanism involving HIF1a signaling. We used a cre-loxP transgenic strategy to birth label a discrete cohort of stem cells that experience room air for 30 days (control), 10 days of IH +20 days of recovery in room air ($IH_{10+20RA}$), or 30 days of IH ($IH_{30}$) in wild-type reporter mice (Ai27) and in Ai27-$HIF1a^{+/flox}$ mice. In wild-type mice, exposure to $IH_{10+20RA}$ led to higher proportion of birth-labelled neurons compared to the control (+19% ± 5%, n=6) while the proportion of neurons following $IH_{30}$ decreased (−40% ± 10%, n=4). In Ai27-$HIF1a^{+/-}$ mice, the proportion of birth-labeled neurons was similar between control and $IH_{10+20RA}$ groups. However, following $IH_{30}$ the proportion of birth-labeled neurons was markedly decreased when compared to control in Ai27-$Hif1a^{+/-}$ and to the $IH_{30}$ wild-type group. Dendritic complexity distribution, as determined by Sholl analysis, was similar among labeled neurons in both wild-type and Ai27-$HIF1a^{+/-}$ control and $IH_{30}$ groups. There is a modest increase in distance of maximum complexity from the cell body in $IH_{10+20RA}$ in wild-type (+40% ± 10%, n=5) and Ai27-$HIF1a^{+/-}$ animals (+40% ± 20%, n=6), indicating a potential change in neuron morphology following IH, independent of Hif1a. These findings indicate that Hif1a signaling is important in making up for IH-induced neuron loss, mediating the effects on adult hippocampal neurogenesis associated with sleep apnea.

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**C28**

**DIFFERENTIAL MODULATION OF DORSOLATERAL AND DORSOMEDIAL STRIATUM BY PARTIAL M1 MUSCARINIC RECEPTOR AGONIST ATTENUATES REPETITIVE BEHAVIORS IN THE BTBR MOUSE MODEL OF AUTISM**

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Autism spectrum disorder (ASD) is characterized by repetitive behaviors, restricted interest and social-communicative impairments. At present, there is limited knowledge about the pathophysiology underlying core symptoms, as well as effective treatments. Post-mortem studies from autistic individuals suggest altered muscarinic receptor functioning may contribute to an autism phenotype. Further, there is evidence that central muscarinic receptors can modulate glutamate transmission that has been proposed as a key neurotransmitter disrupted in ASD. The BTBR T+Itpr3$^{tf}$/J (BTBR) mouse serves as a polygenic model of autism displaying elevated repetitive motor behaviors. The present study determined whether systemic treatment with a partial $M_1$ muscarinic receptor agonist, CDD-0102A, attenuates repetitive motor behaviors in BTBR and B6 mice. In a second study, the effects of CDD-0102A on dorsal striatal glutamate changes during repetitive motor behaviors in BTBR and B6 mice was investigated. Mice were first left in their home cage that contained bedding and nesting material. Time spent digging and grooming was measured for 10 minutes. Subsequently, nesting material was removed, and the time spent digging in the bedding and self-grooming behavior was measured for 10 minutes. Thirty minutes prior to the test mice received an i.p. injection of saline or a dose of CDD-0102A (0.06, 0.12 or 0.30 mg). Removal of nesting material significantly increased digging behavior in saline-treated B6 mice and digging and grooming behavior in BTBR mice. CDD-0102A, dose-dependently, reduced digging and grooming behavior in BTBR mice and reduced elevated digging in B6 at the highest dose. In the second study the same behavioral test was employed but, in addition, an enzyme-based,

glutamate biosensor was inserted into the dorsolateral or dorsomedial striatum of each mouse. Change in glutamate efflux from both striatal subregions increased ~1500nM in BTBR compared to ~1000nM in B6 mice during behavior. CDD-0102A treatment reduced magnitude glutamate change in the dorsomedial striatum to ~700nM, whereas it increased glutamate change the dorsolateral striatum to ~1800nM during digging and grooming. The current findings suggest that glutamate transmission is dysregulated in BTBR mice, contributing to the elevated stereotyped motor behaviors. Moreover, activation of $M_1$ muscarinic receptors modulates glutamate signaling in the dorsal striatum in distinct ways based on subregion. Overall, the results suggest that treatment with a partial $M_1$ muscarinic receptor agonist may alleviate repetitive behaviors and restricted interests in part by modifying glutamate signaling.

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**C29-UG**

**PRAZOSIN EFFECTIVENESS IN THE ALLEVIATION OF PTSD IS ELICITED BY MECHANISTIC PATHWAYS SEPARATE FROM STRESS AXIS ELEMENTS POMC, CRH, GR, AND CORTISOL**

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The formation and maintenance of Post-Traumatic Stress Disorder (PTSD) symptoms are heavily regulated by adrenergic hormones and neurotransmitters such as epinephrine and norepinephrine. Today, there are limited efficacious treatment options for PTSD, although there has been promise found in medications involved in the blocking of adrenergic hormone receptors. One medication in particular that has shown an alleviation of symptoms is prazosin, an α-1 adrenergic receptor antagonist. While there have been many studies indicating the efficacy of prazosin in the treatment of PTSD symptoms, no studies fully elucidate mechanistic changes induced by this treatment. The use of zebrafish (Danio rerio) has been growing in popularity, in part, due to the homology of the stress response system with mammals. In this study, the zebrafish model was utilized to determine underlying mechanistic effects that may account for the alleviation of PTSD symptoms by prazosin. Specifically, this study identified alterations in anxiety-like behavior by using the novel tank test and discovered differences in full body cortisol levels utilizing ELISA testing kits. In addition, this study elucidated changes in brain markers involved with regulating stress such as pro-opiomelanocortin (POMC), glucocorticoid receptors (GR), and corticotropin-releasing hormone (CRH) by reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR). It was observed that the chronic unpredictable stress (CUS) model was successful in recreating PTSD-like symptoms such as a decrease in basal levels of full body cortisol and reduced exploratory behavior. However, the expression of GR, POMC, and CRH showed no significant change after CUS. There was a trend indicating prazosin alone decreased basal levels of cortisol and increased exploratory behavior; however, there was no normalization of CUS-induced alterations in these measures by prazosin. In addition, prazosin did not significantly alter brain markers associated with stress hormone regulation. Therefore, the effectiveness of prazosin likely involves an alternative mechanistic pathway different from the specific stress axis elements under investigation in the current study.

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**C30**

**CINNAMON AND ITS METABOLITE MITIGATES PARKINSONIAN PATHOLOGY IN A MPTP MOUSE MODEL OF PD VIA ASTROCYTIC GDNF**

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Glial cell line-derived neurotrophic factor (GDNF) has potent neurotrophic effects and is known to promote the dopaminergic (DA) neuronal survival in cellular and animal models of Parkinson's disease (PD). However, long-term ectopic GDNF delivery is associated with long-lasting adverse side effects in PD patients. Therefore, finding safer and effective ways to elevate endogenous GDNF levels is an active area of research. During PD and other neurodegenerative disorders, while neurons die, usually glial cells such as astroglia do not die, but undergo activation and gliosis. Moreover, astrocytes are major cell type in the CNS, indicating that any contribution to nigral trophic effect from astrocytes would be significant. Here, we delineate that cinnamon metabolite sodium benzoate (NaB) upregulates GDNF in mouse and human astrocytes and that oral administration of cinnamon and NaB protect the nigrostriatum in MPTP mouse model of PD via astrocytic GDNF. We first investigated the effect of NaB on Gdnf mRNA levels using RT-PCR and real-time analyses and GDNF protein levels by immunoblotting and immunofluorescence analyses. Next, using battery of assays that include immunoblotting and densitometric analyses, immunohistochemistry, HPLC, rotarod and open field tests, we monitored nigral dopaminergic neuronal protection, striatal innervation, striatal neurotransmitters restoration and locomotor activities in control and MPTP insulted non-transgenic littermates ($Gfap^{cre}$) and astrocyte specific Gdnf conditional knockout ($Gdnf^{\Delta astro}$) mice. Interestingly, we notice that NaB significantly upregulated GDNF mRNA and protein levels in mouse and human astrocytes. Furthermore, oral administration of NaB and cinnamon increased astroglial expression of GDNF in the nigra of normal as well as MPTP-intoxicated mice. Interestingly, NaB and cinnamon also protected nigral dopaminergic neurons, preserved striatal innervation, restored striatal neurotransmitters, and improved locomotor activities in MPTP-intoxicated $Gfap^{cre}$ mice, but not in $Gdnf^{\Delta astro}$ mice. These findings highlight the importance of astroglial GDNF in cinnamon and NaB-mediated protection of the nigrostriatum in MPTP mouse model of PD and suggest possible therapeutic potential of cinnamon and NaB in PD patients.

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**C31-PD**

**ELEVATED GLUTAMATE TRANSPORTER EXPRESSION IN FEMALES WITH DEPRESSION**

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Major depressive disorder (MDD) is a common mental illness that has a strong association with suicidality. Conventional antidepressant treatments target the monoamine system, but only one-third of patients substantially improve with treatment. Mounting evidence indicates that abnormal function of the glutamate system contributes to the pathophysiology of depression. We have previously shown increased glutamatergic gene expression in the dorsolateral prefrontal cortex (DLPFC) of depressed females. Here, we have tested the hypothesis that genes regulating the glutamate transporters, rather than the monoamine transporters, have abnormal expression in depression. We extracted RNA from the gray matter of the DLPFC from three groups of subjects: MDD suicides (n=51), MDD patients who did not complete suicide (n=28), and controls (n=32). We measured the expression of genes encoding transporter proteins within the glutamate (EAAT1, EAAT2, VGLUT1, VGLUT2) and monoamine systems (SERT, NET, DAT, PMAT, VMAT) using QPCR, and performed multivariate analysis of covariance to investigate effects of diagnosis and sex using SPSS v. 24. We detected a significant increase in glutamate transporter gene expression [$F(4,48)=3.45$, $P=0.015$] in females with MDD, but these differences were not observed in males. The monoaminergic genes had similar expression in all diagnostic groups. Our analyses reveal altered expression of glutamate transporters in the DLPFC of depressed females. The results may indicate novel biomarkers for MDD, possibly representing targets for improved drug treatment. Further studies are planned to test if these gene expression markers predict antidepressant efficacy in depressed females.

*This work was performed in collaboration with Joel Kleinman MD PhD.*

**C32**

**THE EFFECTS OF DUAL-TASK COGNITIVE INTERFERENCE ON GAIT AND TURNING IN HUNTINGTON'S DISEASE**

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Huntington's disease (HD) is characterized by motor dysfunction (chorea), cognitive impairment, and psychiatric disturbances. The progression of HD leads to a loss of automaticity, such that previously automatic tasks, such as ambulation, require more attentional resources. Dual-task (DT) paradigms and fast paced gait may stress the locomotor system and reveal or exacerbate gait deficits not seen under single-task (ST) conditions. However, the impact of these gait "stress tests" on gait and turning domains in HD needs further investigation. Therefore, the aims of this study were to determine 1) how cognitive dual-tasking and increased walking speeds impacts gait and turning, 2) potential associations between these gait stress tests and falls in HD and 3) whether gait measures from wearable inertial sensors are sensitive to motor symptom severity in HD. Seventeen HD participants (55 $\pm$ 9.7 years) and 17 age-matched controls (56.5 $\pm$ 9.3 years) underwent quantitative gait testing via a two minute walk test (2MWT) with APDM$^{TM}$ inertial sensors. Gait was assessed under a 1) ST, self-selected pace, 2) fast-as-possible (FAP) pace and 3) verbal fluency DT. The Unified Huntington's disease Rating Scale-total motor scores (UHDRS-TMS) was administered and self-reported retrospective fall history within the past 12 months was recorded. A cognitive test battery was also administered to examine potential associations with gait deficits. During ST, DT, and FAP conditions, HD participants demonstrated significantly slower gait speed and shorter stride length, as well as greater lateral step and stride length variability compared to controls ($p < 0.00001$ to $0.034$). Significant dual-task costs were observed during turns with HD participants taking more time ($p = 0.013$) and a greater number of steps to complete a turn ($p = 0.028$) while dual-tasking compared to controls. Higher UHDRS-TMS correlated to greater stride length variability, more time in double support, and less time in single limb stance and swing phase all conditions ($p = 0.002$ to $0.016$). Decreased processing speed was associated with increased gait variability under all conditions. Unexpectedly, the number of participant's falls self-reported in the past year did not correlate with any gait or turn parameters under any conditions. HD participants demonstrated significantly greater DTC for turning, which is less automatic than straight walking, requiring dynamic coordination of multiple body segments, anticipatory control and perhaps cortical regulation. Turn complexity likely makes it more susceptible to the negative effects of DT cognitive interference in HD.

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**C33**

**NON-INVASIVE DETECTION OF SOLUBLE AMYLOID-β OLIGOMERS USING MRI IN THE NEW ZEALAND WHITE RABBIT**

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After being first described in 1998, the amyloid-β oligomer (AβO) hypothesis of Alzheimer's disease (AD) has rapidly become one of the central foci in Alzheimer's research. The AβO hypothesis posits that cell death and brain atrophy leading to AD is instigated by soluble species of the amyloid-β peptide. This hypothesis is based on the initial discovery that fibril-free synthetic preparations of the amyloid-β peptide were sufficient to inhibit long-term potentiation and cause nerve cell death (Lambert et. al., 1998). Additionally, AβOs accumulate in an AD-dependent fashion. In animal models since that time, AβOs have been shown to impair learning and memory and elicit hallmark pathophysiological features of AD such as tau hyperphosphorylation, synapse loss, oxidative damage, and synapse deterioration. Finally, AβOs are among the first biomarkers of AD to begin to accumulate and therefore present the earliest pathology for diagnosis and therapeutic intervention. Given all of this information, we have developed a probe detectable with magnetic resonance imaging (MRI), ACUMNS, from the AβO-specific humanized monoclonal antibody ACU-193 (Acumen

Pharmaceuticals), coupled to a magnetic nanostructure for *in-vivo* detection. In the present study, New Zealand white rabbits, which have the same amino acid sequence for amyloid-β as humans, received injections of stabilized, synaptotoxic preparations of AβOs before receiving a single injection of ACUMNS for MRI visualization of injected AβOs. Validation of probe specificity was performed using immunohistochemical staining of the rabbit brains and comparison of confocal images to MRI. The migration and binding of ACUMNS to injected AβOs was determined by comparison of signal intensity in regions of the brain known to be vulnerable to amyloid-beta accumulation. The hippocampus exhibited a difference in mean intensity in AβO-injected rabbits relative to sections from vehicle injected rabbits. Immunohistochemical analysis using the AβO-specific antibody NU-2 of these regions showed that sections from AβO-injected rabbits display diffuse puncta-like staining associated with the presence of soluble AβOs; sections from control group rabbits did not. Experiments are ongoing with additional animals to examine AβO-induced impairments in learning and memory in hippocampal dependent behavioral tasks such as trace eyeblink conditioning.
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**C34-G**
**TESTOSTERONE RECOVERS CHRONIC VESTIBULAR IMPAIRMENT FOLLOWING REPEAT MILD TRAUMATIC BRAIN INJURY**

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Traumatic brain injury (TBI) is defined as the impact of an external force to the head, causing vestibular, motor, cognitive and emotional impairment. TBI is quickly becoming a major public health concern. Vestibular symptoms, one of the most common complaints of TBI, and hypogonadism occur acutely following a single TBI and may develop into chronic deficits. Vulnerable populations such as military personnel and the elderly are at an increased risk for repeat mild TBIs (rmTBI), which have been shown to exacerbate impairment. Our lab has previously indicated a neuroprotective role of testosterone (T). Loss of T following TBI disrupts hormonal rhythms and prevents neuroplasticity that is required to repair damage at the time of injury, which may induce greater chronic vestibular development. Here, we first sought to create a clinically relevant rmTBI animal model with chronic vestibular deficits. Using this model, we tested whether T can recover chronic vestibular dysfunction.
TBIs were performed on Long Hooded male rats five times, each 48 hours apart, using an electromagnetic controlled cortical impactor. Sham TBI animals did not receive impact. Animals were subdivided into castrated or intact, creating 4 separate groups. Castration (CAS) was performed to remove endogenous T to simulate hypogonadism in a subset of rmTBI patients. Sham surgery animals were incised but gonads were not removed. To test the therapeutic effects of T, half of the animals of each group received T replacement via subcutaneous silicon capsules in the nape of the neck five weeks post TBI #5. Vestibular dysfunction was detected by a battery of five behavioral tests. Tests were scored out of 2 points, with the medians of each test contributing to a mean total vestibular score that was used to assess overall vestibular function. Higher scores indicated greater vestibular dysfunction.
At 1-month post TBI #5, a significant difference was found between all groups, with TBI intact and TBI castrated animals exhibiting the greatest vestibular deficiency scores. Following T treatment, vestibular scores did not improve at 1-week post treatment, but TBI T treated animals were insignificant compared to sham TBI animals at 1-month post treatment. Untreated TBI animals exhibited persistent chronic vestibular deficit at all time points. The therapeutic effects of T continued 6 months post TBI. Therefore, T replacement following TBI induced hypogonadism should be considered as a potential therapeutic strategy for recovery of chronic vestibular dysfunction.
*We would like to thank the support of the Loyola University Department of Otolaryngology: Head and Neck Surgery for funding this research.*

**C35**
**NEUROLOGICAL DEFICITS FOLLOWING SUBARACHNOID HEMORRHAGE MAY RESULT FROM DIFFERENTIAL EFFECTS OF BLOOD PRODUCTS ON CENTRAL NERVOUS SYSTEM CELL POPULATIONS**

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Subarachnoid Hemorrhage (SAH) is a disproportionately devastating neurological injury most frequently caused by the rupture of a cerebral aneurysm. Despite accounting for only 5-10% of strokes annually, it accounts for 25% of all years of life lost due to cerebrovascular disease as well increased risk of neurological deficits. While it is known that a large degree of neurological damage can result from SAH, it is not understood why. This study investigated the effects of intracranial hemorrhage on the central nervous system (CNS) cell types and how these effects might manifest into neurobehavioral changes. Longitudinal monitoring of rats with induced SAH was performed using the open field test to measure a variety of behavioral parameters. It was found that rats with SAH exhibited decreased time in the center of the open field (a proxy for increased anxiety) as well as decreased ambulatory distance and velocity which may suggest either functional or motivational deficits. Functional impairment was corroborated by administration of neurological assessments which revealed increased motor and sensory deficits in the SAH rats. In order to seek out a mechanism for impairment, an in-vitro model was used to investigate the effects of blood on CNS cell populations. Because SAH often causes neuronal loss, it was hypothesized blood would have a cytotoxic effect on some cell types, namely neurons, while inducing an activated phenotype in others, namely microglia. Live-cell imaging of microglia following whole blood exposure showed a shift from a resting, ramified to an activated, amoeboid morphology. This morphological change is similar to that induced by the immunogen lipopolysaccharide (LPS) which also stimulates increased microglial phagocytic activity, so it is suspected that future studies will demonstrate analogous effects of blood products on phagocytosis. One such blood product of interest is the molecule hemin which has been suggested by previous studies to trigger functional and morphological changes. Cytotoxic assays revealed hemin causes a dose-dependent increase of cell death in both

primary mouse microglia and human neuron-like SY5Y cells, and preliminary data suggests blood is more cytotoxic to neurons than microglia. Taken together, this suggests neurons may be more susceptible to injury following intracranial bleeding while microglia are more likely to take on an activated phenotype. These changes may both contribute to the functional and behavioral deficits observed following SAH. Future studies will test the cytotoxic effects of hemin against mouse neurons and astrocytes, and interactions between microglia and neurons will be sought out in-vivo.

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**C36**

**Heparan Sulfate Analog SPGG- a Potent Inhibitor of Human Cytomegalovirus Infection**

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**Introduction**: Human cytomegalovirus (HCMV) infection is the leading cause of permanent hearing and vision loss and can cause neurological impairment. While anti-HCMV drugs targeting virus DNA replication are available, increasing drug-resistance poses a major clinical concern. This highlights the critical need to identify novel agents that prevent infection and improve current anti-HCMV therapy. It has previously been shown that the sulfated pentagalloylglucoside (SPGG) exhibits anti-viral activity against herpes simplex virus (HSV). We reasoned that this compound will also inhibit HCMV entry and spread since it mimics cell surface heparan sulfate (HS), a molecule that is utilized by herpes viruses in the early stages of entry. By mimicking HS, it is believed to interfere with virus to host HS binding and block the infection. Using multiple assays, we provide evidence that the HS-mimetic "SPGG" functions as a potent inhibitor of HCMV entry and spread.

**Methods**: A lactate dehydrogenase (LDH) based-assay was used to determine if SPGG has any cytotoxic effects on the cells. Afterwards, to determine the potential of SPGG as an anti-HCMV agent, viral entry was measured using a β-galactosidase reporter virus pretreated with 100μM SPGG in human foreskin fibroblasts (HFF) (1 MOI). Additionally, virally induced immediate-early (IE) gene 1 and 2 expressions was measured by Cell-ELISA in HFF cells in a dose-dependent manner of SPGG-virus (0.1 MOI) pretreatment and in neuroblastoma (SKNMC) cells with 100 μM SPGG-virus (0.1 MOI) pretreatment. Confocal microscopy was used for qualitative analysis of SPGG's potential to inhibit HCMV infection using a GFP tagged HCMV (5MOI) reporter virus.

**Results**: The data presented support the potential of SPGG as an anti-HCMV agent at a non-toxic concentration. The analysis of the plaque reduction assay showed that SPGG was able to inhibit viral entry by 86% in HFF cells. Quantification of these findings by Cell-ELISA, testing dose-response, supported the previous findings and resulted in an IC50 value of 2.04 μM. The neuroblastoma cell line (SKNMC) also showed a significant reduction of 71% in immediate-early gene 1 and 2 expression after infection with 100 μM SPGG pretreated HCMV. Confocal microscopy of HFF and SKNMC cells infected with SPGG pre-treated HCMV supported the previous quantitative analysis.

**Conclusions**: This study provides first evidence of the anti-viral potential of "SPGG" against HCMV infection in both fibroblasts and neuronal cells.

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**C37**

**CELL TO CELL SPREADING OF TDP-43 C-TERMINAL FRAGMENTS MAY LEAD TO TOXICITY IN *CAENORHABDITIS ELEGANS***

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Many neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and prion diseases are characterized by abnormal accumulation of disease proteins in nerve cells leading to selective neurotoxicity. Moreover, a prion-like spreading mechanism might play a role in disease progression, where misfolded disease proteins spread from affected to unaffected neurons. Interestingly, ALS exhibits a focal clinical onset followed by a regional spreading of protein misfolding and cell death. Evidence points towards TAR DNA-binding protein 43 (TDP-43) as the major pathological protein in sporadic and certain familial forms of ALS where aggregates in affected neurons contain full length and fragmented forms of phosphorylated and ubiquitinated TDP-43. Despite recent advances in biomedical research on ALS disease associated proteins like TDP-43, a mechanistic explanation that links toxicity with cell to cell transmission remains unclear.

To explore whether TDP-43 spreads from cell to cell, we established a *C. elegans* model that expresses a human TDP-43 C-terminal fragment (TDP-25) fused to red fluorescent protein in the body wall muscle cells. We employed high-resolution time-lapse imaging and observed the intercellular movement of TDP-25 from body wall muscle cells to the hypodermis, intestinal cells and gonad in living animals. These results confirm that at least certain fragments of TDP-43 are released from donor cells into neighboring receiving cells. To determine if the accumulation of TDP-43 C-terminal fragments in receiving tissues leads to toxicity, we monitored the function of the gonad. We found that accumulation of TDP-25 had no significant effect on fecundity or embryogenesis compared to wild type animals. Furthermore, expression of TDP-25 in body wall muscles did not reduce thrashing activity suggesting that the expression of TDP-43 C-terminal fragments in the body wall muscle alone does not produce a toxic phenotype. Currently, we are mapping the movement of TDP-43 C-terminal fragments from donor cells to receiving cells using strains expressing tagged lysosomal and endosomal components. Evidence of phosphorylation and co-localization would support the model that the cell to cell spreading of toxic TDP-43 fragments contributes to the progression of disease pathology.

**C38**

**The Effect of Binge Alcohol and Traumatic Brain Injury on Hippocampal Neural Precursor Cell Proliferation and Survival**

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We determined the effects of traumatic brain injury (TBI) and binge alcohol on neural precursor cell (NPC) responses in the dentate gyrus (DG) of the hippocampus. Rats underwent binge alcohol (3g/kg/day) by gastric gavage for 3 days prior to TBI. We assessed the DG NPC response by utilizing the proliferation marker BrdU along with other markers for neurogenesis such as Doublecortin. We found that TBI injury alone significantly increased DG proliferation 7 days post injury. However, a combined binge alcohol and TBI regimen resulted in decreased DG proliferation at 7 days post-TBI. Long-term survival of DG hippocampal cells was also assessed at 6 weeks post-TBI. We found that TBI did not affect the overall survival of $BrdU^+$ cells, but binge alcohol reduced the number of $BrdU^+$ cells that survived. Taken together, these results suggest that TBI and binge alcohol separately increased short-term DG proliferative responses but in combination, attenuated DG proliferation. However, binge alcohol alone decreased the number of surviving DG cells long term. These results point to important consequences for public health as alcohol misuse conditions such as binge drinking are currently on the rise.

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**C39-UG**

**ROLE OF UNC5C, AN ALZHEIMER'S RISK GENE IN LATE-ONSET ALZHEIMER'S DISEASE IN A NOVEL MOUSE MODEL**

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Alzheimer's Disease (AD) is a devastating and currently incurable progressive neurodegenerative disease that affects 5 million Americans every year. It is the most common form of dementia that is characterized by memory loss and problems with cognitive ability and behavior. The two most significant pathological hallmarks of AD are amyloid plaques and neurofibrillary tangles. Though it is known that neurons are dying in the AD-afflicted brain, the exact mechanism behind the cell death pathway is unknown. Recently, a rare autosomal dominant coding mutation found in the gene of Uncoordinated 5C (UNC5C) was discovered to be linked with late-onset AD. This mutation alters a conserved amino acid in the death domain hinge region of netrin receptor UNC5C and is thought to increase activation of the neuronal death pathway. In primary hippocampal neurons, it was shown that overexpression of T835M UNC5C increased cell death in response to neurotoxic stimuli including beta-amyloid (Aβ). Other studies in cell culture suggest that T835M UNC5C mediates an intracellular death-signaling cascade involving death-associated protein kinase and other executioners of apoptosis. However, the effect of this T835M UNC5C mutation on the neuronal death pathway in an animal model is not well understood. To this end, T835M UNC5C knock-in mouse model was created (UNC5C KI/KI). We hypothesize that T835M UNC5C predisposes to late-onset AD by increased activation of the apoptotic pathway. We are currently investigating the mechanism of neuronal death in the presence of Aβ pathology using an amyloid mouse model, 5XFAD, crossed with UNC5C KI/KI. These studies will identify important proteins involved in the T835M UNC5C-mediated apoptotic pathway which can serve as therapeutic targets to prevent neuronal loss in AD.

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**C40**

**ROLE OF MICROGLIA IN A MOUSE MODEL OF NEURONAL CEROID LIPOFUSCINOSES**

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The late infantile form of neuronal ceroid lipofuscinoses (LINCL) is a lethal neurodegenerative disease that presents in children with inactivating mutations in tripeptidyl peptidase 1 (*TPP1*), and is characterized by epilepsy, vision loss and decay of psychomotor function. The disease leads to lysosomal accumulation of autofluorescent storage material, but astrogliosis and microglial activation seem to be a better indicator of areas of neuronal loss. We are using a mouse model ($Tpp1^{-/-}$) in which *Tpp1* expression was disrupted by gene targeting and exhibits a progressive neurological phenotype similar to that of LINCL. RNA-seq experiments indicated that the neuroinflammation process develops between 2 and 4 months in this model. From this data, we identified transcriptional upregulation of genes such as *Clu*, a chaperone protein involved in lipid transport. *Hexb*, which is involved in the degradation of fatty compounds within lysosomes, and *Ctss*, a lysosomal protein. By mRNA in-situ hybridizations we confirmed upregulation of *Ctss* and *Hexb* in microglia; moreover, there was upregulation of *Clu* in astrocytes of the cortex, thalamic region, and cerebellum of the $Tpp1^{-/-}$ brains. In other neurodegenerative diseases, depleting microglia was beneficial in stalling the neurodegenerative process. Thus, we depleted microglia using inhibitors of the CSF1 receptor (PLX5622; PLX3397) in both an *in vivo* and slice culture system in order to establish the involvement of microglia in this model. In both systems, there was a downregulation of microglial genes when treated with the inhibitor accompanied by an upregulation of astrogliosis, reflected by increased expression of *Gfap* and *Aqp4* in control and $Tpp1^{-/-}$ brains. Furthermore, long term exposure to PLX5622 accelerates lethality in $Tpp1^{-/-}$ mice. This increase in astrogliosis in $Tpp1^{-/-}$ mice indicates that microglia play a protective role during the neuroinflammation process by possibly slowing down the neurodegenerative process.

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**C41**

**Creating a Tool Kit for the Structural Characterization of Neurotoxic Amyloid Beta Oligomers in Alzheimer's disease**

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Alzheimer's disease (AD) is a progressive, neurodegenerative disease and is the sixth leading cause of death in the U.S. Amyloid beta oligomers (AβOs) are neurotoxins that contribute to AD pathogenesis and cause pathologies like synapse loss and neuronal death. However, it has been difficult to structurally characterize AβOs as they are unstable and tend to aggregate in low abundances in the human AD brain. In this project, various methodologies were used to separate and stabilize neurotoxic AβO populations to aid in the structural characterization of AβOs. In order to pull out AD-relevant AβO subpopulations, the AβO-specific antibody NUsc1 was used. Through multiple techniques, NUsc1 was found to bind a AβO subpopulation > 50 kDa. To test if this AβO population was neurotoxic, experiments were conducted in vitro as well as in vivo. When mice were injected with NUsc1-depleted fractions, they didn't have memory deficits. This suggests that the AβO > 50 kDa population is neurotoxic and causes AD pathologies. The NUsc1 data indicates that >50 kDa targeted subpopulation is complex so I proposed to decrease sample complexity by decreasing starting Aβ concentration through SEC analysis. As the starting Aβ concentration decreased, the sample molecular weight (MW) range decreased. At the lowest concentration, only one molecular weight (~100 kDa) was targeted. This illustrated that low Aβ concentrations could be utilized to target MW-specific AβO subpopulations. We also have started to use NUsc1 to investigate the structure & stability toxic AβOs in the brain of an AD mouse model. Preliminary data indicates there may be stable AβO >250 kDa populations already existing in the AD brain. This population appears stable as the addition of AβO-stabilizing DFDNB didn't affect the detected AβO signal. By using these tools together, it will allow for structure-function analysis of AD-relevant AβOs, which can be applied to the development of AD therapeutics/diagnostics.

**C42-PD**

**REGULATION OF BACE1 TRAFFICKING THROUGH C-TERMINAL MOTIFS**

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The transmembrane aspartyl protease β-site APP cleaving enzyme 1 (BACE1) is critical for initiation of the sequential cleavage of the amyloid precursor protein (APP) to generate Alzheimer's disease β-amyloid peptides. BACE1 undergoes secretory and endocytic trafficking. Several studies show the C-terminal tail of BACE1 regulates its trafficking through post-translational modification and involves binding with other cargo proteins. However, how BACE1 trafficking is regulated in neurons is not entirely understood. Here, we study the dynamics and the localization of a series of BACE1 C-terminal mutants in cultured HeLa cells and primary neurons. The following BACE1 mutants were examined in our study: D495R (lacks AP2 binding site), L500I (lacks GGA binding site), LL/AA (lacks AP2 and GGA binding sites), S498A and S498D (phosphorylation site mutants), and K501R (lacks the ubiquitination site). We observed a delay in the rate of endocytosis of surface mutant BACE1 D495R, LL/AA, and K501R in HeLa cells. In mature neurons, we observed increased spine localization and axon/dendrite ratios (ADR) for BACE1 D495R and LL/AA. Interestingly, we also observed decreased spine localization of BACE1 K501R in mature neurons. Our results suggest that the dendritic spine localization of BACE1 is dynamically regulated by endocytosis via AP2 binding whereas GGA binding does not affect this process. Our ongoing studies characterize how the BACE1 mutants affect the dynamics of BACE1 mutant localization in dendritic spines and axons neurons.

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**C43**

**Exosomes secreted by diseased ALS cerebral cortex include messages to modulate disease progression**

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Exosomes are mediators of intercellular communication between different cells in the body, and are small vesicles typically 30-150nm in size. They carry a cargo of important biomolecules (protein, RNA, miRNA and lipids), which is used to transmit signal to recipient cells. Their ability to cross the blood brain barrier enables flow of information to distant locations within central nervous system (CNS), and between the CNS and the periphery. Building evidence suggests the importance and involvement of cortical component of motor neuron circuitry in the establishment and progression of disease pathology in amyotrophic lateral sclerosis (ALS). This study was conceived to identify differential protein content of the exosomes secreted by mixed cortical neuron cultures from 3 day old hSOD1$^{G93A}$ and prpTDP-43$^{A315T}$ mice, two well-defined mouse models of ALS. We investigated if diseased cortical neurons utilize exosomes to inform other cells and neurons about their physiological condition and whether this information serves to propagate the disease or information as a "warning signal" to other cells and neurons. Our preliminary results suggest that hSOD1$^{G93A}$ and prpTDP-43$^{A315T}$ cortical neurons include a very distinct set of proteins in exosomes, some of which are common and some are unique. Proteins present in these early-age exosomes suggest encoding a "warning signal" to other cells and neurons. This study begins to shed light on how diseased cortical neurons utilize exosomes to communicate their disease state. Our findings may reveal novel treatment strategies to prevent disease progression and to improve motor neuron health in ALS and related motor neuron diseases.

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**C44**

**HORMONAL CONTRACEPTIVE USERS EXHIBIT BLUNTED REWARDING EFFECTS OF ALCOHOL**

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Epidemiological evidence shows that women exhibit a more severe course of alcohol use disorder (AUD); they progress from initial use to dependence at a faster rate, are more susceptible to the toxic effects of alcohol, and exhibit higher relapse rates than men. Preclinical and clinical data indicate a biological basis for sex differences in the development of AUD and that ovarian hormones likely contribute to these differences. However, to date no studies to our knowledge have assessed the influence of synthetic ovarian hormones, including hormonal contraceptives, on alcohol effects and drinking in controlled laboratory studies. Here, we compared subjective responses to alcohol and alcohol self-administration between men, naturally cycling (NC) women, and women using hormonal contraceptives (HC). Participants (N=175) completed two experimental sessions with double-blind administration of 0 and 0.8 g/kg alcohol in randomized order. They completed standardized questionnaires to rate mood and drug effects, and heart rate and blood pressure were measured before and at repeated times after administration of beverages. At a third experimental session, participants first consumed a priming dose of alcohol (0.2g/kg), followed by a free drinking paradigm during which they could consume up to 8 additional 0.2g/kg doses of alcohol. Alcohol significantly increased self-reported subjective stimulation and euphoria among men (N=111) and NC women (N=36), but not among women using HC (N=28). The groups did not differ in baseline mood, cardiovascular responses to alcohol or in breath alcohol concentrations (BrAC). In addition, demographic (including drug and alcohol use) and personality characteristics (including trait and behavioral impulsivity) did not differ between NC women and women using HC. During the free drinking session, men and NC women chose to consume significantly more drinks than women using HC. These data suggest that HC use blunts the stimulant-like and euphoric subjective effects of alcohol, and reduces alcohol self-administration. The absence of differences in demographic and personality characteristics between NC women and women using HC suggests that differences in the rewarding effects of alcohol are related to use of HC and are not due to selection bias. Together, the findings suggest that administration of exogenous ovarian hormones may protect against alcohol abuse.

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**C45-G**

**INERTIAL SENSOR-BASED TREMOR AND BRADYKINESIA QUANTIFICATION AND POTENTIAL FOR EARLY DISEASE IDENTIFICATION IN FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME (FXTAS)**

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FXTAS is a neurodegenerative disorder characterized by tremor and cerebellar gait ataxia. It occurs in some carriers of a 55-200 CGG repeat size premutation in the *fragile X mental retardation 1* gene. However, early predictors of FXTAS onset are needed and quantitative measurements of tremor, bradykinesia and coordination may be useful in natural history studies, response to medications and as outcome measures in future clinical trials. The objective our work was to quantify the severity of upper extremity (UE) tremor subtypes, bradykinesia and incoordination in FXTAS and potentially identify preclinical symptoms in premutation carriers (PMC) without a diagnosis of FXTAS using an inertial sensor system. 39 PMC with FXTAS (Mean age = 67.8± 8.5), 20 PMC without FXTAS (Mean age = 53.5 ± 10.6), and 27 healthy controls (Mean age = 65.4 ± 9.1) performed a series of UE motor tasks while wearing an *ETsense™* sensor with the *Kinesia One* system which quantifies several types of tremor, bradykinesia and rapid alternating movements. Regression analyses controlling for age, sex and CGG repeat size with FXTAS diagnosis group as the main predictor was performed to detect potential group differences. The FXTAS Rating scale (FXTAS-RS) was administered to determine whether these clinician-rated scores correlate with severity scores from the Kinesia system.

We found that PMC with FXTAS had significantly worse postural and kinetic tremor compared to PMC without FXTAS ($p$=0.04; 0.03) and controls ($p$=0.001; 0.0001), respectively, and worse finger tap ($p$=0.0009), hand movement ($p$=0.0001) and rapid alternating movement speed ($p$=0.003) and amplitude ($p$=0.04) than controls. PMC without FXTAS had significantly worse finger tap ($p$=0.004), hand movement ($p$=0.01) and rapid alternating movement speed ($p$=0.003) and amplitude ($p$=0.02) than controls. All quantitative scores were significantly correlated with the FXTAS-RS scores (p=0.02 to < 0.0001) except for finger tap speed and amplitude. The *ETSense™* system is a feasible, portable and low-cost method for quantifying UE tremor, bradykinesia and dysdiadokinesia in FXTAS and may have potential in detecting preclinical symptoms of UE speed and coordination deficits in PMC without FXTAS. Further validation of these measures and confirmation of preclinical disease identification in longitudinal studies with higher subject numbers is needed.

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**C46**

**EFFICACY OF LONG TERM INTRATHECAL 2-HYDROXYPROPRL-ß-CYCLODEXTRIN TREATMENT ON BALANCE AND GAIT DEFICITS IN NIEMANN-PICK TYPE C1**

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Niemann-Pick Type C (NP-C) is an autosomal recessive neurodegenerative storage disorder characterized by lysosomal accumulation of cholesterol in brain and peripheral tissues. NPC is caused by mutations in NPC1 or NPC2, proteins that normally transport cholesterol. There is great phenotypic variability but cerebellar ataxia, apraxia, and cognitive decline are seen in many patients. 2-Hydroxypropyl-ß-cyclodextrin (HP-ß-CD) extends life and slows disease in NPC animal models. We examined the efficacy of HP-ß-CD in slowing neurological deterioration in patients with NPC via balance and gait

testing. Six patients were treated with HP-ß-CD intrathecally in an Investigational New Drug (IND) FDA approved protocol at Rush University Medical Center (RUMC) for 15 – 60 months. Six additional patients with the ability to perform these same outcome measures were enrolled in a RCT (VTS301) at the RUMC site. Balance and gait outcome measures were tracked longitudinally with computerized dynamic posturography (CDP) and an inertial sensor system respectively, to determine potential modification of disease course and longitudinal change over time. The primary balance outcome measure was the composite postural sway score on CDP. Gait variables analyzed were in the domains of pace, rhythm, variability, gait phase cycle and turning. Percent of scores improved by >10%, changed by <10% (unchanged/stable), and worsened by >10% from baseline was quantified. Global function was assessed by the NPC-Neurological Severity Scale (NPC-NSS). Balance outcome measures to track disease course showed overall NPC disease stability or slight improvement in this HP-ß-CD treatment protocol. Stride length and velocity were stable in 8/12 patients; cadence was stable in 11/12; double support and swing times were stable or improved in 10/12 patients; turn duration was stable in 7/12 patients; gait variability worsened in the majority of patients (9/12 patients). These findings, in general, support the concurrent lack of worsening or mild improvement on the NPC-NSS, which deviates from the expected disease trajectory based on the natural history of NPC. The primary outcome measure (CDP composite postural sway scores) to track disease course shows overall NPC disease stability or slight improvement in this HP-ß-CD treatment protocol which is in agreement with the overall NPC-NSS scores. Gait pace, cadence and time in double support and swing phase showed overall disease stabilization while gait variability worsened. CDP balance measures and inertial sensor based gait and turn outcomes are feasible to determine efficacy of pharmaceutical interventions in neurological populations. Ongoing tracking with these sensitive measures and repeated measures statistical analyses will quantify the chronic impact of HP-ß-CD on balance and gait function in NPC and may help differentiate good responders from poor responders.

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**C47**

**DEVELOPMENT OF A CRE-DEPENDENT TRANS-SYNAPTIC TRACER TO ANALAYZE THE OUTPUTS OF NEURONS CARRYING MUTATIONS**

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In the developing brain, somatic mutations cause cortical malformations associated with pediatric intractable epilepsy. The mechanisms of disease by which a relatively small percentage of cells carrying mutations disrupt the organization of the cortical circuits is mostly unknown. To analyze the outputs from the neurons carrying mutations during development, we are creating a Cre-dependent AAV vector expressing a wheat germ agglutinin (WGA)-GFP fusion. We will take advantage of the fact that when WGA is expressed in neurons, it is transported throughout the cell, secreted, and taken up by synaptically-connected neurons. We also plan to assess whether the cells connected to the neurons carrying somatic mutations have altered intrinsic activity. We will modify our newly generated virus and replace the WGA-GFP for a WGA-GCamp6 fusion protein. While this line of investigation has great potential, it is presently unknown whether the WGA fusion proteins would be: 1) expressed and functional, and 2) transferred trans-synaptically. Therefore, we plan to overexpress the newly generated vectors in HEK293T cells to check if the fusion WGA proteins are expressed in the presence of Cre recombinase. Once this is established, the function of the protein will also be determined in vitro (i.e., can WGE-GCaMP6 detect calcium transients in a similar manner to GCaMP6?). Finally, virus will be packed and primary neurons in culture will be infected to assess the efficiency of trans-synaptic transfer. We believe this technology will be valuable to uncover the extent to which somatic mutations can disrupt the integration of neurons into a nascent neural network, and how these disruptions affect other developing regions.

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**C48**

**ABCA1 ACTIVATION IN THE CNS AS A THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE-LIKE PATHOLOGY IN A NOVEL TRANSGENIC MOUSE MODEL**

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*APOE4* is the greatest genetic risk factor for Alzheimer's disease (AD), increasing risk up to 15-fold compared to *APOE3*. However, few AD therapeutics target pathology through apoE4. *APOE4* is associated with accelerated amyloid-beta (Aβ) accumulation, both as amyloid plaques and soluble oligomeric Aβ (oAβ), the latter considered a proximal neurotoxin. In brains of humans and transgenic mice expressing human *APOE,* apoE4 levels are lower than apoE3. Thus, our general therapeutic goal is to increase apoE4 levels and decrease soluble Aβ levels. The EFAD-Tg mouse model overexpresses Aβ42 and expresses human *APOE4* (E4FAD) or *APOE3* (E3FAD). ABCA1 is the major transporter of lipid to apoE-containing lipoproteins in the brain parenchyma. Thus, we predict that activation of ABCA1 will increase the lipidation of apoE4, improving stability and restoring apoE4 levels. Artery Therapeutics, Inc. developed novel ABCA1 agonists, including CS6253 (Cs), for cardiovascular disease. Cs demonstrates high selectivity and potency for ABCA1-mediated cholesterol efflux. *In-vitro*, Cs increased apoE levels 10-20-fold and lipoprotein cholesterol efflux capacity using primary astrocytes expressing apoE3 or apoE4. For *in vivo* studies, male and female E4FAD and E3FAD mice were treated with Cs using both a prevention (4-8 months/M) and reversal (8-10M) paradigm. There were no significant results with the reversal paradigm. Cs increased ABCA1 levels and reduced soluble and insoluble Aβ and amyloid deposition in male E3FAD and E4FAD mice. Additionally, in male E3FAD mice, Cs increased synaptic viability and reduced astrogliosis. Although ABCA1 levels increased, indicating direct target

engagement, there were no significant effects in female E3FAD and E4FAD mice. In summary, ABCA1 activation by Cs effectively prevented synaptic loss, neuroinflammation, Aβ deposition, and reduced soluble Aβ levels in male EFAD mice (E3FAD>E4FAD). Future work will optimize treatment paradigms and examine mechanisms underlying sex-specific responses to Cs-based ABCA1 agonism.
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**C49**

**THE AGE-DEPENDENT EFFECT OF *APOE* AND SEX ON ALZHEIMER'S DISEASE PATHOLOGY IN A NOVEL TRANSGENIC MOUSE MODEL**

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While age is the greatest risk factor for Alzheimer's disease(AD), *APOE4* is the greatest genetic risk factor, increasing risk up to 15-fold compared to the common *APOE3* and the rare but protective *APOE2. APOE4* is associated with the accelerated accumulation of amyloid-β (Aβ) peptide, which aggregate to form both amyloid plaques and soluble oligomers of Aβ. Recently, studies have shown that female (♀) *APOE4* carriers have a higher risk for developing AD than male (♂) *APOE4* carriers. In our novel EFAD transgenic mice, expressing human *APOE* and overexpressing human Aβ42, we have demonstrated that male 6-month old (M) E4FAD mice exhibit an increase in neuroinflammation and Aβ deposition. However, the effects of both age and sex, two important AD risk factors that modulate pathology with age in EFAD mice, have not yet been characterized. Thus, male and female EFAD mice aged 4M to 18M were compared for measures of AD pathology that included neuroinflammation (microgliosis and astrogliosis), Aβ deposition and amyloid load. While the Kaplan-Meier survival curve for the human population showed % survival decreased with age for ε4/4 < ε3/4 < ε3/3 < ε2/3 < ε2/4, indicating ε4 is the dominant allele. The Kaplan-Meier curves from our EFAD mice include sex as well as APOE genotype and demonstrate that ♀ sex is dominant compared to *APOE4.* With age, the regional progression of pathology begins in the hippocampus, specifically the subiculum, spreading to the frontal cortex, posterior cortex and then the thalamus. Both neuroinflammation (astrogliosis, microgliosis), and Aβ pathology (Aβ deposition and amyloid load) increase in E4FAD > E3FAD and are consistently greater in females compared to males in both E3FAD and E4FAD mice. Because the EFAD mice develop pathology dependent on age, sex, and *APOE* genotype, they are a novel preclinical AD mouse model that mirror risk factor-induced pathology in humans.
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**C50**

**EFFECTS OF AGE, *APOE* GENOTYPE, AND SEX ON THE PLASMA LIPOPROTEIN PROFILE OF A NOVEL ALZHEIMERS DISEASE TRANSGENIC MOUSE MODEL**

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Alzheimer's disease (AD) is the 6th leading cause of death in the United States with no cure, few palliative treatments, and no prognostic biomarker. The lack of a surrogate biomarker that is both reliably prognostic and sensitive to changes over time has limited drug discovery and will be a barrier for targeted treatment of at-risk populations. The greatest genetic risk factor for AD is *APOE4*, increasing risk 5- to 15-fold compared to the common *APOE3*, while *APOE2*, though rare, reduces risk. Importantly, female (♀) *APOE4* carriers have a greater lifetime risk and rate of cognitive decline compared male (♂) *APOE4* carriers. Apolipoprotein E (apoE), encoded by *APOE*, is a protein component of both plasma lipoproteins and the primary apolipoprotein expressed in the brain. In the CNS and periphery, apoE to regulates cholesterol transport. Typically, blood lipid panels report total lipid levels and lipids levels associated with isolated lipoproteins, specifically VLDL, LDL and HDL, with an emphasis on the HDL/LDL cholesterol ratios. In contrast to blood lipid panels, plasma lipoprotein profiles elute intact lipoprotein particles from largest to smallest i.e., Chylomicrons/VLDL, LDL, HDL-2, HDL-3, and free proteins that can be further analyzed for lipid/protein content (e.g., cholesterol, apoE). This profile and its lipid content are affected by *APOE* genotype. The effect of *APOE* genotype on plasma lipoprotein profiles and the ability to detect shifts (i.e., leftward indicating a dyslipidemic profile) over time may act as a surrogate blood biomarker for AD. We hypothesize that the plasma lipoprotein profile is a prognostic biomarker for AD, reflecting the AD risk associated with age, *APOE4* genotype, and ♀ sex. In the novel EFAD transgenic mice, expressing the human *APOE* genotypes and overexpressing specifically human Aβ42, our lab previously demonstrated that cholesterol in the plasma lipoprotein profiles of E4FAD mice co-eldued with HDL and, in older mice, cholesterol co-eluded in Chylomicrons/VLDL. The current study will extend this work to include the effect of sex, thus the interaction among age (8 and 18-months), *APOE* genotype (*APOE3* vs. *APOE4*), and sex (♂ vs. ♀) on the plasma lipoprotein profile can be determined. Plasma lipoprotein profiles were quantified using fast protein liquid chromatography and the fractions were further analyzed using cholesterol assays. ♀ sex appears to exacerbate the effects of *APOE* genotype on the plasma lipoprotein profiles and the co-elution of cholesterol. In conclusion, this work, in combination with future studies in human samples, will help establish whether the plasma lipoprotein profile is a surrogate biomarker for cognition in AD.
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**C51**

**TOLL-LIKE RECEPTOR-4 ANTAGONISM AS A THERAPEUTIC FOR AD-ASSOCIATED NEUROINFLAMMATION**

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Alzheimer's disease (AD) is the most common form of dementia with no cure and only palliative therapeutics. The rare familial form of AD (FAD) is caused by autosomal dominant mutations that increase the peptide amyloid-β (Aβ), which aggregates to form both amyloid plaques and soluble oligomeric forms (oAβ), the latter considered a proximal neurotoxin. *APOE4* is the greatest genetic risk factor for AD, compared to the common *APOE3* and the rare but protective *APOE2*. The mechanism underlying *APOE* modulation of AD risk remains unclear. Even less understood is the critical link between female sex and *APOE4*-induced AD risk. A common and early symptom of AD pathology is Aβ-induced neuroinflammation modulated by *APOE*. Importantly, our *in vitro* studies demonstrated that the increase in oAβ-induced neuroinflammation is mediated by Toll-like receptor-4 (TLR4), a key component in the innate immune response. Thus, our hypothesis is that blocking the TLR4 pathway will reduce AD pathology, particularly in female *APOE4* carriers. To test this hypothesis, we used the novel EFAD-Tg mice, which overexpress specifically Aβ42 and express *APOE4* (E4FAD) or *APOE3* (E3FAD). Male and female E4FAD and female E3FAD mice were treated with IAXO101 (IAXO), a TLR4 antagonist, using both prevention (4-6M) and reversal (6-7M) paradigms. There were no significant effects with the prevention paradigm. In the reversal paradigm, IAXO decreased microgliosis and IL-1β levels in both male and female E4FAD mice. IAXO induced a significant a decrease in total Aβ42, soluble oAβ, and a amyloid deposition, with a recovery of learning and memory in the female E4FAD mice. Thus, the inhibition of the TLR4 pathway by IAXO101 affected selective readouts for both neuroinflammation and Aβ solubility, two components of AD-related pathology. Further investigation is needed to understand the use of TLR4 antagonists for AD therapeutics

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**C52**

**THE EFFECTS OF SEX AND *APOE* GENOTYPE ON THE GUT MICROBIOME IN EFAD TRANSGENIC MICE.**

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While the gut microbiome (GM), the collective genome of gastrointestinal bacteria, is primarily studied in metabolism and immune defense, the GM may also serve as a therapeutic target for the treatment of Alzheimer's disease (AD). AD patients exhibit dysbiosis, with the GM becoming a source of endotoxins rather than essential metabolites. To understand the potential of the GM as an AD therapeutic target, the effects of the known AD risk factors must be determined. Although rare, familial AD (FAD) is caused by autosomal dominant mutations that increase amyloid-β peptide (Aβ). Age is the greatest risk factor for AD and *APOE4*, the e4 allele of *APOE*, is the greatest genetic risk factor for AD, increasing risk up to 15-fold compared to the common ***APOE3.*** *APOE4* is associated with increased Aβ, resulting in increased levels of both amyloid plaques and soluble neurotoxic oligomeric Aβ (oAβ). Importantly, female (♀) *APOE4* carriers have a greater lifetime risk for developing AD, an increased rate of cognitive decline and an accelerated accumulation of Aβ compared to male (♂) *APOE4* carriers. To study the interactions among these AD risk factors, we developed the EFAD transgenic (Tg) mice by introducing the human-*APOE* genotypes into the 5xFAD-Tg mice (E3FAD, E4FAD). **Our hypothesis is that *APOE* genotype and sex interact to modulate the GM composition during AD pathogenesis in EFAD mice.** In a preliminary study, microbial analysis of fecal samples from 4-month (M) EFAD mice demonstrate that *APOE* genotype has a significant effect on the GM across different taxonomic levels (Operational Taxonomic Unit (OTU), Genus, and Family). Additionally, there is a significant difference in the GM of ♂E4FAD vs ♀E4FAD, though only at OTU level. This synergistic effect of *APOE4* and female sex on the GM was further validated by a bootstrap similarity comparison. In addition, heatmap analysis of the abundance of 29 specific bacterial sequences demonstrated clustering of ♀E4FAD and ♂E4FAD samples, again suggesting that *APOE* genotype and sex interact to alter the EFAD GM. This study will help define the composition of the GM in ♂E3FAD, ♀E3FAD, ♂E4FAD and ♀E4FAD. This is a critical step in establishing GM as a function of AD progression influenced by *APOE* and sex. Ultimately, defining the GM that distinguishes ♂E3FAD, ♀E3FAD, ♂E4FAD and ♀E4FAD will be used to develop a potential AD therapeutic that corrects the GM, particularly for the at risk ♀*APOE4* carriers.

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**C53**

**THE EFFECT OF AGE, SEX, AND *APOE* GENOTYPE ON Aβ PATHOLOGY IN AN ALZHEIMERS DISEASE TRANSGENIC MOUSE MODEL**

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While age is the greatest risk factor for Alzheimer's disease (AD), *APOE4* is the greatest genetic risk factor, increasing risk up to 15-fold compared to the common *APOE3* and the rare but protective *APOE2.*

*APOE4* is associated with the accelerated accumulation of amyloid-β (Aβ) peptide, which aggregates to form both amyloid plaques and soluble oligomers of Aβ (oAβ). Recently, studies have shown that female (♀) *APOE4* carriers have a higher risk for developing AD than male (♂) *APOE4* carriers. In our novel EFAD transgenic mice, expressing the human *APOE* genotypes and overexpressing human Aβ42, we demonstrate an increase in soluble oAb in 6M ♀ and ♂ E4FAD compared to ♀ and ♂ E3FAD mice. We hypothesize that the interactive effects among age, *APOE4,* and female sex will increase total levels of Ab42 and soluble oAb. To generate biochemical extraction profiles for Ab and apoE, the cortices of 4-18M ♂ and ♀ E3FAD and E4FAD mice were extracted via a 3-step sequential method, producing soluble (TBS), detergent-soluble (TBSX/triton X-100) and insoluble (FA/formic acid) fractions. Total levels of apoE increase with age for both sexes and genotypes, with a 2-step increase at 8M. Total levels of Ab increase with age, with E4FAD > E3FAD and ♀ >♂. The apoE extraction profile reveals that TBSX- and FA-apoE increases with age while TBS does not increase. Compared to E4FAD, E3FAD exhibited greater levels of lipidated apoE, extracted in the TBS-X fraction. Levels of FA-apoE were greater than TBS- and TBS-X-apoE, likely due to the co-deposition of apoE with Ab. For the Ab42 extraction profile, TBS, TBSX- and FA-Ab42 increased with age. Levels of Ab42 were greatest in FA fraction, with E4FAD > E3FAD and ♀ >♂. Importantly, soluble oAb levels increased with age in all genotypes (♂E3FAD<♂E4FAD<♀E3FAD<♀E4FAD), while soluble Ab42 levels plateaued (♂E3FAD<♀E3FAD<♂E4FAD<♀E4FAD). This is critical as even in EFAD brain tissue, soluble oAb tracks disease progression. Biochemical analysis of the EFAD mice reveals an age induced increase in Ab pathology that mirrors the increased AD risk in humans (♂E3FAD≤♂E4FAD≤♀E3FAD<♀E4FAD). Thus, the EFAD mice serve as a viable therapeutic pre-clinical mouse model.

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**C54**

**OAb IN HUMAN PLASMA AS A MECHANISTIC BIOMARKER FOR ALZHEIMER'S DISEASE IN HUMAN PLASMA**

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Alzheimer's disease (AD) is a fatal neurodegenerative disease that is the 6th leading cause of death in the United States with no cure and few palliative treatments. Currently, there is no preventative treatment, and even if such a therapeutic could be identified, without a predictive biomarker, a target population for treatment could not be determined. Although the mechanism remains unclear, AD is caused by increased levels of the amyloid-β peptide (Aβ), which aggregates to form both amyloid plaques and soluble oligomeric Aβ (oAβ), the latter considered a proximal neurotoxin. We believe that levels of oAβ in human plasma are a prognostic biomarker, and have developed and licensed a method for their detection (LOD <100pMol). While age is the greatest risk factor for AD, *APOE4* is the greatest genetic risk factor, increasing risk up to 15-fold compared to the more common *APOE3*. Importantly, female (♀) *APOE4* carriers have an increased risk for AD compared to male (♂) *APOE4* carriers. Key to the success of this project has been the stratification of both control and AD patients by sex within *APOE* genotype, with the results that plasma oAβ levels are: ♀*APOE4* > ♂*APOE4* ≥ ♀*APOE3* > ♂*APOE3.* This response was observed in two large human post-mortem cohorts. However, stratification, the principle of personalized medicine, is simply not applied to AD populations. We now seek to threshold oAβ levels using longitudinal and human AD trial data to establish prognostic potential, with the goal of partnering with the private sector for commercialization.

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**C55-G**

**BINGE ALCOHOL DRINKING ALTERS THE EXPRESSION OF THE TRANSCRIPTION FACTOR ORTHODENTICLE HOMEOBOX 2 (OTX2) IN THE VENTRAL TEGEMENTAL AREA**

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The ventral tegmental area (VTA), which contains dopamine neurons that project to regions involved in motivation and reward, plays an important role in the development of both alcohol use disorder (AUD) and affective disorders. Stressing mice during a critical juvenile period induces a transient decrease in the expression of OTX2 in the VTA and increases susceptibility to depression in adulthood. Because there is a significant comorbidity between alcohol abuse and depression, we hypothesized that OTX2 in the VTA may be involved in alcohol drinking. In this study, we first determined if ethanol exposure, using a mouse model of binge drinking, altered OTX2 gene and protein expression in the VTA of adult mice. In addition, we investigated if depleting VTA OTX2 in adult mice would alter binge-like drinking. To determine if binge-like drinking patterns regulated VTA OTX2 gene and protein expression, 10 week-old male and female C57BL6/J mice underwent 4 days of the drinking in the dark (4 DID) procedure with a 20% ethanol solution. The VTA was dissected from mice immediately (0 hours) and 24 hours after the 4 DID. VTA OTX2 gene and protein levels were measured by qPCR and western blotting, respectively. To determine if VTA OTX2 regulated binge drinking in adult mice, we injected a lentivirus carrying the gene for Gfp and Otx2 or Scr (control) shRNA utilizing stereotaxic surgery to locally knockdown OTX2 in the VTA. Mice were allowed to recover for 3 weeks and given ethanol via the 4 DID model for 3 weeks. After the ethanol administration, we allowed mice to have access to 2% sucrose solution for 4 days to measure anhedonia. There was a significant decrease in VTA Otx2 mRNA in both sexes immediately after the ethanol drinking session. At the 24-hour time point after drinking, there was a significant increase in VTA Otx2 mRNA in the female mice. Interestingly, VTA OTX2 protein levels were increased in the female ethanol group immediately after the drinking session and in both sexes 24 hours after drinking. Knockdown of Otx2 in the VTA of adult mice (a 30% decrease) did not change the amount of ethanol or sucrose solution consumed. These results demonstrate

that binge-like drinking modifies OTX2 gene and protein expression in the VTA of adult mice. Surprisingly, modulating levels of VTA OTX2 in adult mice does not affect their binge-like drinking. In addition, the combination of depleting VTA OTX2 and binge-like drinking does not promote anhedonia. Future experiments will examine whether decreasing OTX2 in the VTA during the critical juvenile period results in increased binge drinking in adulthood.
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**C56**
**SEIZURE SUSCEPTIBILITY IN A PCDH19 EPILEPSY MOUSE MODEL**

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PCDH19-related epilepsy is an early-onset epileptic encephalopathy characterized by short and repeated seizure clusters. Patients present with predominantly focal seizures, which are often followed by developmental decline and intellectual disability. PCDH19-related epilepsy is caused by heterozygous loss-of-function mutations in the X-linked gene, *Protocadherin 19* (*PCDH19*). Pathogenic *PCDH19* variants are inherited in an atypical X-linked dominant pattern in which heterozygous females present with seizures, while hemizygous carrier males are asymptomatic. It is hypothesized that this unusual pattern of inheritance results from cellular interference, a mechanism in which the co-existence of neurons expressing wild-type or mutant *PCDH19* disrupts cell-cell interactions. Recent cases of affected males with somatic mosaicism for *PCDH19* mutations provide further support for cellular interference as the disease mechanism. To investigate seizure susceptibility in a PCDH19 epilepsy mouse model, we induced generalized and focal seizures in female *PCDH19* heterozygous and knock-out mice, male *PCDH19* hemizygous mice, and their wild-type littermates. All genotypes showed comparable levels of seizure susceptibility to induced generalized seizures. However, female *PCDH19* heterozygous and knock-out mice showed significantly increased susceptibility to induced focal seizures. Interestingly, they displayed comparable levels of increased seizure susceptibility and severity. These results suggest that a pathogenic mechanism in addition to cellular interference may contribute to the PCDH19 seizure phenotype.
*This study was supported by Feinberg School of Medicine.*

**C57-G**
**DEVELOPMENT OF A NOVEL NAMPT ACTIVATOR AS A POTENTIAL ALZHEIMER'S DISEASE THERAPEUTIC**

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Alzheimer's disease (AD) is characterized by numerous pathophysiological changes in the brain including the accumulation of soluble oligomers of amyloid β (Aβ) and neurofibrillary tangles of hyperphosphorylated tau. Therapies targeting these have been unsuccessful, so an alternative drug target is needed. One potential strategy to prevent or reverse the course of the disease is to target the NAD/NAMPT pathway. NAD levels decline with age and thus negatively affect NAD-dependent enzymes and cellular energy pathways crucial to neuron function. The combination of declining NAD and the pathophysiology seen in AD results in disease progression. The most efficient way to increase NAD is to activate NAMPT, which catalyzes the rate limiting step in NAD biosynthesis. Activating NAMPT will increase NAD levels and feed these crucial cellular processes potentially supporting the normal function of the diseased brain despite the presence of the pathophysiology seen in AD. To test this hypothesis, we employed a high throughput screen (HTS) of 2000 compounds measuring turnover of NAM, the substrate for NAMPT. This produced two hits that activated NAMPT in the nanomolar range. Analogs of hit 1 were synthesized to optimize its pharmacokinetics. We next measured neuroprotection against oxygen-glucose deprivation (OGD), an *in vitro* model of ischemia-reperfusion injury in stroke that simulates some of the toxicity present in AD. An analog, KB-49, showed concentration-dependent neuroprotection on SH-SY5Y cells at various treatment paradigms. Following these results, we hope to optimize this compound for improved potency, *in vivo* stability, and blood-brain barrier penetration. Additionally, a second HTS will be performed to find NAMPT activating scaffolds with superior performance. Finally, a benefit of this effort is that the energy dyshomeostasis seen in AD is similar to that of type 2 diabetes, so this disease state may be explored as well.
*This research is funded by the UICentre at the University of Illinois at Chicago*

## *THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS*

**E1 -UG**
**FEMINIZATION OF BEHAVIOR, PLASMA SEX HORMONE PROFILE, AND GONADAL HISTOLOGY FROM ENDOCRINE DISRUPTION IN SEXUALLY LABILE ANEMONEFISH**

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Endocrine disruptors, such as bisphenol A (BPA) and ethinylestradiol (EE2), are becoming increasingly concentrated in the marine environment from plastic waste and wastewater effluent. Despite significant data on the feminizing effects of these pollutants on the reproductive axis of freshwater fish and terrestrial vertebrates, little is known about effects on marine fish. Since sex determination in many marine fish is labile and subject to environmental cues, endocrine disruptors can be particularly damaging to normal development. The objective of this study was to determine the impact of 6 months exposure to environmentally relevant concentrations of BPA and EE2 on behavior, plasma sex hormone profile, gonadal histology and brain gene expression in *Amphiprion ocellaris*, the false anemonefish. *A. ocellaris* are sequential hermaphrodites and display post-maturational sex change from male to female in nature. Ambisexual, non-reproductive fish were paired together in 10-gallon aquariums and were fed twice a day with normal food (control), or food laced with

either BPA (100 μg/kg) or EE2 (0.2 μg/kg) (n=4 tanks per treatment group). Behavioral responses to a conspecific intruder were measured at 1, 3, and 6 months. Blood plasma was collected at 3 and 6 months to measure estradiol (E2), 11-ketotestosterone (11-KT; main bioactive androgen in fish), and vitellogenin. At the end of the study, fish were euthanized and fixed for gonadal histology, and the brains frozen for aromatase gene expression measurements. By 3 months, BPA-treated fish were more aggressive towards intruders, and individuals displayed higher plasma levels of vitellogenin, E2, and lower 11-KT relative to control. Results suggest BPA significantly feminized the gonads. Quantification of brain gene expression is currently underway. Initial results suggest BPA exposure induces substantial feminizing effects in a sexually labile marine fish.

*Supported by indirect costs recovered and private funding to (JSR)*

**E2-PD**

**THE SUBFORNICAL ORGAN RECRUITS PHASIC DOPAMINE SIGNALLING TO WATER AVAILABILITY VIA MULTI-ORDER PATHWAYS**

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Changes in physiological state, including hunger, satiety, and body fluid homeostasis, can strongly modulate phasic dopamine signalling and goal-directed behaviors. Here we examine the novel hypothesis that the subfornical organ (SFO), a key central thirst detector, relays need state information to mesolimbic dopamine pathways to regulate thirst-motivated behaviors. To capture phasic dopamine dynamics, we utilized in vivo fiber photometry in rats that express protein-based fluorescent sensors to measure ventral tegmental area (VTA) dopamine neuron activity (Cre-dependent gCaMP6f in TH-Cre+ rats) or dopamine release (dLight1.2) in the nucleus accumbens shell (NAc shell). In water-restricted rats allowed intermittent, cued sipper access, we first demonstrated that VTA dopamine neuron activity and NAc shell dopamine release develop to cues associated with water. After training under water-restriction, we find a lack of cue-evoked VTA and NAc phasic dopamine activity when rats are water-sated. SFO glutamatergic neurons ($SFO^{glu}$) are engaged during thirsty states and selective activation of $SFO^{glu}$ neurons engages robust water intake in water-sated animals. We found that DREADDs mediated activation of $SFO^{glu}$ neurons mimics thirst in recruiting phasic dopamine activity, as $SFO^{glu}$ activation increases water-cue evoked VTA dopamine responses. To identify potential relay nodes, we find that activation of $SFO^{glu}$ increases c-fos expression not only in the VTA and NAc, but also the lateral hypothalamus (LH). Preliminary tract-tracing experiments further support the LH as a relay region between the SFO and VTA dopamine neurons. Overall, our findings reveal that thirst powerfully influences phasic dopamine signalling and that this occurs via multi-order SFO to VTA pathways.

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**E3-UG**

**GENETIC DISSECTION OF THE CONTRIBUTION OF CENTRAL AND PERIPHERAL CIRCADIAN CLOCKS TO *DROSOPHILA* FEEDING RHYTHMS**

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The circadian system produces ~24-hr rhythms and consists of three major components: a central molecular clock in the brain that keeps time, input pathways that allow organisms to stay synchronized with changes in their environment, and output pathways that couple the clock to various behavioral and physiological processes such as locomotion. Recent studies have demonstrated circadian control of feeding independent of locomotor activity, but the neuronal circuitry governing feeding rhythms is not understood. In addition to the central brain clock, circadian clocks are present in many peripheral tissues, such as the *Drosophila melanogaster* fat body, which is homologous to the mammalian liver and regulates metabolism. Here, we investigated the feeding behavior of transgenic flies in which we eliminated or changed the speed of the brain or fat body clock to identify the contributions of central and peripheral circadian clocks to feeding rhythms. We find that genetically-induced acceleration of the central brain clock, but not the fat body clock, is sufficient to shorten the period of rhythmic feeding behavior in conditions of constant darkness. We additionally conducted immunohistochemical analysis to confirm molecular clock speed alterations in these flies. Similar results were observed following selective elimination of molecular clock function. Thus, flies with no functional molecular clocks in the brain showed arrhythmic feeding behavior while flies with no functional fat body clock exhibited normal feeding patterns. These results demonstrate that the brain clock is the chief orchestrator of feeding rhythms.

**E4-G**

**CENTRAL EXENDIN-4 SELECTIVELY SUPPRESSES CUE-EVOKED PHASIC DOPAMINE SPIKES AND RESULTANT BEHAVIOR**

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Cues predicting food reward evoke phasic increases in mesolimbic dopamine activity, appetitive and consummatory behaviors. We have previously shown that the magnitude of cue-evoked dopamine activity scales with hunger or central activation ghrelin receptors. Activation of central receptors for glucagon-like peptide 1 (GLP-1R), via long-acting analogs, suppresses food intake and food motivated appetitive behavior but its effects on cue-evoked, phasic dopamine – a signal critical for reinforcement and goal-directed action – remain unknown. Here, food restricted rats received daily sessions of 30 trials of a tone followed by 1) brief availability of a sipper that delivered 0.3M sucrose and 2) an inter-trial interval. Latency to begin licking and number of licks/trial were measured. After training, rats underwent surgery to express a calcium indicator (proxy for neural activity) selectively in dopamine neurons, implant a fiber optic in the ventral tegmental area and a guide cannula in the lateral ventricle. Following recovery, calcium transients were measured during cue→sipper sessions. Doses of the GLP-1R agonist, exendin-4 (0, 0.05 or 0.1μg; ICV), were delivered just prior to sessions. While exendin-4 had no effect on spontaneous transient activity, it did dose-dependently suppress the magnitude of cue-evoked dopamine responses (0.39±0.06, 0.27±0.06, 0.04±0.05 $\Delta F/F$ for 0, 0.05 and 0.1μg, respectively; $p<0.05$). Linear regressions show an inverse relationship between cue-evoked dopamine activity and lick latency and a direct relationship with number of licks/trial. As cue-evoked dopamine promotes approach and consumption, exendin-

4 may be therapeutic in suppressing neural substrates involved in cognitive and reinforcement related overeating.
*This study is funded by NIH grant DA025634 (MFR).*

**E5 -UG**
**GESTATIONAL EXPOSURE TO POLYCHLORINATED BIPHENYLS SHOW SEX AND BRAIN REGION SPECIFIC EFFECTS ON DOPAMINE MODULATING SYSTEMS IN ADOLESCENT RATS**

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Polychlorinated biphenyls (PCBs) are environmental contaminants known to be acutely neurotoxic, immunotoxic, and endocrine-disrupting. However, little is known about how PCBs affect hormone-sensitive immune signaling in the brain. Exposure to PCBs is highest during gestation and infancy, periods crucial to neurodevelopment and sensitive to hormones and therefore perturbation. Development of dopaminergic systems linked to reproductive and behavioral maturity continue to occur through adolescence. Dopaminergic signaling is sensitive to disruption by both PCBs and neuroinflammation. Therefore, this study tests the hypothesis that perinatal PCB exposure with or without later inflammatory challenge alters expression of dopaminergic genes in hypothalamic and mesocorticolimbic systems in adolescence. To do so, Sprague-Dawley rats were exposed to an environmentally relevant mixture and dose of PCBs (or vehicle) perinatally and adolescent offspring were given lipopolysaccharide (LPS, or vehicle) 3-4 hours prior to brain tissue collection. Exposure to PCBs increased expression of both *Drd1a* and *Drd2* dopamine receptors only in males in the hypothalamus but not midbrain, prefrontal cortex, or striatum. Given the greater hormone sensitivity of the hypothalamus relative to the other brain regions studied, and the sex-specific effects, these results indicate endocrine mechanisms of PCB action. These adolescent results differ from those found in neonatal animals, where dopaminergic enzymes and transporters but not receptors were altered by PCBs. It is possible that neonatal changes in outcomes related to dopamine content later drive adolescent changes in dopamine sensitivity. This highlights the importance of studying endocrine disrupting compounds in both sexes and in developmental contexts.
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**E6-G**
**ACTIVE FEMINIZATION OF THE PREOPTIC AREA OCCURS INDEPENDENTLY OF THE GONADS IN *AMPHIPRION OCELLARIS***

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Sex differences in the anatomy and physiology of the vertebrate preoptic area (POA) arise during development, and influence sex-specific reproductive functions later in life. Relative to masculinization, mechanisms of feminization of the POA are not well understood. The purpose of this study was to induce sex change from male to female in the anemonefish *Amphiprion ocellaris*, and track the timing of changes in POA cytoarchitecture, composition of the gonads and circulating sex steroid levels. Reproductive males were paired together and then sampled after 3 weeks, 6 months, 1 year and 3 years. Results show that as males change sex into females, number of medium cells in the anterior POA (parvocellular region) approximately double in females over the course of 1 year. Feminization of gonads, and plasma sex steroids occur independently, on a variable timescale, up to years after the POA sex change has completed. Findings suggest the process of POA feminization is orchestrated by factors originating from within the brain as opposed to being cued from the gonads, consistent with the dominant hypothesis in mammals. Anemonefish provide an opportunity to explore active mechanisms responsible for female brain development in an individual with male gonads and circulating steroid levels.
*This work was supported through indirect costs recovered from federal grants, and gifts to JSR.*

**E7 -UG**
**Elevated cortisol and alpha-amylase levels in behaviorally inhibited individuals exposed to physiologic stress: Implications for enhanced associative plasticity with anxiety vulnerability**

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A number of studies have used elevated levels of CO2 inhalation to activate physiological stress responses. While these studies reliably activate increased respiratory responding, activation of salivary stress hormones has been mixed. Our study examined stress hormone activation following exposure to 7% CO2 while controlling for stress/anxiety vulnerability. Behaviorally inhibited (BI) temperament has been identified as a key vulnerability factor for stress and anxiety disorders (e.g., Gladstone and Parker, 2005). Recently, a number of studies in both human (e.g., Allen and Miller, 2016) and non-human (e.g., Beck et. al, 2010) participants have demonstrated that organisms that are consistently inhibited across the lifespan show increased associative plasticity, especially when reinforcement of the environmental stressor is uncertain. We have hypothesized that stress vulnerable BI individuals may show enhanced stress hormone responses to environmental stressors. To test that hypothesis, we had participants perform a simple spaceship-based computer task (Sheynin et. al., 2014). Participants received 7% CO2 administration either during the first 7 min or the second 7 min of the game. A control group received air only throughout the testing. Air and CO2 were administered using a Hans Rudolph breathing apparatus. Two saliva samples from each participant were analyzed, one sample acquired 15 min prior to beginning the computer task, and a second sample taken immediately following the computer task. All samples were analyzed for alpha-amylase and cortisol levels using ELISAs. Level of BI was identified using the Adult Measure of Behavioral Inhibition (Gladstone and Parker, 2005). All participants regardless of level of BI showed increases in respiratory tidal volume immediately upon exposure to 7% CO2. Individuals who scored high in BI appeared to show decreases in alpha-amylase activity shortly after exposure to 7% CO2. We did not see similar changes in individuals who scored low in BI. Cortisol concentration appeared to remain consistent across groups. Our data indicate that, only stress vulnerable individuals appeared to show

changes in salivary alpha-amylase response within our time frame. Our ongoing research examines whether sex differences may have contributed to our current findings. Our preliminary data suggest that, given the significant consistency of enhanced associative plasticity in the human and non-human BI literature, stress hormone responding to environmental stressors may contribute to the enhanced learning that has been observed.

**E8**
**DEVELOPMENTAL EFFECTS OF POLYCHLORINATED BIPHENYLS (PCBS) ON ACTIVATIONAL MORPHOLOGY OF MICROGLIA IN THE ADULT BRAIN**

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Perinatal brain development is sensitive to the internal and external environment. As such, exposure to environmental contaminants, including polychlorinated biphenyls (PCBs), can perturb the dynamic processes that occur during this period with long-lasting effects on brain function in adulthood. PCBs have been shown to cause sex-specific changes in hormone signaling in the brain as well as perturbations in peripheral immune function. The possible sex-specific effects on microglia, an immune cell in the brain, however, are not known. This study tests the hypothesis that developmental exposure to PCBs has sex-specific effects on microglia in the adult prefrontal cortex, either on basal number or activational status, or microglial responses to an immune challenge by lipopolysaccharide (LPS). Pregnant Sprague Dawley rats were given either an environmentally relevant mixture and dose of PCBs or oil orally during gestation. Pups were raised until adulthood when half were given an injection of LPS or saline 24 hours prior to euthanasia. Brains were collected and immunohistochemistry performed to label microglia with IBA1 and then quantify activational status according to morphology. Microglia tend to exist in a ramified state in basal conditions, and then become hyperramified and then reactive upon detecting an inflammatory signal. Preliminary data indicate that males are more sensitive to the low doses of LPS used in this experiment, as males exposed to LPS showed a greater number of hyperramified microglia than saline-exposed animals. However, effects of PCBs and interactions between PCB and LPS exposure on the number of ramified and reactive microglia was found in females but not males. Analysis of an additional series of tissue co-labeled for IBA1 and TLR4, a receptor for pathogen associated molecular patterns, is ongoing. These results indicate that developmental PCBs can alter microglial activity in the adult brain; this is of great interest given the role of microglia and neuroimmune functions in a host of neural disorders.
*This study is funded by DePaul University Research Council, College of Science and Health, and Department of Biological Sciences*

## *THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA*

**F1-G**
**NMDAR-ACTIVATED PP1 DEPHOSPHORYLATES GLUN2B TO MODULATE NMDAR-PLASTICITY**

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N-methyl-D-aspartate receptors (NMDARs) are glutamate receptors which control fundamental neuronal processes such as synaptic plasticity and synaptic maturation and are involved in learning and memory. In mature neurons, postsynaptic NMDARs are segregated into two populations, synaptic and extrasynaptic NMDARs, which differ in localization, function, and associated intracellular cascades. Receptor localization is dynamic, as these two populations are connected via lateral diffusion, and receptor exchange between them modulates synaptic NMDAR content (NMDAR-plasticity). Key to this modulation are posttranslational modifications.

Here, we identify the phosphorylation of the PDZ-ligand of the GluN2B subunit of NMDARs (at S1480; GluN2B-pS1480) as a critical determinant in dynamically controlling NMDAR subsynaptic localization. Our previous work demonstrated that this phosphorylation results in the disruption of NMDARs from scaffolding proteins to reduce the synaptic content of the receptor. We find now that GluN2B-pS1480 maintains NMDARs segregated at extrasynaptic membranes as part of a protein complex containing Protein Phosphatase 1 (PP1). Global activation of NMDARs lead to the activation of extrasynaptic PP1, which mediates dephosphorylation of GluN2B at S1480 to promote an increase in synaptic NMDAR content. Thus, PP1-mediated dephosphorylation of the GluN2B PDZ-ligand modulates activity-dependent NMDAR-plasticity in mature neurons, a process with profound consequences for synaptic and structural plasticity, metaplasticity, and synaptic neurotransmission.
*Support for this work was provided by the NIH (R00 AG041225) and the Northwestern University CMBD Training Program (T32 GM08061).*

**F2-PD**
**THE ROLE OF POTASSIUM IN THE SYNAPTIC TRANSMISSION BETWEEN TYPE I HAIR CELL AND CALYX IN VESTIBULAR SYSTEM OF TURTLES**

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In the vertebrate nervous system, ions accumulate in diffusion-limited synaptic clefts during ongoing activity. Dual recordings from hair cells and associated afferents in vestibular system of turtle have demonstrated that $K^+$ ions can accumulate in the synaptic space. This accumulation alters the driving force and permeation through ion channels facing the synaptic cleft. Upon elevating the potassium in the cleft, hair cells are depolarized to potentials where transduction currents are sufficient to depolarize them further to voltages necessary for calcium influx. The calyx is depolarized, in turn, to potentials where single EPSPs can generate action potentials. We have used kinetic and pharmacological dissection of the hair cell conductances to understand how two potassium conductances are involved in elevating the concentration of potassium in this restricted cleft.
*This research is funded by NIH grant R21 to J.J Art*

**F3-G**

**ANTIOXIDANTS PROTECT AGAINST REACTIVE ASTROCYTOSIS-INDUCED SENSITIZATION TO OXIDATIVE STRESS**

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Clinical evidence suggests a pathological role of increased levels of oxidative stress in glaucomatous tissues, including the optic nerve head. The purpose of this study was to determine whether antioxidants exert glioprotective effects against reactive astrocytosis-induced sensitization to oxidative stress. Primary adult rat optic nerve head astrocytes (ONHAs) were pre-treated for one hour with 100 μM Trolox, 50 μM resveratrol, 1 μM Xanthohumol, 0.005% manganese(III) tetrakis(1-methyl-4-pyridyl) porphyrin (Mn-TM-2-PyP) or vehicle. ONHAs were then subjected to ambient or to hyperbaric pressure (25 mmHg above ambient) to induce reactive astrocytosis and subsequently exposed to exogenously-applied chemically-induced oxidative stress using *tert*-butyl hydroperoxide (tBHP; 0 to 1 mM). Oxidative stress was quantified using 2',7'-dichlorodihydrofluorescein diacetate ($H_2$DCFDA) or CellROX®. MTT uptake and lactate dehydrogenase (LDH) release assays for cell viability and proliferation were performed to determine glioprotective potential of test compounds. Reactive astrocytosis resulted in significantly elevated levels of cellular oxidative stress. Specifically, CellROX® fluorescence increased from 10.4% to 47.9% of nuclear area; Trolox completely prevented generation of oxidative stress (2.9%). Similarly, levels of oxidative stress measured by DCF fluorescence increased two-fold after a 2 hr exposure to hyperbaric pressure; this increase was similar following exposure to 100 μM tBHP. Accordingly, reactive astrocytosis shifted both the $IC_{50}$ for tBHP in the MTT assay and the $EC_{50}$ for tBHP in the LDH assay by > 80 μM. Pre-treatment with Trolox resulted in a proportional right-shift of the $IC_{50}$ value for tBHP under ambient (73.0 μM to 135.2 μM) and hyperbaric pressures (50.0 μM to 99.3 μM; *n=3*). A similar effect on $IC_{50}$ values was observed following pre-treatment with resveratrol under ambient pressure (79.9 μM to 119.9 μM). The superoxide dismutase mimetic, Mn-TM-2-PyP, fully prevented any loss of cell viability in response to oxidative stress. The glioprotective effects of resveratrol and Xanthohumol on reactive astrocytes was significantly attenuated. Protein expression levels of enzymes of the endogenous antioxidant system revealed differential effects by the various antioxidants. Our data suggest that reactive astrocytosis in ONHAs is associated with significantly elevated levels of oxidative stress. Furthermore, antioxidants can exert potent glioprotective effects on ONHAs, supporting the continued preclinical development of antioxidant approaches for glaucoma.

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**F4**

**THE REGULATION OF NMDA RECEPTORS SYNAPTIC AND EXTRASYNAPTIC DISTRIBUTION**

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NMDA receptors (NMDAR) are a subtype of ionotropic glutamate receptors that mediate excitatory synaptic transmission and synaptic plasticity. NMDAR are located in two distinct populations: synaptic (sNMDAR) and extrasynaptic (exNMDAR). These populations are interconnected via lateral diffusion of GluN2B-containing NMDAR. sNMDAR regulate synaptic plasticity and trigger pro-survival signaling (ERK and CREB pathways). In contrast, exNMDAR have modulatory roles and exNMDAR overactivation triggers excitotoxic cell death pathways. Overactivation of exNMDAR is implicated in neurodegenerative diseases like Alzheimer´s disease, and Huntington´s disease.

Our goal is to identify molecular mechanisms underlying the regulation of s/ex NMDAR balance Our preliminary data demonstrate that the phosphorylation of the PDZ-ligand of GluN2B (at S1480; GluN2B-pS1480) maintains NMDAR at extrasynaptic membranes and they need to be dephosphorylated in order to be reinserted into the PSDs. Here, we show that the synaptic exclusion is dependent on the phosphorylation itself and not due to disrupted PDZ binding. We hypothesized that phosphorylated NMDAR are stabilized at extrasynaptic sites via interaction with an unidentified “scaffolding” protein. To identify this protein, we have generated a series of chimeras containing different GluN2B mutant attached to the transmembrane domain of CD4. We have characterized these chimeras by overexpressing them in HEK cells and analyzing their interaction with MAGUKs proteins. Our future experiments include the expression of these chimeras in vivo and identify the unknown protein using co-immunoprecipitation and mass-spectrometry techniques.

The deeper understanding of s/exNMDAR distribution is needed because the selective blockade of exNMDAR is a prospective therapeutic strategy to ameliorate NMDAR-mediated excitotoxicity.

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**F5-G**

**EXTRACELLULAR AND INTRACELLULAR SPHINGOSINE-1-PHOSPHATE DISTINCTLY REGULATES EXOCYTOSIS IN CHROMAFFIN CELLS**

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Sphingosine-1-phosphate (S1P) is a bioactive sphingosine lipid involved in many neurological disorders, and sphingosine kinase 1 (SphK1), a key enzyme for S1P production, is concentrated in presynaptic terminals. However, the role of S1P/SphK1 signaling in exocytosis remains elusive. By detecting catecholamine release from single

vesicles in chromaffin cells, we show that a dominant negative SphK1 ($SphK1^{DN}$) reduces the number of amperometric spikes and increases duration of foot, which reflects release through fusion pore, implying critical roles of S1P in regulating the rate of exocytosis and fusion pore expansion. Extracellular S1P treatment increases the number of amperometric spikes, and this increase is inhibited by a selective S1P3 receptor blocker, suggesting extracellular S1P may regulate the rate of exocytosis via activation of S1P3. Furthermore, intracellular S1P application induces a decrease in foot duration of amperometric spikes in control cells, indicating intracellular S1P may regulates fusion pore expansion during exocytosis. Taken together, our study represents the first demonstration that S1P regulate exocytosis through distinct mechanisms: extracellular S1P may modulate the rate of exocytosis via activation of S1P receptors and intracellular S1P may directly control fusion pore expansion during exocytosis.

**F6-G**

## Understanding the molecular mechanisms involved in the intercellular transport of the Activity-Regulated Cytoskeleton-associated (Arc) protein

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The Activity-Regulated Cytoskeleton-associated (Arc) protein has been recognized as imperative to learning and memory processes and the progression of Alzheimer's disease. In the mid-90s, Arc was discovered to be an immediate early gene (IEG), and its mRNA was found to localize to the soma and dendrites of activated neurons. The Arc protein was implicated in a process deemed "inverse synaptic tagging" where it concentrates within inactive dendritic spines via its interaction with CaMKIIb, and further facilitates endocytosis of AMPA receptors by interacting with Dynamin2, Endophilin3 and AP-2. Now, Arc was shown to have evolved from a *Ty3/Gypsy* LTR retroelement, whose family consists of retroviruses. These retroviruses share a Group-specific antigen (GAG) domain that will form the oligomeric capsids, and Arc has homology to the GAG protein suggesting structural similarities to retroviral capsids. In fact, recombinant Arc forms its own capsid structure, and when overexpressed in cells, was present in the extracellular vesicle fraction. We believe that Arc not only shares structural but also functional similarities with retroviruses. HIV has a residue that becomes myristoylated allowing for its interaction with the plasma membrane, which is required for virus assembly thus necessary for HIV infectivity. Arc contains a conserved sequence of amino acids (CLCRC) that becomes palmitoylated. We hypothesize that this addition of a palmitoyl group is required for Arc's capsid assembly and release from cells. In order to test this, we are developing a renilla luciferase assay to quantify the amount of WT Arc and palmitoylation-free mutant (C9S) Arc being released from cells.

**F7**

## CHARACTERIZATION OF DE-IDENTIFIED HUMAN BRAIN CULTURE BY IMMUNOFLUORESCENCE

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**Background**: Microglia, the resident macrophages of the central nervous system, play an important role in immune defense and removing damaged neurons and cellular plaques. When microglia become activated they release mediators (i.e. reactive oxygen intermediates, eicosanoids, cytokines, and metalloproteinases) which are cytotoxic to neurons and may lead to neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and HIV encephalopathy. Although rodent microglia have been studied extensively for immunological and pharmacological research, knowledge regarding human microglia becomes difficult to extrapolate from the rat model. The purpose of our collaborative research was to establish cultures of de-identified human brain tissue and characterize the cell types in one human brain tissue culture by immunohistochemistry. **Methods**: A research collaboration was established between Cook County Hospital and the Pharmacology Department, College of Graduate Studies, Midwestern University to receive human brain biopsies, which were cultured *in vitro* and progressively developed into human brain tissue cultures. To characterize the cell types in one these human brain tissue cultures (i.e. #464), we performed immunohistochemistry using the following antibodies: for microglia: a primary mouse anti-rat CD11b/c antibody (AbD SeroTec, Raleigh, NC), and secondary donkey anti-mouse antibody (Thermo Fischer, Waltman, MA); for astrocytes: a primary anti-chicken GFAP antibody (Aves Labs, Davis, CA), and secondary goat anti-chicken antibody (Aves Labs, Davis, CA); for neurons: a primary anti-mouse Neu-N antibody (Millipore Sigma, Burlington, MA), and secondary goat anti-mouse antibody (Thermo Fisher, Waltman, MA); for oligodendrocytes: a primary anti-mouse MBP antibody (BioLegend, San Diego, CA), and secondary goat anti-mouse antibody (Thermo Fisher, Waltman, MA). **Results**: The immunohistochemistry of the human brain culture # 464 revealed the presence of microglia, astrocytes, neurons and oligodendrocytes. This resulted in the interesting yet unexpected finding that human brain culture #464 appeared to be a mixed culture. **Conclusions**: In order to confirm and quantitate our immunohistochemical observations, we are planning to use flow cytometry. If the presence of microglia in de-identified human brain culture # 464 is confirmed by flow cytometry studies, we will isolate microglia with the purpose of conducting pharmacological and toxicological research with marine-derived natural products in future studies.

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**F8-G**

**Matrix Metalloproteinase-9 Release From Ultrapure *Porphyromonas gingivalis* Lipopolysaccharide (LPS) Treated Rat Brain Microglia *in vitro***

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**Background:** The putative association between periodontal disease (PD), a chronic inflammatory disease and neuroinflammation, a condition which involves brain microglia, remains under investigation. We have reported that ultrapure *Porphyromonas gingivalis* (Pg) lipopolysaccharide (LPS), a bacterium implicated in periodontitis, activates both classical (M1-type) and alternative (M2-type) activation of neonatal rat microglia (BMG) with concomitant release of superoxide anion, thromboxane $B_2$, cytokines, and chemokines (Faseb Journal 32.1 Supplement: 702.2, 2018). We hypothesized that matrix metalloproteinase 9 (MMP-9) release by Pg-treated microglia might be detectable by both ELISA and visualized by confocal fluorescence imaging. **Methods:** ultrapure *P. gingivalis* LPS (Pg LPS) $10^5$ ng/mL from InvivoGen (San Diego, CA) and *Escherichia coli* LPS (Ec LPS) 026:B6 1 ng/mL from Difco Lab, Detroit, MI (positive control) were used to treat rat BMG for 18 hours at 35.9°C *in vitro*. MMP-9 release was assessed with a rat MMP-9 ELISA kit (R&D Systems). Confocal fluorescence imaging with a Nikon A1R laser confocal microscope was used to identify BMGs using a primary mouse anti-rat CD11b/c antibody (Ab) (AbD SeroTec, Raleigh, NC), and secondary donkey anti-mouse Ab (Thermo Fischer, Waltman, MA). MMP-9 was visualized with a primary rabbit anti-rat MMP-9 polyclonal Ab, and secondary goat anti-rabbit Ab, both from Abcam, Cambridge, MA. **Results:** MMP-9 presence in tissue culture supernates was detectable by ELISA in both Ec LPS and Pg LPS-treated BMG. In contrast, MMP-9 was observed by confocal fluorescence imaging only within Ec LPS-treated BMG but not in Pg LPS-treated BMG. **Conclusions:** Both ELISA and confocal fluorescence imaging provided additional support for our working hypothesis, because Pg LPS stimulated BMGs to release MMP-9. Thus, our current observations extend our studies on the effect of Pg LPS on rat brain microglia activation and contribute to further characterize the putative role of Pg LPS in both periodontitis, neuroinflammation and neurodegeneration.

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**F9**

**V-ATPase dysfunctions contribute to lysosome-autophagosome mediated proteinopathy in early stages of Alzheimer's disease pathogenesis**

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by abnormal protein aggregates and synaptic deficits. To regulate these processes, intracellular organelles (lysosomes) require highly acidic microenvironments. To maintain this, the vacuolar H+-ATPase (V-ATPase) pumps in $H^+$ ions against a concentration gradient. In lysosomes, this process is essential for autophagy, a catabolic pathway to degrade abnormal proteins. In AD, V-ATPase disruption can lead to abnormal β-amyloid and tau accumulation and deficient synaptic transmission. A concurrent mechanism with V-ATPase defects is intracellular $Ca^{2+}$ dyshomeostasis, which alters ion exchange and thus pH within these organelles. We hypothesize that altered $Ca^{2+}$ signaling disrupts V-ATPase ion exchange and instigates AD pathology. We used immunoassays and live cell imaging in model cells, induced human neurons (iN) transformed from AD patient, and AD mouse models to explore this hypothesis. Immunohistochemistry in fixed hippocampal slices from 3-month old 3xTg-AD mice revealed diminished expression of V-ATPase subunits (V1B2, V0a1), lysosomes (Lamp1), and increased expression of mature autophagosomes (LC3B) relative to non-transgenic (NTg) controls. These phenotypes in 3xTg-AD were restored to NTg levels with a 30-day Ryanodex treatment (NAM of ryanodine receptor (RyR); 10mg/kg). This reflects impaired lysosomal and synaptic vesicle functionality, which is mediated through upstream RyR-$Ca^{2+}$ dyshomeostasis. Live cell imaging of iN and RyR-overexpressing HEK293 cells using a lysosomal-pH indicator (LysosensorDND-160) revealed lysosomal alkalization with RyR stimulation (caffeine 10mM), suggesting that aberrant RyR-$Ca^{2+}$ signaling disrupts autophagosome-lysosome mediated protein degradation. Protein aggregates, such as β-amyloid and hyperphosphorylated tau, were increased in iN treated with 500nM bafilomycin (V-ATPase inhibitor). Expression of these protein aggregates was resolved with Ryanodex treatment. Therefore, increased RyR-mediated $Ca^{2+}$ release alkalizes lysosome pH resulting in abnormal protein aggregation. Prior to overt histopathology or cognitive deficits, abnormal $Ca^{2+}$ signaling in AD disrupts intracellular organelle function leading to altered autophagic-mediated protein clearance, resulting in neuronal stress that impinges on synaptic transmission.

**F10-G**

**THE ROLE OF ASTROCYTE CALCIUM SIGNALS IN THE PRODUCTION OF INFLAMMATORY FACTORS AND MODULATION OF SYNAPTIC FUNCTION**

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Astrocytes play a central role in inflammation by releasing inflammatory factors such as cytokines. These cytokines are elevated in a growing list of pathologies, including Alzheimer's Disease (AD), that exhibit altered synaptic function. Currently, it is unclear how these cytokines are produced and how they contribute to synaptic dysfunction. However, cytokine production has been linked to extended intracellular calcium elevations, which requires store operated calcium entry (SOCE) in many non-excitable cells. In astrocytes, SOCE is mediated by the channel protein, Orai1, and a calcium sensor, Stim1. The goal of my project is to understand how cytokines regulated by astrocytic SOCE affect synaptic function. My results show that astrocytes rely on SOCE to produce multiple cytokines. Orai1 KO astrocytes have impaired activation of transcription factors NFAT and NFκB, indicating that SOCE may

regulate cytokine production through these transcription factors. The effects of these cytokines on neuronal function is being tested through glutamate uncaging on single dendritic spines and calcium imaging with gCaMP6f to measure the synaptic responses. My preliminary results indicate that conditioned media from thrombin-stimulated astrocytes induces an increased glutamate response in spines. Taken together, these studies examine the role of astrocytic SOCE in inflammation, providing a framework for understanding how astrocytes modulate neuronal function in health and in inflammatory diseases.

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**F11**

**β-CATENIN NEGATIVELY REGULATES IL-6 AND IL-8 EXPRESSION AT TRANSCRIPTIONAL LEVEL AND INDUCES REACTIVITY IN HUMAN ASTROCYTES**

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HIV invades the brain during acute infection, setting the stage for persistent neuroinflammation despite combined antiretroviral therapy (cART) and leads to HIV-Associated Neurocognitive Disorders (HAND), which occurs in ~50% of HIV-infected individuals. Our lab is focused on understanding the role of Wnt/β-catenin signaling in HAND. Here, we evaluated the impact of β-catenin on inflammatory mediators associated with neuroinflammation, chemotactic molecules, and regulation of A1 (proinflammatory)/A2 (protective/repair) phenotypes of astrocytes. We demonstrate that knockdown (KD) of β-catenin in normal human astrocytes (NHAs) significantly induced IL-6 and IL-8 at the transcription and protein levels and conversely, induction of β-catenin significantly downregulated these two molecules. These findings are intriguing given that no role for β-catenin to date is associated with IL-6 and IL-8 regulation. Further, KD of β-catenin induced three genes associated with A1 phenotype by 2.4-6.4 fold. These findings indicate that β-catenin expression in astrocytes is a critical regulator of anti-inflammatory responses and its disruption can potentially mediate persistent neuroinflammation.

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**F12-PD**

**IMPAIRED M-CURRENT IN KCNQ2 EPILEPTIC ENCEPHALOPATHY EVOKES DYSHOMEOSTATIC MODULATION OF EXCITABILITY IN PATIENT-DERIVED NEURONS**

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Mutations in KCNQ2, which encodes a pore-forming $K^+$ channel subunit responsible for neuronal M-current, have been associated with neonatal epileptic encephalopathy (NEE). This complex disorder manifests as severe early-onset seizures and impaired neurodevelopment due to an imbalance in neuronal circuit activity in the brain. While the effects of *KCNQ2* mutations have been studied extensively in heterologous expression systems, their effects on the inherent properties of human neurons have not. Specifically, what remains unclear is how the likely defects in M-current affect the electrophysiological properties of human neurons during a critical period of neuronal maturation.

Here, we used induced pluripotent stem cells and gene editing to establish a disease model, and measured the functional properties of patient-derived neurons using electrophysiological and optical approaches. We find that while patient-derived excitatory neurons exhibit reduced M-current early, they develop intrinsic and network hyperexcitability progressively over time in culture. This hyperexcitability is associated with faster action potential repolarization, larger post-burst afterhyperpolarization, and a functional enhancement of $Ca^{2+}$-dependent $K^+$ (BK and SK) channels. These properties facilitate a burst-suppression firing pattern that is reminiscent of the interictal electroencephalography pattern in patients. Importantly, we were able to phenocopy these excitability features in control neurons only by chronic but not acute pharmacological inhibition of M-current. Our findings suggest that dyshomeostatic mechanisms compound KCNQ2 loss-of-function and lead to alterations in the neurodevelopmental trajectory of patient-derived neurons. Our work has therapeutic implications in explaining why KCNQ2 agonists may not be beneficial once maladaptive compensatory features arise at later stages of the disease.

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**F13-G**

**ESTRADIOL ENHANCES ETHANOL-STIMULATED FIRING OF VTA NEURONS THROUGH AN ERα AND MGLUR1-DEPENDENT MECHANISM**

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Although more men drink than women, this gender gap is narrowing and women face more severe alcohol-related pathophysiological effects at lower drinking levels; therefore, it is imperative to examine the biological factors that promote binge drinking in females in order to design effective interventions and treatments that would reduce drinking in women. Evidence suggests that the hormone estrogen might contribute to higher levels of alcohol drinking in women. The ventral tegmental area (VTA) is an estrogen-sensitive region in the brain that plays a critical role in reward and reinforcement in alcohol addiction. We previously demonstrated that ethanol excitation of VTA dopaminergic (DA) neurons is enhanced during high estrogen states, both in ovariectomized (OVX) mice supplemented with estradiol (E2) and in gonadally intact females. Two estrogen receptors, ERα and ERβ, are expressed in the VTA, but it is not yet known which of these receptors, and which downstream signaling pathways, might mediate

E2 modulation of ethanol-induced excitation of VTA DA neurons. To begin to identify the specific receptors involved, extracellular single unit recordings were performed to measure VTA neuronal firing in response to ethanol. Mice were OVX and treated with an ERα agonist, ERβ agonist, or vehicle. Treatment of mice with the ERα-selective agonist PPT enhanced ethanol-induced excitation of VTA neurons compared to VEH and the ERβ agonist DPN. Acute treatment of brain slices from gonadally intact female mice in the diestrus phase with the ERα antagonist MPP decreased ethanol excitation, whereas treatment with the ERβ antagonist PHTPP had no effect on ethanol excitation. Membrane bound ERs can signal through rapid signaling pathways through activation of metabotropic glutamate receptors (mGluRs). In order to determine if mGluR1 is required for the estradiol enhancement of VTA DA sensitivity to ethanol, the mGluR1 antagonist JNJ16259685 was applied to slices from OVX female mice supplemented with either E2 or VEH and gonadally intact female mice in diestrus or estrus. Treatment of slices with JNJ16259685 significantly reduced ethanol-stimulated firing of VTA neurons from mice in the diestrus phase and in E2-treated OVX mice, but not from mice in the estrus phase or in VEH-treated OVX mice. Together, these results indicate that the ability of E2 to increase VTA dopamine neuron responses to ethanol is mediated by ERα and mGluR1, suggesting that ERα and mGluR1 may be potential targets for agents useful in reducing binge drinking in females.

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**F14-G**

**THE ROLE OF STORE OPERATED CALCIUM ENTRY IN ASTROCYTE GENE EXPRESSION**

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In non excitable cells, calcium influx is important for many cellular functions including gene expression. A major route for $Ca^{2+}$ entry in these cells is store operated $Ca^{2+}$ entry (SOCE) through Calcium Release Activated Calcium (CRAC) channels. The effect of SOCE on cellular functions like gene expression has been studied extensively in immune cells. These studies show that deficits in SOCE lead to a decrease in the production of cytokines through $Ca^{2+}$ dependent transcription factors such as the nuclear factor for activation of T cells (NFAT). However, this relationship between SOCE and cytokine production has not been studied in astrocytes despite evidence indicating that like immune cells, astrocytes can respond to and produce cytokines. The understanding of this relationship has major implications for numerous neurological diseases because increases in neuroinflammation from immune and non immune cells are often associated with neurodegenerative diseases. We hypothesize that store operated calcium entry in astrocytes regulates cytokine production through the calcium dependent transcription factor NFAT. To address this question, we first set out to identify if neuroactive factors, phenylephrine (PE) and estradiol (E2), serve as physiologically relevant agonists of SOCE in astrocytes. Further, we will determine if these agonists affect the translocation of the calcium dependent transcription factor NFAT into the nucleus and the downstream production of cytokines. Our preliminary data indicate that phenylephrine, but not estradiol, induces calcium signals in astrocytes which are blocked with the CRAC channel antagonist BTP-2, indicating that these calcium signals are mediated by CRAC channels. Estradiol had no effect on astrocyte calcium signaling. Our next experiments will determine if the signaling produced by PE is blocked in astrocytes lacking critical molecular components of SOCE (STIM1/Orai knockouts) and additionally whether cytokine production is altered by PE through NFAT. Our overall goal is to identify the role of CRAC channels and astrocytes in neuroinflammation. As the dysregulation of cytokines and the activity of astrocytes are both implicated in neuroinflammation understanding the pathways by which astrocytes produce cytokines can have important implications in the treatment of neurological pathologies such as Alzheimer's Disease.

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## *THEME G. NOVEL METHODS AND TECHNOLOGY DEVELOPMENT*

**G1**

**Astrocyte-derived HIV evolution in humanized mice**

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HIV infects the brain during acute infection and persists in the CNS despite suppressive antiretroviral therapy. While ample data demonstrates HIV genetic compartmentalization between the CNS and the periphery, it is unclear if HIV undergoes significant evolution within the CNS and whether CNS egress contributes to peripheral HIV quasispecies. We previously developed a humanized mouse model where HIV infected human fetal astrocytes were xenotransplanted into NSG mice and reconstituted with human PBMCs. Using this model, we demonstrated that astrocytes, the predominant brain cell type, support replication competent HIV which can egress from the CNS to peripheral organs (spleen, lymph node). In this study, we assessed genomic changes in HIV that egressed from astrocytes. Using single genome amplification and direct sequencing, the gold standard for HIV quasispecies characterization, we show that virus had evolved, with 24% of spleen sequences showing mutations from the original viral inoculum. The mutated genomes showed random diversification, APOBEC mutations, Poisson distribution, star-like phylogeny, and time to most recent common ancestor analysis correctly identified the duration of infection (95% CI=27-61 days, actual=33 days), suggesting that viral evolution in this model fits the mathematical model of acute HIV-1 diversification in humans. Thus, astrocyte-derived HIV evolves and mimics the viral evolution observed in early peripheral infection and can contribute to peripheral genetic diversity. Ongoing studies are assessing HIV evolution within astrocytes over time.

**G2**

**THE INFLUENCE OF THE VAL66MET POLYMORPHISM OF THE BRAIN DERIVED NEUROTROPHIC FACTOR GENE ON PATHOLOGY IN AN ISOGENIC HUMAN IN VITRO MODEL OF NEUROTRAUMA**

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Neurotrauma morbidity varies widely between patients. Common single nucleotide polymorphisms (SNPs) drive some of this variability. The val66met SNP in the bone-derived neurotrophic factor gene is one such variant. In this study, a human in vitro model was used to study the role of this SNP in neurotrauma pathology. A line of induced pluripotent stem cells (iPSCs) with the val/met genotype was genetically edited to produce val/val and met/met isogenic lines (isogenic lines are genetically identical with the exception of a single variant). These 3 lines of iPSCs were differentiated into either cortical or motor neurons and then cultured on silicone membranes for 48 hours before stretch injury. Cells were injured with a 28% biaxial, stretch pulse lasting 30 ms. Cortical neurons expressed green fluorescent protein while motor neurons were labeled with calcein AM. Nuclei were stained with Hoechst 33342. Fluorescent images were acquired 4 hours after injury and analyzed to quantify total neurite outgrowth. The neurite outgrowth in naïve cultures varied across genotypes at the 48 hour timepoint. Cortical neurons carrying at least one met allele had more outgrowth than their val/val counterparts. By contrast, naïve, met-carrier motor neurons had less outgrowth than their val/val counterparts. Naïve outgrowth was similar between val/val and val/met genotypes for both cortical and motor neurons. Motor neurons were resilient to the traumatic insult, with little decline in outgrowth across all genotypes. Cortical neurons, by contrast, exhibited substantial declines of outgrowth after trauma. Met/met cortical neurons appeared more vulnerable to trauma than their val/met counterparts. These experiments isolated the val66met SNP against a uniform, genetic background in the context of a uniform, traumatic insult. They therefore offer a powerful complement to observational studies of human subjects and have the potential to inform clinical trial stratification and personalization of therapy.

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**G3**

**ILLUMINATING THE MOLECULAR LANDSCAPE OF INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELLS: A MULTIFACETED APPROACH**

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Since their discovery, melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs) have made their mark as bonafide photoreceptors. ipRGCs are a diverse class of cells with six described subtypes, M1-M6, which are implicated in image forming (pattern detection) and non-image forming (circadian rhythm, pupillary light reflex) vision. The six ipRGC subtypes have diverse morphology, electrophysiological properties and brain projection patterns. These diverse properties suggest that there is underlying molecular diversity amongst the ipRGC subtypes, but this has not yet been studied. Defining the molecular differences between ipRGC subtypes will allow for better understanding of the contribution of each subtype to visual processing and allow us to develop intersectional genetic tools to manipulate single RGC populations. We have performed single cell RNAseq on M1-M4 ipRGCs to identify possible molecular markers of ipRGC subtypes and developed a new melanopsin (Opn4) FlpO line for use in intersectional studies of ipRGC function. The goal of this study is to develop a system combining small molecule fluorescent *in situ* hybridization and immunofluorescence in the whole mount mouse retina to test genetic marker candidates for ipRGC subtypes, and to validate the new $Opn4^{FlpO}$ line. Our data indicate that we can reliably perform smFISH and visualize RNA molecules both in genetically engineered mice with endogenous fluorescence and in combination with immunofluorescence in wild type mouse retinas, and that RGCs are labeled in the $Opn4^{FlpO}$ mouse line. The manipulation of single ipRGC subtypes will open the doors for more in-depth understanding of how light influences behavior and physiology.

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**G4-G**

**QUANTIFYING THE ABILITY OF A LINEAR CLASSIFIER TO DISCRIMINATE BETWEEN SHOULDER TASKS IN PARETIC AND NON-PARETIC ARMS OF INDIVIDUALS WITH CHRONIC HEMIPARETIC STROKE**

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Stroke is the leading cause of long-term disability in the U.S. and most commonly affects strength and coordination in an upper-extremity. Intense physical therapy and repetitive training, whether through robotics or a therapist has led to a small improvement in paretic arm function but larger gains remain elusive. After stroke, use of proximal shoulder muscles cause an unintentional abnormal activation of muscles throughout the paretic limb, primarily elbow, wrist, and finger muscles. This phenomenon is referred to as abnormal synergy and presents proportionally to the amount of cortical drive, or effort that is put into using the shoulder. Reducing effort of the shoulder reduces the effect of this phenomenon and increases the functional range of motion of the elbow, wrist, and fingers. One possible solution is to support the hemiparetic shoulder during functional tasks. A simple wearable exoskeleton which could assist in lifting the paretic arm is feasible, but a useable control paradigm is not yet known. This study tests the ability of a linear discriminant analysis (LDA) based classifier to discriminate between shoulder tasks under different loading conditions using electromyography (EMG) signals, the forces and moments generated, and their combination.

Paretic and non-paretic arms of 12 participants with moderate to severe motor impairments post-stroke were tested, as well as one arm of 12, age and gender matched controls. Maximal isometric shoulder strength was measured. Participants were then attached to a haptic robot ($ACT^{3D}$) via a cast and custom device. The robot generated forces requiring participants to abduct and adduct at 0, 25, and 50% of their

maximum strength. Trials consisted of 5 seconds of pure abduction or adduction followed by 5 seconds of internal or external humeral rotation while maintaining the different load levels. The data sources and their combination were used to create LDA based classifiers.
Classification accuracies for the combined data set were best and averaged 98% for control arms, 95% for non-paretic arms, and 89% for paretic arms. Classification using EMG data fared worst, averaging 96%, 91%, and 83% respectively. Between arm differences indicate that there is a negative effect of stroke on classification; more pronounced in the paretic arm, but also present in the non-paretic arm. Regardless, classifier performance is adequate to warrant further testing into real-time control of a device that will support the paretic shoulder, minimize the effects of shoulder weakness as well as the negative effects of the abnormal synergy, thus enabling greater use and function, and possibly other rehabilitative interventions.
*Research supported in part by Interdisciplinary Graduate Education in Movement and Rehabilitation Sciences (IGE-MRS) Training Program NIH T32 Grant (EB009406).*

**G5-G**
**CEREBRAL ORGANOIDS AS A MODEL TO STUDY FOCAL CORTICAL DYSPLASIA**

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Focal cortical dysplasia (FCD) encompasses many types of structural abnormalities in cerebral tissue caused by abnormally migrating cells during development. FCD is the most common known cause of seizures in patients with focal intractable epilepsy. FCD has been primarily studied with electroporated mouse models or by analyzing surgically resected tissue. While these techniques have provided valuable knowledge, they do not enable monitoring within the organism during development. Here we utilize cerebral organoids as a novel system to study this disease. Organoids are three dimensional with structural complexity, use human cells, and allow real-time monitoring of many physiological aspects. After characterizing the cerebral organoid system, we plan to determine FCD disease mechanisms through techniques such as morphological assessment, calcium imaging, live cell tracking, and electrophysiology. Though significant work in FCD has been accomplished, this system will allow us to study disease mechanisms in novel ways.

**G6**
**A NETWORK ANALYSIS OF SNPS IN MULTIPLE GENES REVEALS POLYGENIC EFFECT ON PAIN IN SICKLE CELL DISEASE**

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Sickle cell disease (SCD) is a fatal hereditary blood disorder. While therapeutic advancements have significantly increased average life-span of patients, they experience frequent, recurring episodes of acute crisis pain along with persistent chronic pain throughout their lives. Pain management remains inadequate largely because of the high inter-individual variability in pain perception. Genetic polymorphisms including single nucleotide polymorphisms (SNPs) on relevant genes may explain the variability in sickle cell pain. However, pain is a complex trait and individual SNP analysis is limited by the small effect size of variants. We hypothesized that the combined effect of multiple SNPs across different genes will be able to account for the variability in sickle cell pain to a greater extent and exhibit stronger association with the phenotype. In total, 131 SCD patients were recruited at the UI Hospital and Health Sciences System upon obtaining written informed consent. Composite Pain Index (CPI) recorded as self-reported baseline pain score on a computerized version of the McGill Pain Questionnaire served as a marker for chronic pain. DNA was extracted from collected blood samples, followed by genotyping candidate SNPs using the MassARRAY iPLEX platform. We annotated 221 SNPs to 80 genes. We used Markov cluster algorithm (granularity parameter = 2) on Cytoscape to analyze protein-protein interaction networks and identified a highly interconnected cluster of 10 genes. Utilizing R package SKAT (SNP-set Kernel Association Test), we found significant associations with pain scores ($p < 0.05$) at the gene-level for 5 of the 10 genes. These 5 genes had 13 annotated SNPs. When collectively analyzed using a 5-fold cross validation model, the 13 SNPs explained ~32% of the variability in CPI and had an average pain prediction accuracy of ~75%. This study supports our hypothesis that polygenic SNP analyses can improve the detection power and account for the variability of chronic pain in SCD.

**G7 -UG**
**ACCURACY OF DEEPLABCUT MACHINE LEARNING TO MARKERLESSLY TRACK FOOT POSITION DURING SKILLED WALKING**

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Spontaneously occurring behaviors afford a unique opportunity for the assessment of rodent-based models of neurological disorders; however, quantifying the organization of these behaviors is locked behind time intensive scoring techniques. For example, the performance of rats on the rung walking task depends on sensorimotor function and has been shown to indicate damage localized to cortical and subcortical structures. Scoring performance on the rung walking task involves frame-by-frame detection of foot slips of varying magnitude. Machine learning architectures have shown promise in affording markerless tracking of an animal's body while in motion and may provide novel characterization of behavior on the rung walking task. The current study examines the accuracy of a DeepLabCut machine learning algorithm to accurately track foot position as rats performed the rung walking task. The DeepLabCut machine learning algorithm was trained with subsets of digitized frames. The trained network was then used to digitize the remaining frames. The resulting topographic data of foot position was compared to manually tracked videos. Preliminary analysis has supported the accuracy of DeepLabCut

in identifying movement topography. Provided that machine learning accurately tracks foot position, this approach will be used to investigate other brain and behavior relationships that may influence movement organization.

## *THEME H. SENSORY AND MOTOR SYSTEMS*

**H1**

### RESPONSES OF NEURONS IN SPINAL TRIGEMINAL NUCLEUS INTERPOLARIS (SpVi) TO STIMULATION OF THE WHISKERS IN DIFFERENT DIRECTIONS AND AT DIFFERENT SPEEDS

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An important open question in the study of somatosensation is how animals integrate signals from an array of spatially distributed tactile sensors. The present study seeks to address how spatial information is integrated across sensors at the earliest stage of the somatosensory system, using the rat whisker (vibrissal) array as a model. Rats have approximately 30 whiskers on each side of their face arranged in an orderly array of rows and columns. The base of each whisker is embedded within a follicle filled with mechanoreceptors that send signals to primary sensory neurons in the trigeminal ganglion. From there, information is sent to several nuclei in the trigeminal brainstem, including spinal trigeminal nucleus interpolaris (SpVi). Neurons in SpVi have been shown to integrate inputs from multiple whiskers[1]. One recent study suggested that SpVi may encode information about the speed and direction of a stimulus moving through the whisker array[2]. However, hardware constraints limited whisker stimulation to the rostral-caudal direction. The present experiments use a novel multi-direction stimulation device to further test the hypothesis that neurons in SpVi encode information about both stimulus direction and speed. We designed and built a stimulator that can mechanically stimulate whiskers in any direction and with a range of speeds mimicking natural tactile interactions. Importantly, we show that the stimulator can also detect whisker contacts as it passes through the array. Using this novel stimulation technique, we performed recordings from a set of SpVi neurons in anesthetized rats. Preliminary data reveal clear differences in spike rates associated with different stimulation speeds and directions, showing tuning of these recorded neurons to object orientation and passing speed through the array. We expect these results to improve our understanding of how spatial information is processed and encoded in more central structures of the somatosensory pathway.

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**H2 -UG**

### STRUCTURAL DIFFERENCES IN MITOCHONDRIA ADJACENT TO THE CUTICULAR PLATE IN TYPE 2 HAIR CELLS

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Mitochondria play a vital role in every cell of the body by synthesizing ATP, the primary energy source in the body. These ATP molecules are produced by ATP synthase enzymes found in the cristae of mitochondria. Mitochondria have also been implicated in previous studies as precursors for hair cell apoptosis and as causes for certain forms of both syndromic and non-syndromic hearing loss (Mangiardi et al. 2004). As a result, because very little research has focused specifically on mitochondria in the inner ear, this study aims to investigate the structural and functional differences among mitochondrial populations in inner ear hair cells. In mitochondria, cristae have been shown to interact with the inner mitochondrial membrane at points termed cristae junctions (CJs) (Rabl et al. 2009). These CJs likely enable transport of ATP and $Ca^{2+}$ to regions of interest. A previous study, for example, has shown that mitochondria in type 1 hair cells are polarized towards the striated organelle, synapses, and other structures that require large amounts of energy. In this study, we used IMOD software to create 3D reconstructions of mitochondria in order to analyze crista junction density with respect to the cuticular plate (CP) in type 2 hair cells. To determine if these mitochondria were polarized towards the cuticular plate, we counted the number of cristae junctions on the sides of the mitochondria facing towards and away from the CP using our 3D model. The CJ density on the side of the mitochondria associated with the CP was found to be significantly larger than that of the side facing away, suggesting that these cristae direct ATP and $Ca^{2+}$ to the CP.

**H3**

### FUNCTIONAL IMPACT OF DIVERSE SODIUM CURRENTS ON VESTIBULAR AFFERENT NEURON FIRING PATTERNS

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An outstanding issue in neural coding is the impact of diverse ionic currents on the transmission of sensory stimuli information by neurons. The vestibular system transmits sensory information with two populations of vestibular afferent neurons (VAN), which differ in the regularity of timing of action potentials (AP). The two kinds of AP timing are specialized for different encoding strategies (rate and temporal)[1], which are optimized for different kinds of sensory information. We ask how the two sensory encoding methods arise from differences in the voltage-dependent sodium ($Na_V$) currents that initiate APs. Recent work from our lab indicated expression of all Na channel proteins in VAN[2], which differ in key properties affecting their voltage dependence and time course, and may carry currents of different modes (i.e., transient, persistent, resurgent). I seek to determine how diverse $Na_V$ currents influence the shape and timing of

APs. Using whole-cell patch-clamp recordings, I discovered that some neurons expressed persistent $Na_V$ current elicited with slow voltage ramps and that other neurons express resurgent $Na_V$ current. I hypothesize that these non-inactivating modes repolarize VAN after each spike, promoting the sustained firing that distinguishes the VAN population that fires with regular timing. My long-term goal is to explain how biophysical properties have evolved to analyze sensory stimuli into key features.

(1) Jamali M., et al, (2017). Nature Communications 7(13229),
(2) Liu X.P., et al, (2016). Journal of Neurophysiology 115(2536).

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**H4-G**

**SINGLE LOW DOSE OF SIMULATED SPACE RADIATION DISRUPTS FINE MOTOR CONTROL**

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During missions to space, beyond the international space station and passed the Van Allen belt, astronauts are exposed to space radiation which may disrupt central nervous system function. These disruptions may influence neural systems that mediate sensorimotor functions involved in fine motor control that are critical for mission success. Rats spontaneously engage in highly organized string-pulling behavior that depends on fine motor control. Focal cortical damage has been shown to disrupt the topographic (i.e., path circuity) and kinematic (i.e., moment-to-moment speed) organization of rat string-pulling behavior. The current study used rat string-pulling behavior to characterize disruptions in fine motor control following a single low dose of simulated space radiation (5 cGy Silicon). Following radiation exposure, rats initially took longer to pull in an unweighted string. Increased mouth contacts and decreased pull time was observed in subsequent testing with the unweighted string. Despite this compensation, rats exposed to radiation missed the string more often with the mouth. Lateralized deficits on the left side were also observed in distance and direction (i.e., concentration and heading) after radiation exposure. Once rats were switched to a weighted string, no differences were observed between groups in any measures. These results demonstrate that low dose space radiation disrupts several aspects of string-pulling behavior dependent on task demands. This work establishes a foundation for future studies to examine the effectiveness of countermeasures to attenuate the effects of space radiation on fine motor control.

*This study is funded by NIU and EVMS.*

**H5-UG**

**INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELL LOSS IN THE 5xFAD MOUSE MODEL FOR ALZHEIMER'S DISEASE**

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Alzheimer's disease is a neurodegenerative disease that is characterized by dementia and cognitive decline. Recent research has demonstrated a strong association between Alzheimer's disease and disruptions in circadian rhythms. Furthermore, a report has shown that the density of intrinsically photosensitive retinal ganglion cells, or ipRGCs, was significantly lower in Alzheimer's patients compared to people without the disease. The authors hypothesized that loss of ipRGCs could contribute to disrupted circadian rhythms in Alzheimer's patients because ipRGCs relay light information to the suprachiasmatic nucleus to align the body's circadian rhythm to the external light-dark cycle. However, this study was conducted post-mortem which made it impossible to determine when ipRGC loss occurs in the context of disease progression. To determine when ipRGCs are affected in Alzheimer's disease, we counted the number of ipRGCs in a mouse model for Alzheimer's disease (5xFAD mouse line) and compared them to ipRGC counts in wildtype littermate controls. 5xFAD mice exhibit memory impairment at 4 months, and hence retinas were dissected before and after this point at 1, 2, 4 and 6 months of age. Our data shows that 5xFAD mice exhibit lower ipRGC counts compared to wildtype controls starting as early as two months. Retinas were also stained for Brn3a, which labels 70 % of all RGCs and not ipRGCs, to determine if cell loss was specific to ipRGCs. Preliminary data from the Brn3a counts suggests that cell loss is indeed specific to ipRGCs and does not occur in other RGCs. Our results suggest that ipRGC loss could contribute to circadian dysfunction that precedes cognitive decline in Alzheimer's patients. These results have important implications for the early detection of Alzheimer's disease because there are well-established clinical tools to directly measure ipRGC function such as pupillometry.

*This study is funded by the Northwestern Education and Undergraduate Research on Neuroscience program.*

**H6 -UG**

**MTK Analysis of Interactions Between Crista Junctions in Subcuticular Mitochondria**

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Cytoskeletal tethers connecting mitochondria to other organelles, such as the endoplasmic reticulum, have been well studied and are known to have an important role in molecule and ion transport (Pernice et al., 2018). However, the existence and function of tethers connecting mitochondria to other mitochondria are not as widely confirmed. We have observed such tethers in mitochondria bordering the stereociliar rootlets of a Type 1 vestibular hair cell. These mitochondria were three-dimensionally reconstructed using electron microscope tomographic images and the 3D modelling program, IMOD (Kremer et al., 1996). The tomograms and models show a collection of mitochondria whose lamellar cristae are aligned, forming what seems to be a mega-mitochondrial structure. Tethers were observed in some neighboring regions between these mitochondria and absent in others. Using the MTK function of IMOD, a proximity (nearest neighbor) analysis was conducted to examine the relationship of neighboring crista junction pairs that were separated by 2 outer mitochondrial membranes and the intramembranous space. To confirm the presence of these novel connecting structures, the distances between crista junctions of neighboring mitochondria in a tethered zone were

compared to distances found in an untethered zone by constructing histograms of each region's data, which were then statistically analyzed using the data analysis package in Excel. Tethers observed within this model could possibly serve the purpose of reducing distances between mitochondria in order to allow for the flow of ATP and $Ca^{2+}$ ions through the crista junctions to a series of tethered mitochondria, ultimately reaching the cuticular plate.

**H7 -UG**
**THERMOSENSORY EFFECTS ON DROSOPHILA CIRCADIAN BEHAVIOR**

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The circadian clock is a highly conserved molecular oscillator responsible for the daily organization of an organism's biochemical, physiological, and behavioral processes. These patterns, known as circadian rhythms, display a basal ~24 hour period and can be synchronized to external environmental cues. Temperature profoundly effects circadian cycling on both a molecular and behavioral level, but it is unknown how temperature information is received and processed by clock-containing cells to produce daily rhythms, particularly the generation of normal activity and sleep patterns. In principle, temperature may modulate the molecular clock directly by altering biochemical reaction rates, act through temperature-sensitive channels in clock neurons, or be communicated by the thermosensory system. Because of their relatively simple brain structure, predictable behavioral patterns and poikilothermic nature, the fruit fly, *Drosophila melanogaster*, provides a powerful model in which to study the functional connection between external sensory systems and internal circadian pacemakers. *Drosophila* detect changes in environmental temperature at the periphery using specialized temperature receptor neurons (TRNs) located in the antenna. TRNs then synapse onto second-order thermosensory projection neurons (TPNs), which transmit temperature information to higher brain centers. To test the possibility that a direct circuit connection may control circadian behavior, we systematically silenced TR/TP neurons and exposed flies to a range of temperatures while recording their sleep and locomotor activity. Our results show that flies robustly alter their normal pattern of sleep and wakefulness in accordance with the environmental temperature, and that the removal of antennal sensory input or the silencing of select TP circuits impairs these temperature effects.
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**H8**
**Juxtaposing Energy Models to Describe Inner Ear Hair Cell Mitochondria**

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The main objective of this study was to understand and illustrate the energy production of mitochondria in inner ear hair cells. Cells of sensory systems require high energy output and therefore the mitochondria providing the energy should produce higher amounts of adenosine triphosphate (ATP) in order to satisfy their energy requirements. The cells of interest are type I and type II vestibular hair cells and cochlear inner and outer hair cells. 3D tomograms were created, using IMOD, a modeling program used to reconstruct electron microscopic tomograms into 3D models. Mitochondrial structures such as cristae, and inner and outer mitochondrial membranes are visible and easy to trace. The IMOD program is then able to report the extent of surface area and volume given the dimensions of the individual meshed elements of the 3D tomograms. Mitochondrial function is known to be related to overall size (surface area and volume) and internal structures such as crista surfaces and crista junctions (Frey et al., 2002; Mannella, 2006). Another component to increase ATP production in a given cell is the combined efforts of multiple mitochondria to form a "super" mitochondrion (Picard et al. (2015). The mechanism of how this comes to be is unknown, however in Kuhlbrandt's model (Kuhlbrandt 2016), it is possible that the positioning of complexes such as VDAC, OPA1, MICOS, and ATP synthase dimers are key in order to describe the creation of elaborate cooperating structures (van der Laan et al 2016). Several mitochondria were reconstructed, and an equation derived from Song's model (Song et al. 2013) was used to calculate the amount of ATP based on surface area. This was compared against Iwasa's model which pertained to cochlear outer hair cells (Iwasa, personal communication). The amount of ATP produced based on surface area (SA) was converted to energy. The analyses of energy comparisons were normalized using ratios of cristae membrane SA over the outer membrane SA, which indicate the density of membrane packing in the mitochondria. The discrepancy between the two models calls for another analysis which may be done via experimental mitochondrial energetic measurements, such as those derived from Seahorse Metabolic Analyzer. The latter experiments are underway in our laboratory.

**H9-G**
**NOTCH SIGNALING IN ZEBRAFISH OLFACTORY NEUROGENESIS**

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The vertebrate olfactory epithelium (OE) is a complex tissue composed of different types of olfactory sensory neurons (OSNs) that detect a wide range of odors and other signals. We've previously shown that the two main types of OSNs in the zebrafish OE, microvillous (mOSNs) and ciliated (cOSNs), come from two different stem cell populations, namely neural crest stem cells (NCCs) and placodal progenitors, respectively. In the murine OE, *notch3* has been shown to be expressed in the neuroepithelium, but the molecular mechanisms through which Notch signaling might regulate cellular processes such as migration, differentiation, and axonal pathfinding of vertebrate OSNs remain largely unexplored. We performed RNA in situ hybridization for zebrafish Notch signaling receptors and found that *notch1a, notch1b,* and *notch3* were expressed in the OE in discrete patterns that varied dynamically during early stages of olfactory morphogenesis. To understand the role of Notch signaling in OE development, we blocked γ-secretase activity using a chemical inhibitor during specific time windows and found significant variation in the number of both OSN subtypes and a disruption of a subset of axons. Furthermore, expression of a Wnt receptor in the OE led us to examine possible connections between Notch and Wnt signaling. Upon blocking both Notch and Wnt signaling using chemical inhibitors, we found a drastic

disorganization of the olfactory rosette and substantial abnormalities in axon projections of both subtypes of OSNs. Taken together, our preliminary data suggest that Notch signaling plays a spatiotemporally-critical role in regulating olfactory neurogenesis, possibly in coordination with Wnt signaling. We are currently validating our results with heat shock-driven transgenic lines to up- or downregulate Notch signaling and developing new genetic tools to selectively inhibit Notch receptors *in vivo* so as to further understand how Notch signaling may contribute to olfactory neurogenesis.
*This study was funded University of Illinois Start-up fund and Chicago Biomedical Consortium.*

**H10-G**
**Functional divergence at the mouse type 6 retinal bipolar cell terminal**

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Purpose: While neurons were long thought to represent the fundamental computational units of the nervous system, a large body of work over the last 50 years has revealed subcellular functional compartmentalization. We hypothesize that such subcellular compartmentalization in retinal bipolar cells allow individual bipolar cells to transmit different functional signals through different synapses. To test this hypothesis, we examined the output of the type 6 bipolar cell onto two potential downstream retinal ganglion cell types ($Pix_{ON}$ and On Alpha RGC types).

Methods: Light sensitive retinas were extracted from adult mice and whole mounted. Light responses of retinal ganglion cells (RGCs) were recorded under cell attached and whole cell configurations. After physiological recording, the retinas were imaged with two-photon microscopy, underwent immunohistochemical labeling and confocal microscopy, or were sectioned and underwent serial electron microscopy (SEM). Detailed anatomy was used to construct a NEURON model of the type 6 bipolar cell terminal.

Results: Immunohistochemical staining shows that the majority of excitatory input synapses to the On Alpha and $Pix_{ON}$ RGCs are made by the type 6 bipolar cell. SEM shows that the same type 6 bipolar cell makes synapses onto both the On Alpha and $Pix_{ON}$ RGC. Additionally, high cross-correlation of excitatory input between these two cells, indicate that they both receive excitatory input from the same neuron. Although receiving excitatory input from the same cell, excitatory input to the On Alpha RGC has weak surround suppression while excitatory input to the $Pix_{ON}$ RGC has strong surround suppression. This difference was reduced by application of GABA receptor antagonists or voltage-gated sodium channel blockers. NEURON simulations show active channels combined with the nonlinear release of glutamate in response to voltage changes allows for differing suppression at different ribbon synapses within the same type 6 bipolar cell.

Conclusions: We show that an individual type 6 bipolar cell is able to provide input with strong surround suppression to the one type of RGC ($Pix_{ON}$ RGC) while simultaneously providing input with weak surround suppression to a different type of RGC (On Alpha RGC). This subcellular signal divergence occurs at the terminal of the type 6 bipolar cell via GABAergic presynaptic inhibition from wide-field spiking amacrine cells. These findings indicate that each terminal of a single bipolar cell could potentially carry a unique visual signal. This expands the number of visual channels in the inner retina allowing for increased parallelism at the earliest stages of visual processing.

**H11-G**
**IMPLICATION OF DOPAMINERGIC SYSTEM ON MOTOR PERFORMANCE DURING HABITUATION TO FORCED EXERCISE**

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Habituation or familiarization to exercise consists on a progressive increase of the training load (time and speed). This initial phase is determinant to improve motor performance during training programs in forced running conditions. However, the neurobiological mechanisms associated with this improvement remain unknown. The aim of the present study was to determine the role of dopamine D1-like and D2 receptors in the observed motor response. Sprague-Dawley rats were subjected to an habituation exercise protocol in a forced running wheel. Locomotor performance was assessed by an incremental exercise test. Animals were injected 20 minutes before the test with dopamine receptor antagonists, agonists, or saline for the control group.
D1(SCH23390) and D2(Raclopride) receptor antagonists cause a significant decrease of the locomotor performance (Control: 40.4±3.6min; SCH23390: 5.23±0.2min, p=0.01; Raclopride: 8.78±0.78min, p=0.00). D1(SKF81297) receptor agonist did not affect the total running time (SKF81297: 41.26±1.2min) while D2(Quinpirole) receptor agonist significantly increased the motor performance (Quinpirole: 120±0min, p=0.00)
These data suggest that D2 dopamine receptors could mediate an important dopaminergic role in the improvement of locomotor performance in the first stages of exercise training programs in forced models.
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**H12-UG**
**FREQUENCY-DEPENDENT EFFECTS OF BACKPROPAGATING ACTION POTENTIALS ON SENSORY ENCODING**

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Most sensory neurons encode information in the rate, number, or the timing of action potentials that propagate orthodromically from the sensory dendrites to the central nervous system. Sensory neurons are also known to generate ectopic action potentials in secondary locations along their axons, far from their sensory encoding sites. These action potentials travel not just orthodromically, but also antidromically towards the periphery, and can alter the cell's response to sensory information when they invade the sensory dendrites. For

example, changes in ectopic frequency alter the duration and the number of spikes in the sensory burst of the crustacean anterior gastric receptor neuron - a proprioceptive neuron that encodes muscle tension of two large muscles in the animal's stomach. AGR produces high frequency (~20-30 Hz) bursts of action potentials in response to muscle tension, and lower frequency (~2-10 Hz) ectopic action potentials in-between bursts. Our previous studies demonstrate that with increasing ectopic spike frequency the duration of the sensory burst shortens and the number of its action potentials decreases. Initial modeling suggests that the time constant of a hyperpolarizing current in the sensory dendrites determines how strongly changes in ectopic spike frequency affect the sensory burst. It however remains unclear whether this effect depends on the initial activity of the sensory neuron, i.e. whether the initial frequency of the sensory burst contributes to how effective ectopic action potentials are in modulating the burst.

We hypothesize that the effects that ectopic action potentials have on the sensory burst depend on the ratio between ectopic and burst firing frequencies. To test this, we changed the ratio between ectopic and burst frequencies in a model neuron that produces similar ectopic and burst action potentials as AGR. We either changed ectopic firing frequency, while keeping burst frequency constant, or vice versa, to change the ratio. To determine if the sensory burst was influenced, we measured its duration and number of action potentials after ectopic action potentials invaded the encoding region. We found that increasing the ratio between ectopic and burst firing frequencies decreased action potential number and burst duration. Our results thus indicate that the relationship between burst and ectopic firing frequencies contributes to the strength of the influence ectopic action potentials have on information encoding in sensory neurons.

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**H13**
**CHANGES IN SPINAL EXCITABILITY FOLLOWING STROKE**

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Stroke is one of the leading causes of adult-acquired motor disability in the world. While past research has made tremendous strides in understanding the implications of motor deficits following cortical damage, less is known about secondary damage to the spinal cord due to stroke, and how it may influence changes in muscle excitability. By utilizing transcutaneous electrical spinal cord stimulation, we aim to investigate if secondary degeneration in efferent signal propagation of spinal motor neurons occurs following a stroke. Through this study, we hope to broaden our understanding of the spinal cord's role in lower limb muscle activation following stroke, which may provide insight into the development of novel stroke rehabilitation techniques. Six stroke survivors (Age: 56.7+/-5.6 years), six healthy age-matched controls (Age: 54.0+/-8.3 years) and six healthy young controls (Age: 24.3+/-2.9 years), participated in a single evaluation session. Transcutaneous spinal stimulation (BioStim5) was administered at the space between the spinous processes of L1 and L2. Stimulation intensities were delivered in 5mA increments increasing from 5mA to 250mA with three simulations given per intensity. During this process spinal motor evoked potentials (sMEP) were recorded via EMG electrodes (PowerLab 16/35, ADInstruments). From this, a recruitment curve was generated to calculate the resting motor threshold (i.e. the minimum stimulation intensity where the muscles started to activate), slope of the curve, and maximum muscle activation value. The sMEPs test revealed that the stroke group had significantly higher motor threshold in the TA and MG (TAthreshold=126.8+/-40.0mA; MGthreshold =132.3+/-52.7mA) compared to age-matched controls (TAthreshold =87.7+/-10.7mA; MGthreshold =84.2+/-17.4mA) and the young group (TAthreshold= 64.1 +/-24.4mA; MGthreshold =61.3+/-22.9mA) (p's<0.05). Increased motor threshold in the stroke group may reflect a decrease in the spinal motor tract excitability following stroke. Additionally, we observed no difference in spinal excitability between the healthy age-matched group and the young group. This data suggests that an increase in the motor threshold of the stroke group may be due to secondary degeneration in the spinal cord rather than an outcome of normal aging. It should be noted that the spinal cord is considered an independent central controller of gait. Therefore, the current observation provides preliminary evidence that development of neuromodulation strategies targeting the spinal cord may be beneficial to target motor recovery after stroke. However, the small sample size warrants further investigation.

*The study is funded by the Shirley Ryan AbilityLab and a NIH R25GM121231 training grant*

**H14-UG**
**EXPLORING A RAT MODEL OF THE BYSTANDER EFFECT**

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The Bystander Effect is a phenomenon which has been observed and studied in humans for over fifty years. The most prominent hypothesis for why the Bystander Effect occurs is that it occurs due to a "diffusion of responsibility" across groups of humans in emergency scenarios. Using an arena-restrainer paradigm, we examined the possibility of this effect occurring in rats by placing a trapped rat in a restrainer which could only be opened from the outside by other rats. In doing so, we created an effective distress scenario (Bartal et Al., 2011). We observed a strong Bystander Effect in the form of increased time taken to open a restrainer door for a trapped rat by a free rat when experimental confederates dosed with an anxiolytic were present in the arena than when these confederates were absent. The presence of a strong Bystander Effect in rats calls into question the validity of the "diffusion of responsibility" hypothesis which relies on higher cognitive function. We propose the effect occurs because rats and humans take the judgments of a group into account and integrate these judgments with their own reasoning when making decisions. More simply, a rat's decision to help another rat is informed by the perceived decisions and actions of other rats present.*This study is funded by a research award from the Grossman Institute for Neuroscience, Quantitative Biology, and Human Behavior of the University of Chicago.*

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