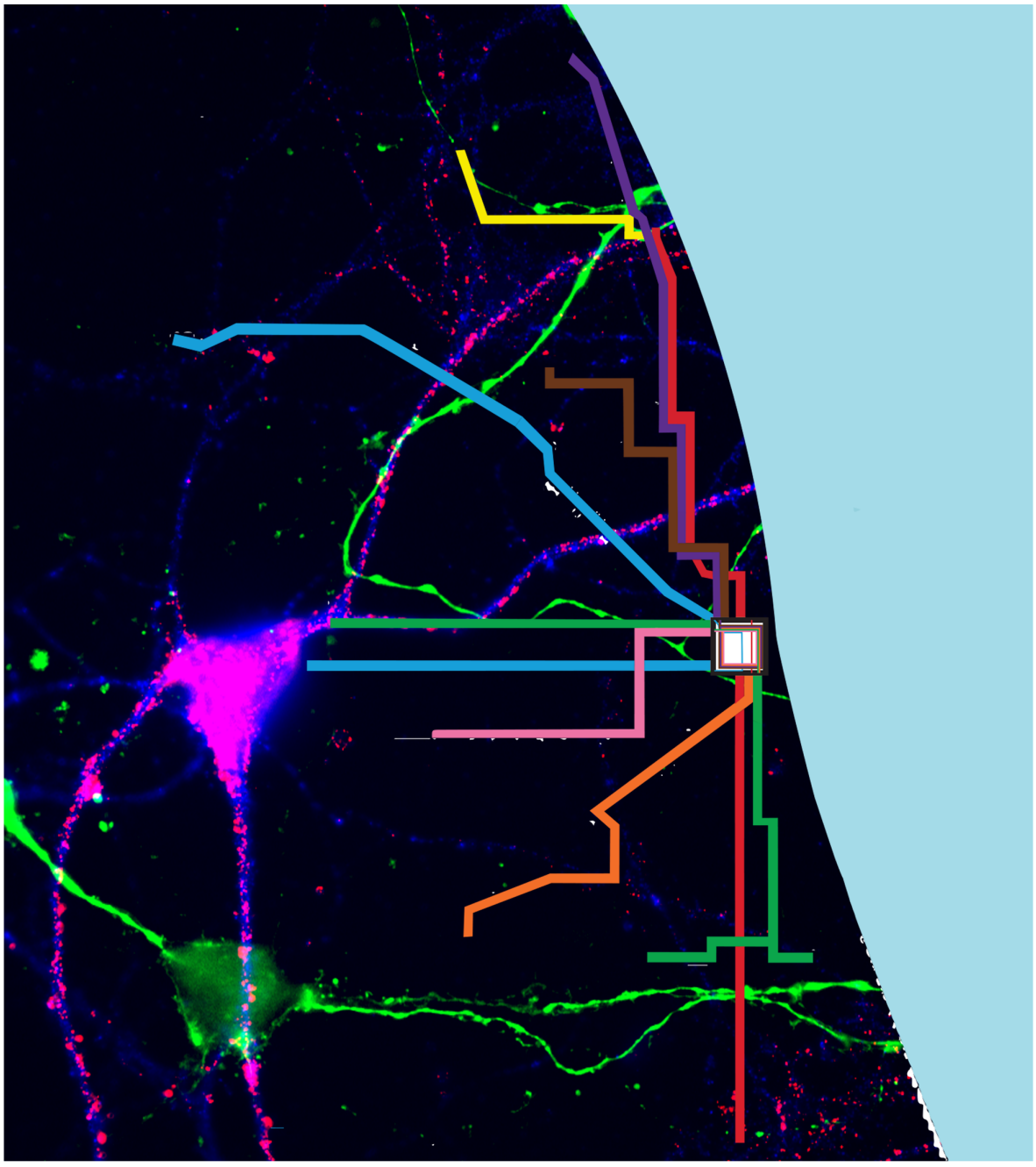
Chicago Chapter of the Society for Neuroscience

2016 Scientific Meeting



Friday, April 8th, 2016
Northwestern Memorial Hospital

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

Meeting site for Chicago Chapter of S*f*N

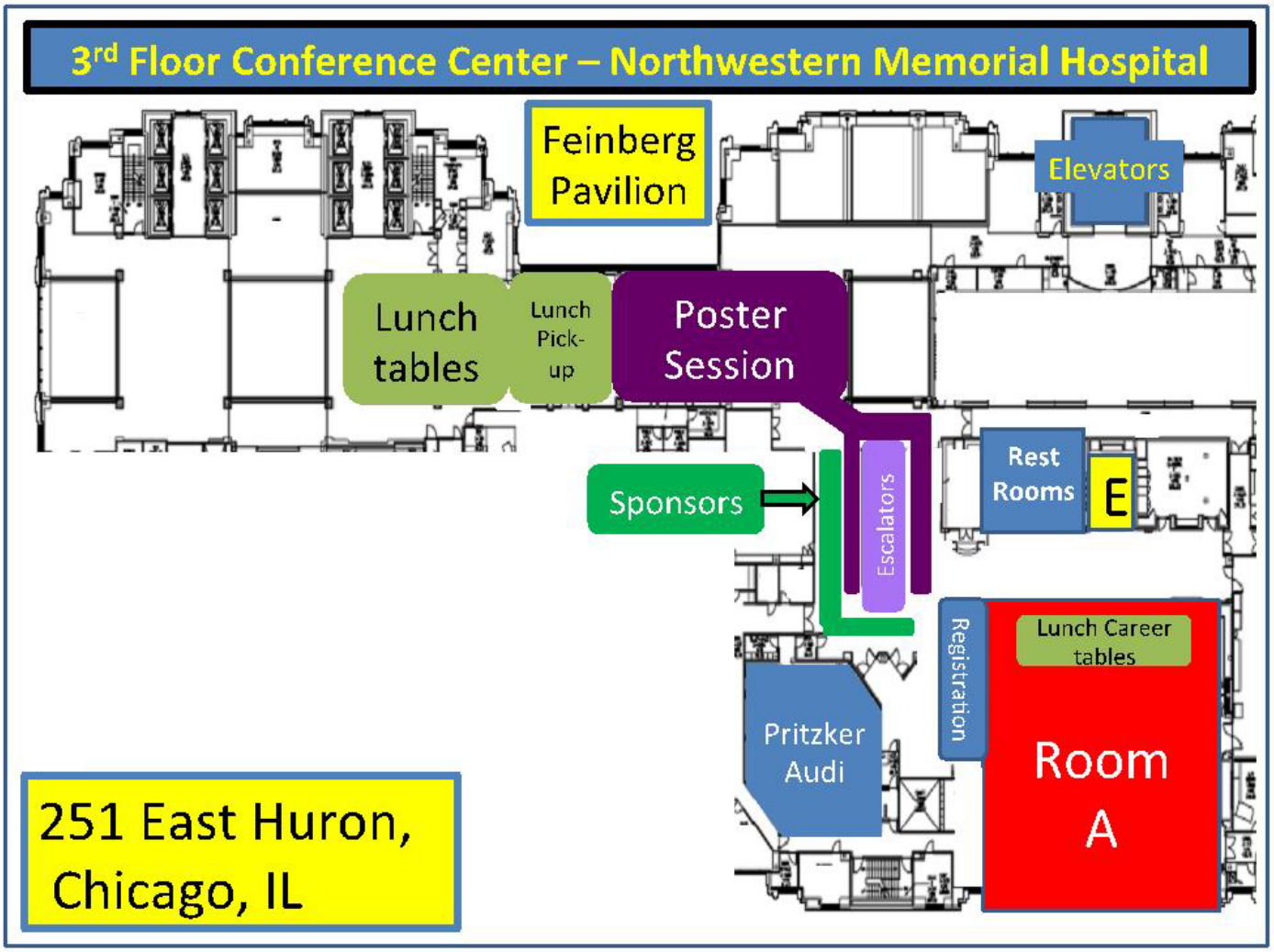
Atrium, 3rd floor

- **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://www.surveymonkey.com/r/JWXNGFK**
- **Please give us your opinion by answering our survey; you will be included in a drawing for a $25 gift card. Your input is critical to making a better meeting next year.**

Parking

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

Cover picture:. The Chicago "El" system map overlaid on an image of a cortical neuron in culture (green) with a medium spiny neuron immunostained for AMPA receptors (pink) and AMPA (blue). Image taken by Conor Murray working with Marina Wolf, Ph.D. (Rosalind Franklin University of Medicine and Science, Department of Neuroscience).


3rd Floor Conference Center – Northwestern Memorial Hospital
Feinberg Pavilion
Elevators
Lunch tables
Lunch Pick-up
Poster Session
Sponsors
Escalators
Rest Rooms
E
Registration
Lunch Career tables
Pritzker Audi
Room A
251 East Huron, Chicago, IL

INDEX


DEPAUL UNIVERSITY
COLLEGE OF SCIENCE AND HEALTH


THE
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ILLINOIS
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UIC


RUSH UNIVERSITY

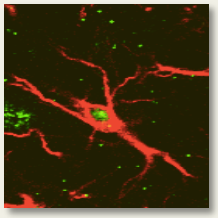
The Northwestern University
Interdepartmental Neuroscience (NUIN)
PhD program is a proud sponsor of the
Chicago Society for Neuroscience.

NORTHWESTERN
UNIVERSITY

THE UNIVERSITY OF CHICAGO

The Grossman Institute for Neuroscience, Quantitative Biology and Human Behavior

The Graduate Programs in Neurobiology and Computational Neuroscience



Loyola University Chicago
Stritch School of Medicine
Neuroscience Research Institute
& Graduate Program

Hands-On Training Opportunities in…

- *Behavioral neuroscience*
- *Biochemistry*
- *Chemistry*
- *Cellular and Molecular Neurobiology*
- *Neuropharmacology*
- *Neuroimmunology*
- *Autoimmune Diseases*
- *Neuroendocrinology*
- *Regeneration and Repair*
- *Stroke*
- *Traumatic Brain Injury*
- *Central and Peripheral Neuropathies*

Neuroscience is one of the most exciting and challenging "frontiers" of the biomedical sciences. The *Neuroscience Program* at Loyola encompasses a vast interdisciplinary track where students are provided with hands-on opportunities to develop and contribute to this rapidly expanding discipline. The student who chooses to join our neuroscience academic community will have options available to them for advanced training in a diverse array of disciplines.

Neuroscience Graduate Program Director:
Evan B. Stubbs, Jr., Ph.D.
Evan.stubbs@va.gov
http://www.stritch.luc.edu/neuroscience/

Neuroscience Institute Director
Wendy Kartje, M.D., Ph.D.
Wkartje@luc.edu
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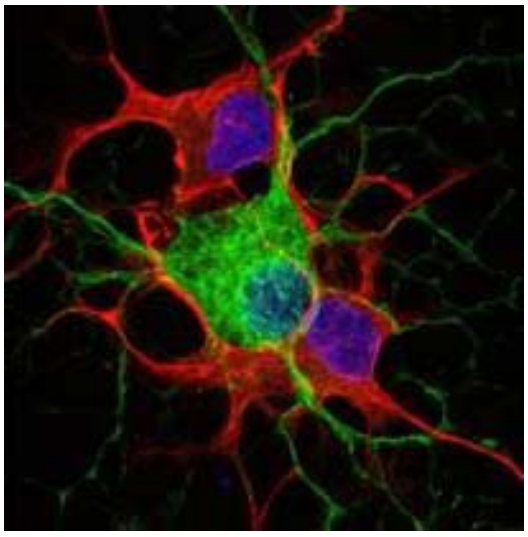


ROSALIND FRANKLIN UNIVERSITY of MEDICINE AND SCIENCE

Save the date!

09.23.16

GENDER BIAS UNDER THE MICROSCOPE

Rosalind Franklin University's Inaugural Women in Medicine and Science Symposium

Join us for a day-long exploration of the achievements, challenges and way forward for women as leaders in the biomedical sciences.

featured lectures

- *Blindspot: Hidden Biases of Good People*
  MAHARZIN BANAJI, PHD / **HARVARD UNIVERSITY**
- *Gender Bias and the Human Genome: the Case for Diversity in Biomedical Discovery*
  SARAH S. RICHARDSON, PHD / **HARVARD UNIVERSITY**
- *The Only Woman in the Room*
  EILEEN POLLACK, MFA / **UNIVERSITY OF MICHIGAN**

With workshops on negotiation skills, mentoring, fostering male allies, women in medicine • Professional Networking • Continuing Education Credit

RECEPTION AND STAGED READING of Anna Zielger's critically acclaimed *Photograph 51*, an intriguing portrait of Dr. Rosalind Franklin's discovery of the structure of DNA, produced by The Theatre School at DePaul University

Registration opens April 1 at **http://rfu.ms/womensymposium**

RFU IS AN AFFIRMATIVE ACTION, EQUAL OPPORTUNITY EMPLOYER

Save the Date – March 31, 2017
Chicago SFN Annual Meeting

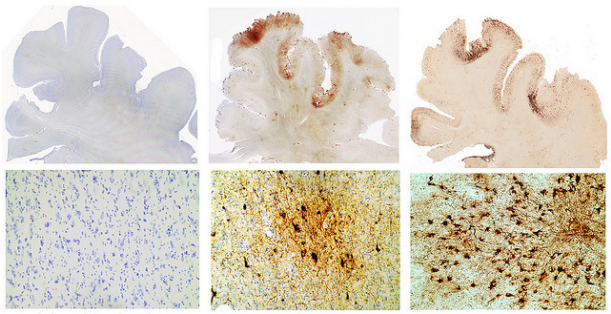
Keynote Speaker:

Ann McKee MD

Professor of Neurology and Pathology,

Boston University School of Medicine

Chronic Traumatic Encephalopathy



A healthy brain (age 65)

Brain of a deceased NFL vet (age 45)

Brain of a deceased boxer (age 73)

Chicago Society for Neuroscience
Career Achievement Award 2016

John Cacioppo, Ph.D.

Dr. Cacioppo has dedicated his academic career by making several outstanding contributions to neuroscience education, the advancement of neuroscience research, and public communication and outreach in the greater Chicago community and beyond. Dr. Cacioppo is the Tiffany and Margaret Blake Distinguished Service Professor at The University of Chicago, the Director of the University of Chicago Center for Cognitive and Social Neuroscience, and the Founding Director of the Arete Initiative of the Office of the Vice President for Research and National Laboratories at the University of Chicago. Awards that he has received include the Scientific Impact Award from the Society for Experimental Social Psychology, a MERIT Award from the National Institutes of Health, the Presidential Citation from the American Psychological Association, and the Troland Research Award from the National Academy of Sciences. He has been elected to the Society of Experimental Psychologists, the American Academy of Arts and Sciences, and the Society of Experimental Social Psychologists. He has served as President of the Association for Psychological Science, the Society for Personality and Social Psychology, the Society for Psychophysiological Research, and the Society for Social Neuroscience. Dr. Cacioppo's research investigating how societal influences and personal relationships affect cognition, emotion, behavior and health by understanding the underlying neural, hormonal, cellular and genetic mechanisms has resulted in over five hundred publications and support from the NIH and NSF. He has mentored an impressive number of undergraduates, graduate students and post-doctoral fellows. Many are now leaders in academia around the world, including in the greater Chicago Community. Dr. Cacioppo has been a tremendous asset to the Neuroscience community in Chicago and we are pleased to honor him with this award.

Schedule of Events

7:30-10:00 AM	**Registration/Continental Breakfast**	**3rd floor**
8:00-8:45 AM	**Mentoring Panel** (with Keynote Speaker and Presidential Symposium Speakers)	***Pritzker Auditorium***
	Poster and Vendor Display set up	***Atrium, 3rd floor***
9:00-4:00 PM	**Poster Viewing and Vendor Display** All posters must be down by 4:00 PM at the latest.	***Atrium, 3rd floor***
9:00-9:15 AM	**2016 Chicago Career Achievement in Neuroscience Award** Presented by Dorothy Kozlowski, Ph.D. & Cindy Voisine, Ph.D.	***Room A***
9:15-10:30 AM	**Presidential Symposium** ***"Sensory Neuroscience"*** Chaired by Dorothy Kozlowski, Ph.D.	***Room A***
10:30-11:30 PM	**Keynote Speaker** **"Natural Products as Probes of the Pain Pathway: From Physiology to Atomic Structure"** David Julius, Ph.D., University of California, San Francisco	***Room A***
11:30-2:00 PM	**Lunch Break** Poster Competitions Viewing/Judging	***Atrium, 3rd floor***
11:30-12:30 PM	Dr. Julius and Graduate Student Symposium participants lunch	***Room E***
12:00-1:00 PM	**Themed Lunch Tables: *"Diversity in Careers"***	***Room A***
2:00- 3:50 PM	**Plenary Afternoon Symposium** ***"Epigenetics of Neurobehavioural Disorders"*** Chaired by Emma Childs, Ph.D. and Shreaya Chakroborty, Ph.D.	***Room A***
4:00- 5:35 PM	**Graduate Student Symposium** Selected Graduate Student Talks Chaired by Cynthia Pervan, Ph.D.	***Room A***
5:45-7:00 PM	**Award Ceremony, Reception and Business Meeting** Reception immediately followed by Business meeting and announcement of awards, recognition and election results	***Atrium, Room A***

Morning Program

8:00-8:45 AM — **Mentoring Panel** — ***Pritzker Auditorium***
(with Keynote Speaker and Presidential Symposium Speakers)
Moderated by Sarah London, Ph.D.

9:00-9:15 AM — **2016 Chicago Career Achievement in Neuroscience Award** — ***Room A***
Recipient: John Cacioppo, Ph.D. University of Chicago
Presented by Dorothy Kozlowski, Ph.D. and Cindy Voisine, Ph.D.

9:15-10:30 AM — **Presidential Symposium** — ***Room A***
"Sensory Neuroscience"
Chaired by Dorothy Kozlowski, Ph.D.

9:15-9:30 *Welcoming Remarks*

9:30-10:00 **PSA**
Decision Making in the Nose
Lisa Stowers, Ph.D.
Associate Professor, Scripps Research Institute

10:00-10:30 **PSB**
Itchy and Scratchy: Molecular mechanisms of acute and chronic itch
Diana Bautista, Ph.D.
Associate Professor, University of California, Berkeley

Keynote Speaker — ***Room A***
10:30-11:30 **Natural Products as Probes of the Pain Pathway: From Physiology to Atomic Structure**

David Julius, Ph.D.

Morris Herzstein Chair in Molecular Biology and Medicine, Professor and Chair of Physiology, University of California, San Francisco

David Julius, PhD, is the Morris Herzstein Chair in Molecular Biology and Medicine, and Professor and Chair of Physiology at the University of California, San Francisco. The Julius lab is interested in understanding how signals are received and transmitted by the nervous system. They have exploited the properties of natural products to discover a family of thermo- and chemosensitive ion channels that enable sensory nerve fibers to detect hot or cold temperatures, or chemical irritants. With the aid of genetic, electrophysiological, and behavioral methods, they have determined how these ion channels contribute to the detection of noxious stimuli, and how channel activity is modulated in response to tumor growth, infection, or other forms of injury that produce inflammation and pain hypersensitivity. Dr. Julius received his undergraduate degree from MIT. He then moved to the University of California, Berkeley, where he worked with Jeremy Thorner and Randy Schekman to elucidate mechanisms of peptide hormone processing and secretion in *Saccharomyces* yeast. For postdoctoral studies, he joined Richard Axel's group at Columbia University, where his focus turned to neuropharmacology and receptor function. Dr. Julius is a member of the US National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, and the Hungarian Academy of Sciences (honorary). His awards include the Perl/UNC Prize, the Unilever Science Prize, the Passano Award, the Prince of Asturias Prize for Technical and Scientific Research, the Shaw Prize in Life Sciences and Medicine, and the Paul Janssen Prize for Biomedical Research.

Lunch Break

11:30-2:00 **Poster Viewing and Competitions** ***Atrium, 3rd floor***

12:00-2:00 Authors in **Post-doctoral Poster Competition** present.
Post-doctoral Poster Competition chaired by **Irina Calin-Jageman, PhD, Dominican University**

12:00-2:00 Authors in **Graduate Student Poster Competition** present.
Graduate Poster Competition chaired by **Eileen Foecking, PhD, Loyola**

12:00-2:00 Authors in **Undergraduate Student Poster Competition** present.
Undergraduate Poster Competition chaired by **Naomi Wentworth, PhD, Lake Forest College**

For poster titles and abstracts, go to pages 27 and 37, respectively.

Themed Lunch Tables (**open to all Trainees**) ***Room A***

Chaired by Cindy Voisine, PhD, Northeastern Illinois University

12:00-1:00 PM ***"Diversity in Careers"***

Know more about your professional options

Table 1 ***Research and Teaching in Academia***
David Carley, PhD, Professor Emeritus Biobehavioral Health Science, Medicine, Bioengineering, University of Illinois at Chicago
Shubhik DebBurman, PhD, Professor of Biology and Neuroscience, Lake Forest College
Robert Calin-Jageman, PhD, Professor of Psychology and Neuroscience Program Director, Dominican University

Table 2 ***Corporate – Takeda***
Thomas Macek, PharmD, PhD, Senior Director, Global Project Leader, CNS Therapeutic Area Unit, Takeda Development Center- Americas
Theresa Peterson, PhD, Associate Director, Publications, Medical Affairs, US, Takeda Pharmaceuticals

Table 3 **Corporate – AbbVie**
Kristin Baldauf, PhD, Senior Manager, Competitive Intelligence, Neuroscience and Oncology, AbbVie
Eric Mohler, PhD
Senior Scientist III, AbbVie

Table 4 ***Alternative Careers***
Elise Covic, PhD, Deputy Dean, The College, University of Chicago
Cody Shults, PhD, Medical Writer, AMICULUM USA
Heather Walsh, PhD, Assistant Director, UChicago Tech, Center for Technology Development and Ventures, University of Chicago

Plenary Afternoon Symposium (For abstracts, see page 22) *Room A*

"Epigenetics of Neurobehavioral Disorders"

2:00-2:05 **Introduction**
Emma Childs, PhD, University of Illinois, Chicago

2:10-2:35 **Molecular Mechanism and Conservation of Epigenetic Transcriptional Memory**
PAS1 Jason Brickner, PhD, Professor, Department of Molecular Biosciences, Northwestern University

2:35-3:00 **Neuroepigenetics and Alcoholism**
PAS2 Subhash Pandey, PhD, Professor, Department of Psychiatry, University of Illinois at Chicago

3:00-3:25 **Biological Sex, Stress, and the Epigenetic Programming of the Juvenile Social Amygdala**
PAS3 Anthony Auger, PhD, Professor, Department of Psychology, University of Wisconsin Madison

3:25-3:50 **Biologic Embedding of Stress and Trauma in an Urban, Population-Based Sample**
PAS4 Monica Uddin, PhD, Associate Professor, Department of Psychology, University of Illinois at Urbana-Champaign

Graduate Student Symposium (For abstracts, see page 23) *Room A*

Chaired by Cynthia Pervan, Ph.D., Loyola University

4:00-4:05 **Introduction**
Cynthia Pervan, Ph.D.

4:05-4:20 **Metabotropic Glutamate Receptor 2 Controls Electrotonic Isolation Of Starburst Amacrine Cells And Responses Of Direction-Selective Ganglion Cells**
GS1 David Koren
Interdisciplinary Scientist Training Program; University of Chicago
Advisor: *Wei Wei, Ph.D.*

4:20-4:35 **AAV9 Gene Therapy Synergizes With Hematopoietic Replacement To Prevent Major Neurological Defects In A Mouse Model Of Krabbe Disease**
GS2 Michael S. Marshall
Department of Anatomy and Cell Biology, Graduate Program in Neuroscience, Medical Scientist Training Program; University of Illinois at Chicago
Advisor: *Ernesto R. Bongarzone, Ph.D.*

4:35-4:50 **Advantages Of Soluble Guanylyl Cyclase Inhibitors For Treating Motor Dysfunction In Parkinson's Disease**

GS3 Vatsala R. Jayasinghe
Department of Cellular and Molecular Pharmacology; Rosalind Franklin University
Advisors: *Kuei Y. Tseng, M.D., Ph.D. and Anthony R. West, Ph.D.*

4:50-5:05 **Examination Of Neurogenesis After Stroke And Anti-Nogo-A Immunotherapy**

GS4 Daniel J. Shepherd
Program in Neuroscience; Loyola University Chicago
Advisor: *Gwendolyn L. Kartje, M.D., Ph.D.*

5:05-5:20 **Cryopreserved Dopamine Neurons Derived From Human IPSCs Reverse Motor Deficits In Animal Models Of Parkinson's Disease**

GS5 David J. Marmion
Department of Neurological Sciences; Rush University
Advisor: *Jeffrey H. Kordower, Ph.D.*

5:20-5:35 **Learning-Related Purkinje Cell Physiology In The Larval Zebrafish Cerebellum**

GS6 Thomas C. Harmon
Neurobiology Department and Interdepartmental Neuroscience Program; Northwestern University ***Advisor:*** *Indira M. Raman, Ph.D.*

5:45-7:00 **Award Ceremony, Business Meeting and Social** ***Atrium, Room A***

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

2016 Chicago Brain Bee winners
2016 Lake Forest College Neuroscience Student Organization SYNAPSE
2016 Northwestern University Brain Awareness Organization (NUBAO)

Announcement of prize winners

Undergraduate Student Poster Competition
Presented by Naomi Wentworth, Ph.D., Lake Forest College
Graduate Student Poster Competition
Presented by Eileen Foecking, Ph.D., Loyola
Post-doctoral Fellow Poster Competition
Presented by Irina Calin-Jageman, Ph.D., Dominical University
Graduate Student Symposium
Presented by Cynthia Pervan, Ph.D., Loyola University

ABSTRACTS

KEYNOTE SPEAKER

NATURAL PRODUCTS AS PROBES OF THE PAIN PATHWAY: FROM PHYSIOLOGY TO ATOMIC STRUCTURE

David Julius, PhD
Professor and Chair, Department of Psychology, University of California, San Francisco

We are interested in determining the molecular basis of somatosensation - the process whereby we experience touch and temperature - with an emphasis on identifying molecules that detect noxious (pain-producing) stimuli. We are also interested in understanding how somatosensation is altered in response to tissue or nerve injury. Our approach has been to identify molecular targets for natural products that mimic the psychophysical effects of commonly encountered somatosensory stimuli, such as heat or cold, and to then ask how these molecules are activated or modulated by noxious stimuli or injury. We have focused on three members of the TRP channel family (TRPV1, TRPM8, and TRPA1) that are expressed by subpopulations of primary afferent sensory neurons and which have been implicated in the detection of thermal stimuli and/or inflammatory agents. Genetic studies support the idea that the capsaicin receptor (TRPV1) and the menthol receptor (TRPM8) function as detectors of heat and cold, respectively, whereas the wasabi receptor (TRPA1) functions as a detector of environmental and endogenous chemical irritants. From a signal transduction and therapeutics perspective, there is great interest in understanding how these channels are activated (gated) by physical and/or chemical stimuli. We have used a combination of molecular genetics, natural product biochemistry, and biophysics to address these issues and probe mechanisms of stimulus detection, channel activation, and coding logic of the somatosensory system.

PRESIDENTIAL SYMPOSIUM

SENSORY NEUROSCIENCE

PSA
DECISION MAKING IN THE NOSE

Lisa Stowers, PhD
Associate Professor, Department of Molecular and Cellular Neuroscience, The Scripps Research Institute

We are leveraging pheromones/kairomones to elicit robust innate behavior in the mouse in order to study the underlying neural code. Our use of purified pheromones enabled us to discover that a subset of the female's sensory receptors are directly regulated by sex-steroids. It had been known that females display dramatically different behavior depending on their state of ovulation. This is thought to occur through sex-specific hormones acting on behavioral centers in the brain. We asked here whether sensory activity also differs across the ovulation cycle to alter behavior and I will show data to indicate that female mouse vomeronasal sensory neurons (VSNs) are temporarily and specifically rendered 'blind' to a subset of male-emitted pheromone ligands during diestrus, yet fully detect and respond to the same ligands during estrus. VSN silencing occurs through the action of the female sex-steroid progesterone. Not all VSNs are targeted for silencing; those detecting cat ligands remain continuously active irrespective of the estrous state and I will show how progesterone targets specific subsets of male-pheromone responsive neurons for inactivation. These findings indicate that internal physiology can selectively and directly modulate sensory input to produce state-specific behavior.

PSB
ITCHY AND SCRATCHY: MOLECULAR MECHANISMS OF ACUTE AND CHRONIC ITCH

Diana Bautista, PhD
Associate Professor of Cell and Developmental Biology, Unviersity of California, Berkeley

Humans rely on the sensations of itch, touch and pain for a broad range of essential behaviors. For example, acute pain acts as a warning signal that alerts us to noxious mechanical, chemical and thermal stimuli, which are potentially tissue damaging. Likewise, itch sensations trigger reflexes that may protect us from disease-carrying insects. In addition, during inflammation or injury, we experience a heightened sensitivity to touch that encourages us to protect the injured site. Despite these essential protective functions, itch and pain can outlast their usefulness and become chronic. In mammals, these sensations are mediated by specialized subsets of somatosensory neurons that innervate the skin and viscera. Non-excitable cells, such as keratinocytes and immune cells, also work in conjunction with somatosensory neurons to promote and maintain acute and chronic inflammatory pain and itch. My lab aims to identify the mechanisms by which these cell types detect itch and tactile stimuli, under normal and pathophysiological conditions.

PLENARY AFTERNOON SYMPOSIUM

NEURAL CIRCUITS & BEHAVIOR

PAS1
MOLECULAR MECHANISM AND CONSERVATION OF EPIGENETIC TRANSCRIPTIONAL MEMORY

Jason Brickner, PhD
Professor, Molecular Biosciences, Northwestern University

Previous expression of genes can lead to mitotically heritable changes in their subnuclear positioning, interchromosomal clustering and chromatin structure by a conserved mechanism called epigenetic transcriptional memory. In yeast and human cells, this phenomenon requires interaction with nuclear pore proteins and leads to the recruitment of RNA polymerase II preinitiation complex (RNAPII PIC), leading to faster future reactivation. As a model for this conserved phenomenon, we have defined the molecular and cellular mechanism of *INO1* transcriptional memory. Active *INO1* interacts with the nuclear pore complex (NPC) and localizes at the nuclear periphery. Upon repression, *INO1* remains associated with the NPC at the periphery. Whereas targeting of active *INO1* requires two *cis*-acting DNA elements and the Put3 and Cbf1 transcription factors, retention at the nuclear periphery requires a distinct DNA element, the Memory Recruitment Sequence (MRS). We have identified a transcriptional repressor that 1) binds to the MRS specifically under memory conditions, 2) is necessary and sufficient for peripheral localization and 3) promotes recruitment of a remodeled form of the H3K4 methyltransferase COMPASS and the Cdk8+ form of Mediator. Remodeling of COMPASS removes the Cps40 module, blocking H3K4 trimethylation, but allowing H3K4 dimethylation. H3K4me2 recruits the SET3 complex, which plays an essential role in memory. Cdk8+ Mediator recruits RNAPII PIC but prevents association of the kinases that phosphorylate the CTD of RNAPII, blocking initiation. This mechanism is utilized by a number of yeast genes that are regulated by different stimuli as well as hundreds of human genes that are induced by interferon gamma. This suggests that memory employs control of transcriptional initiation, regulated by epigenetic inputs.

PAS2
NEUROEPIGENETICS AND ALCOHOLISM

Subhash Pandey, PhD
Professor, Psychiatry, University of Illinois, Chicago

Epigenetic mechanisms including DNA methylation and histone acetylation/methylation have been implicated in regulating gene expression and synaptic plasticity. Changes in epigenetic processes during brain development can lead to persistent effects on adult psychopathology. Here, we examined the effects of adolescent alcohol exposure on brain epigenetic modifications and behavior phenotypes in adulthood. Rats were exposed to adolescent intermittent ethanol/n-saline (AIE/AIS) during post-natal days (PND) 28-41 with a 2-day on/off paradigm and epigenetic marks and related mechanisms in the amygdala and hippocampus as well as behavioral phenotypes such as anxiety and alcohol intake were measured in adulthood. Adolescent alcohol exposure produced a long-lasting impact on the epigenome by increasing DNA methyltransferase (DNMT) activity, histone deacetylase (HDAC) activity, HDAC2 and DNMT3b expression and by decreasing histone lysine demethylating enzyme LSD1 expression in the amygdala in adulthood. Neuropeptide Y (NPY), brain derived neurotrophic factor (BDNF) and activity regulated cytoskeleton-associated (Arc) protein expression, along with the expression of several other synaptic plasticity-associated genes, were decreased in amygdaloid structures of AIE adult rats as compared to AIS adult rats. Interestingly, chromatin was condensed at the NPY, Arc and BDNF exon IV gene promoters in the amygdala of AIE adult rats most likely due to an increase in DNMT and HDAC function, and a decrease in LSD1 and LSD1+8a expression. Treatment with DNMT or HDAC inhibitors attenuated AIE-induced anxiety-like and alcohol-drinking behaviors in adulthood, and also relaxed the chromatin around NPY, Arc and BDNF genes in the amygdala. In addition, hippocampal neurogenesis markers and BDNF expression were decreased by AIE in adulthood that was reversed by HDAC inhibitor treatment. These results suggest that AIE produces an enduring dysregulation in epigenetic processes in the amygdala and hippocampus, which may serve as a vulnerability factor for anxiety and alcoholism in adulthood.

PAS3
BIOLOGICAL SEX, STRESS, AND THE EPIGENETIC PROGRAMMING OF THE JUVENILE SOCIAL AMYGDALA

Anthony P. Auger, PhD
Professor, Psychology, University of Wisconsin, Madison

Epigenetic phenomena have been linked to risk and resilience to numerous mental illnesses, as well as in the control of normative physiological functions and behavior. Furthermore, it has been shown that the brain's epigenetic landscape is sculpted by variations in the early environmental milieu. As such, *gene x environment* interactions can shape brain development and profoundly alter the overall health and behavior of an organism. Importantly, biological sex also appears to be a major factor in gating risk or resilience to a number of neurological and psychiatric disorders. Our lab has

reported numerous sex differences in epigenetic factors during brain development. As subtle differences in the epigenome can influence how cells or an organism responds to stimuli, sex differences in the epigenome may result in differential neuronal responses to similar environmental signals, stress, or other behavioral cues between males and females. Therefore, we hypothesized that sex differences in the brain's epigenome confers risk and resilience to mental health disorders. To elucidate *gene x environment x biological sex interactions*, we focus primarily on the amygdala given its seminal role in the formation of socioemotional and anxiety behaviors. Indeed, neonatal males and females experiencing the same early life stress have both similar and differential epigenetic and behavioral consequences later in life. We have described several differences in methylating and demethylation factors, or in the factors that read the epigenome, during early postnatal brain development. Importantly, neonatal perturbations in some of these factors result in atypical juvenile social development. As epigenetic mechanisms can either be stable or plastic, elucidating the mechanisms involved in reversing these processes could aid in understanding how to reverse pathological epigenetic programming. Overall, we find that the male and female developing brain, in particular the amygdala, has subtle epigenetic differences. These epigenetic differences may underlie how males and females respond differentially to the same early life stressor, producing sex specific consequences later in the juvenile period. That is, biological sex differences in the epigenome may gate how the brain responds to the same stress with differences in neural or behavioral pathology within juvenile social brain.

PAS4
BIOLOGIC EMBEDDING OF STRESS AND TRAUMA IN AN URBAN, POPULATION-BASED SAMPLE

Monica Uddin, PhD
Associate Professor, Psychology, University of Illinois Urbana Champaign

Lifetime experiences have long been recognized as important determinants of mental health and illness; however, the biological mechanisms through which social exposures influence mental health, and how these mechanisms interact with underlying genetic variation to become physiologically and psychologically manifest have, until recently, remained unknown. Epigenetic modifications made throughout the lifecourse provide a plausible and, increasingly, empirically supported explanatory model. The goal of this presentation is to provide an overview of how stressful and traumatic events, experienced throughout the lifecourse, have biological consequences at the molecular level with implications for subsequent mental health. The objectives are to: (i) illustrate how both molecular and environmental variation shape risk of mental illness, using post-traumatic stress disorder and major depressive disorder as an examples; (ii) define DNA methylation and show how it can translate social experiences into risk for, or resilience to, mental illness; and (iii) provide evidence that adverse early life experiences impact stress-relevant molecular phenotypes into adulthood. Examples will be drawn from previous and ongoing research drawn from the Detroit Neighborhood Health Study, an urban, population based cohort of adult residents of Detroit sampled from 2008-2014. Support: R01DA022720, R01DA022720-S1, RC1MH088283

GRADUATE STUDENT SYMPOSIUM

GS1
METABOTROPIC GLUTAMATE RECEPTOR 2 CONTROLS ELECTROTONIC ISOLATION OF STARBURST AMACRINE CELLS AND RESPONSES OF DIRECTION-SELECTIVE GANGLION CELLS

David Koren[1], J. C. Grove[2], W. Wei[2]

[1]Interdisciplinary Scientist Training Program, University of Chicago; [2]Committee on Neurobiology, University of Chicago

Spatial compartmentalization of electrical signaling is crucial for the function of many neural circuits. In the mammalian retina, electrotonic isolation is thought to contribute to direction selectivity in the dendritic processes of starburst amacrine cells (SACs). These processes are strongly depolarized during visual stimuli that move centrifugally (from soma to distal tip) but not during stimuli moving centripetally. Precise GABAergic connectivity between individual SAC processes and direction-selective ganglion cells (DSGCs) enables DSGCs to fire action potentials during motion in their preferred direction, but not during motion in their anti-preferred (null) direction. Importantly, direction selectivity of SAC processes requires that depolarization in one process not propagate to other processes of the same SAC. Previous studies have theorized that this electrotonic isolation may arise from dendritic properties intrinsic to SACs such as ion channel distribution or dendritic diameter. Here, we identify a regulatory mechanism mediated by metabotropic glutamate receptor 2 (mGluR2) signaling that controls electronic isolation of SAC dendritic branches. We use a genetically encoded calcium sensor and patch-clamp electrophysiology to show that mGluR2 blockade increases propagation of electrical signals across SAC dendritic arbors, causing aberrant inhibition of DSGCs during motion in their preferred direction. Our results demonstrate that electrotonic

isolation in this functionally-defined circuit plays a precise role in neural computation and may be dynamic and context-dependent. This study is funded by the National Eye Institute (R01EY024016 to WW and F30EY025958 to DK) and by a Roche/ARCS Fellowship award to DK.

GS2

AAV9 GENE THERAPY SYNERGIZES WITH HEMATOPOIETIC REPLACEMENT TO PREVENT MAJOR NEUROLOGICAL DEFECTS IN A MOUSE MODEL OF KRABBE DISEASE

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Infantile Krabbe disease is a devastating genetic disorder, which causes progressive demyelination of the central and peripheral nervous system, neurosensory deficits, muscle atrophy, and early death. Krabbe disease is due to loss-of-function mutations in the gene encoding for the lysosomal enzyme Galactosylceramidase (GALC). This results in the toxic accumulation of one of its lipid substrates, galactosyl-sphingosine (or psychosine).

Current therapy for patients afflicted with Krabbe is limited to Hematopoietic Stem Cell Transplantation (HSCT) from healthy donors, which has the ability to extend lifespan, but still results in many debilitating disabilities. In this study, we developed and optimized a gene therapy strategy using the adeno-associated virus serotype 9 (AAV9) vector to correct for the deficiency of GALC activity in combination with HSCT.

Using the Twitcher mouse model of Krabbe disease, we show that AAV9 gene therapy restored GALC activity in CNS and PNS, thereby significantly reducing the accumulation of psychosine. Immunohistology demonstrated infection to target primarily into neurons and astrocytes. When combined with neonatal HSCT, AAV9 gene therapy resulted in nearly complete correction of the clinical phenotype and continued survival of affected mice by over 1000% of their expected lifespan. Histopathological analysis showed the reversal of demyelination, neuro-inflammation and gliosis, and neuropathy in treated mice. These results reveal the profound benefit of AAV9 gene therapy could have on human Krabbe's patients when used in conjunction with current therapies. This study is funded by awards to MSM from the NINDS (5F30NS090684) and to ERB from the NIH (R01NS065808 and R21NS087474) and the Legacy for Angels Foundation.

GS3

ADVANTAGES OF SOLUBLE GUANYLYL CYLASE INHIBITORS FOR TREATING MOTOR DYSFUNCTION IN PARKINSON'S DISEASE

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L-DOPA is the gold standard for treating motor symptoms in Parkinson's disease (PD). However, repeated use and frequent escalations in dosage results in severe debilitating side effects termed L-DOPA–induced dyskinesias (LID). Here we compared the potential utility of a non-dopaminergic target to the therapeutic action of L-DOPA. One such target is the striatal soluble guanylyl cyclase (sGC) – cyclic GMP signaling pathway, which becomes abnormally upregulated following chronic dopamine depletion. We found that treatment with the sGC inhibitor ODQ (i.p., one week) was equally effective as L-DOPA in improving stepping behavior in 6-OHDA lesioned rats. These effects were dose-dependent, such that treatment with ODQ at 20 mg/kg elicited improvements in motor behavior equivalent to those observed with L-DOPA at 5 mg/kg. However, rats treated with L-DOPA developed severe LID after the fifth day of treatment. None of the rats treated with ODQ developed dyskinesias over the course of the seven-day treatment period. Interestingly, co-administration of ODQ enhanced the therapeutic effects of L-DOPA and significantly suppressed LID. Our findings indicate that inhibitors of sGC can be used to ameliorate motor deficits in PD or as an adjunct therapy to enhance the beneficial effects of L-DOPA and prevent the development of LID.

Supported by Ply donation, Parkinson's disease Foundation, and NIH grants NS088502 and NS088554.

GS4

EXAMINATION OF NEUROGENESIS AFTER STROKE AND ANTI-NOGO-A IMMUNOTHERAPY

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Ischemic stroke is a leading cause of adult disability worldwide with no approved pharmacological treatments to restore lost function. Our laboratory has shown that treatment with neutralizing antibodies against the well-known neurite outgrowth inhibitor protein Nogo-A promotes neuroplasticity and sensorimotor and cognitive recovery after cortical ischemia in adult and aged rats. As anti-Nogo-A immunotherapy stimulates growth in the adult brain, we investigated whether this treatment was able to enhance neurogenesis in the two major adult neurogenic niches, the subventricular zone (SVZ) and dentate gyrus (DG). Using bromodeoxyuridine injections and quantitative immunohistology *in vivo*, we determined that cellular proliferation in the SVZ and DG were not altered by treatment, nor was the total number of new neurons in the DG produced after stroke. Infusion of both control and anti-Nogo-A antibodies did, however, lead to hippocampal microgliosis. Neither Nogo-A gain of function nor Nogo-A neutralizing antibody treatment have shown an effect on SVZ-derived cell migration *in vitro*. We are currently using gene knockdown to examine the role of intracellular Nogo-A on the migration and morphogenesis of SVZ-derived neurons. This study is supported by the Department of Veterans Affairs and an American Heart Association predoctoral fellowship 15PRE24470136 (to DS).

GS5
CRYOPRESERVED DOPAMINE NEURONS DERIVED FROM HUMAN IPSCs REVERSE MOTOR DEFICITS IN ANIMAL MODELS OF PARKINSON'S DISEASE

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Parkinson's disease (PD) is characterized by the degeneration of dopamine (DA) neurons in the substantia nigra (SN) secondary to loss of striatal DAergic tone. Transplantation of midbrain DA neurons derived from human induced pluripotent stem cells (iPSC-mDA) offers a viable therapeutic. Cryopreservation of post-mitotic iPSC-mDA neurons reduces the need for manipulation in a clinical setting. In the present study, human blood samples were episomally reprogrammed into iPSCs and differentiated to mDA neurons via the floor-plate method. We show that these cryopreserved neurons have high freeze-thaw viability and exhibit a gene expression profile comparable to the human SN. *In vitro*, we show retention of mDA neuron lineage over 1 month by biochemical and histological analysis. Electrophysiological recordings show that iPSC-mDA neurons display spontaneous and evoked action potentials, as well as functional ion channels with channel-inhibitor response. To assess engraftment potential, iPSC-mDA neurons were transplanted into immunosuppressed Sprague-Dawley (SD) rats. Using human specific antigens, immunohistochemistry shows survival of transplanted iPSC-mDA neurons up to 6 weeks in both the striatum and SN of intact rats. To test their therapeutic value in a PD animal model, iPSC-mDA neurons were unilaterally transplanted in the striatum of 6-hydroxydopamine-lesioned immunosuppressed SD rats. Over 6 months, transplanted animals underwent rotation and cylinder behavioral testing and showed a reversal of motor asymmetry in apomorphine and amphetamine induced rotations only. Grafted neurons expressing mDA specific markers projected fibers from the graft to innervate the host striatum. Optical density measurements show a significant increase in tyrosine hydroxylase-ir (TH) fibers in the striatum of grafted rats when compared to vehicle controls. Stereological estimates show that 22.6% (101580 ± 25293) of grafted cells survive 6 months post-transplantation, and 34.5% (26081 ±4921) of the surviving cells are TH-ir. Using Ki-67 as a marker for proliferation, we found no replicating cells. To evaluate survival in a more clinically relevant model, immunosuppressed cynomolgus macaques were transplanted with iPSC-mDA neurons bilaterally in the post-commissural putamen. Monkeys were sacrificed at 4 weeks and 3 months post-transplantation. Immunohistochemistry shows excellent graft survival as well as continued expression of DAergic markers. These data demonstrate the therapeutic potential of cryopreserved iPSC-mDA neurons for the treatment of PD. Funded by Rush Translational Sciences Consortium and Cellular Dynamics International.

GS6
LEARNING-RELATED PURKINJE CELL PHYSIOLOGY IN THE LARVAL ZEBRAFISH CEREBELLUM.

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Cerebellar learning is supported by plasticity at multiple synapses within the circuit. Purkinje cells receive excitatory synaptic inputs from parallel and climbing fibers, both of which are recruited during cerebellar learning and may undergo plasticity that supports the acquisition and retention of a learned movement. To detect plasticity at these synapses, we have made whole-cell, patch clamp recordings from Purkinje cells in larval zebrafish during cerebellum-dependent associative learning. In this task, a light (conditioned stimulus, CS) is paired with a mild electrical stimulus to the tail (unconditioned stimulus, US), which elicits fictive swimming (unconditioned response, UR). With repeated presentations of the CS and US, fictive swimming to the CS (conditioned response, CR) emerges. We have observed three distinct classes of Purkinje cell synaptic and spiking activity displayed during the CR. Multiple complex spiking cells (MCS, n = 12/30) show several complex spikes at the onset of the CR. Integrating EPSP cells (IE, n= 7/30) display parallel fiber EPSPs before the onset of the CR. These EPSPs summate, causing a long-lasting depolarization and simple spikes. Single complex spiking cells (SCS, n=11/30) display one

complex spike at the onset of swimming, followed by either parallel fiber EPSPs and simple spikes or hyperpolarization that lasts several hundred milliseconds after the CR. Plasticity of the cellular response to the CS is evident in each group and progresses towards the synaptic and spiking activity observed during the CR. Also, the cellular response during the CR relates to the topographical location of Purkinje cells, with MCS cells in the medial half, IE cells in the middle, and SCS cells in the lateral half of the cerebellar hemisphere. To probe the contribution of Purkinje cells to the CR, we have used fish that express archaerhodopsin-3 in Purkinje cells, allowing us to preferentially suppress simple spikes during training. Optogenetic hyperpolarization of Purkinje cells impairs acquisition of the CR. Expression of the CR is also impaired by hyperpolarization, but only immediately following acquisition. Together, these results reveal synaptic plasticity during cerebellar learning, demonstrate that the physiological response of a Purkinje cell relates to its location within the cerebellum, and reveal the role of parallel fiber-driven simple spikes to the acquisition and expression of an associative cerebellar memory. This research is supported by: NIH R37-NS39395 (IMR), Brain Research Foundation (IMR, David L McLean), and NIH T32-MH067564 (TCH), and NIH F31-NS095476-01 (TCH).

POSTER ABSTRACT TITLES

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ASO THERAPY RESCUES DISRUPTIONS IN ORGANIZATION OF EXPLORATORY BEHAVIOR ASSOCIATED WITH USHER SYNDROME

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A2

CREB OVEREXPRESSION IN DORSAL CA1 AMELIORATES MEMORY DEFICITS IN AGED RATS

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EFFECTS OF LIGHT AND AMBIENT TEMPERATURE IN A DIURNAL RODENT, THE NILE GRASS RAT

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PHARMACEUTICAL MANIPULATION OF THE DOPAMINERGIC SYSTEM

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THE RELATIONSHIP BETWEEN HEART-RATE VARIABILITY, SLEEP, RESILIENCE, AND BEHAVIORAL HEALTH SYMPTOMS IN A SAMPLE OF INTERNATIONAL CROSS-CULTURAL AID WORKERS

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Navid Nouri, Patricia Jensen, and Rajeshwar Awatramani
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Lillian Perez, Aixa Alfonso

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AAV9 GENE THERAPY SYNERGIZES WITH HEMATOPOIETIC REPLACEMENT TO PREVENT MAJOR NEUROLOGICAL DEFECTS IN A MOUSE MODEL OF KRABBE DISEASE

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C2

ADVANTAGES OF SOLUBLE GUANYLYL CYLASE INHIBITORS FOR TREATING MOTOR DYSFUNCTION IN PARKINSON'S DISEASE

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CRYOPRESERVED DOPAMINE NEURONS DERIVED FROM HUMAN IPSCS REVERSE MOTOR DEFICITS IN ANIMAL MODELS OF PARKINSON'S DISEASE

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Sarah G. Chiren, Naseem Jamnia, Emily Reisenbigler, Robert A. Marr, Grace E. Stutzman, Janice H. Urban, Dorothy A. Kozlowski, Daniel A. Peterson
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EXAMINATION OF NEUROGENESIS AFTER STROKE AND ANTI-NOGO-A IMMUNOTHERAPY

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HIV-1-MEDIATED MPFC PYRAMIDAL NEURON HYPERACTIVITY IS ALLEVIATED BY COMBINED CHRONIC BLOCKADE OF L-TYPE CA2+ CHANNELS AND NMDA RECEPTORS.

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INHIBITION OF SOLUBLE GUANYLATE CYCLASE ALLEVIATES MIGRAINE-ASSOCIATED PAIN

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MEMBERS OF CORTICOTROPIN RELEASING FACTOR (CRF) PEPTIDE FAMILY DIFFERENTLY MODULATE OXYTOCIN RELEASE IN THE BED NUCLEUS OF THE STRIA TERMINALIS (BNST)

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NEUROEPIGENETICS AND ALCOHOLISM

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NON-CODING RNAS ARE ASSOCIATED WITH THE INFLAMMATORY MARKER IL6 AND ARE SENSITIVE TO EX-VIVO CHROMATIN REMODELING IN HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS

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REPEATED SOCIAL DEFEAT STRESS AFFECTS PERIPHERAL IMMUNE SYSTEM IN RATS: POSSIBLE LINK TO NEUROBEHAVIORAL ALTERATIONS IN CHRONIC STRESS DISORDERS.

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TGF-B2 PERTURBATION OF THE KALLIKREIN-KININ SYSTEM IN HUMAN TRABECULAR MESHWORK CELLS

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THE PATHOLOGICAL ROLE OF REGULATORY AND ΓΔ T LYMPHOCYTES IN INTRACTABLE PEDIATRIC EPILEPSY

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THE POTENTIAL THERAPEUTIC ROLE OF CONNEXIN MIMETIC PEPTIDE-43 IN TRAUMATIC BRAIN INJURY (TBI)

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THERAPEUTIC CORRECTION OF APOER2 SPLICING IN ALZHEIMER'S DISEASE MICE USING ANTISENSE OLIGONUCLEOTIDES

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OXYTOCIN IN THE BNST REDUCES ACOUSTIC STARTLE RESPONSE – POSSIBLE ROLE OF PKCΔ NEURONS

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MILD SENSORINEURAL HEARING LOSS TRIGGERS AUDIOGENIC SEIZURE SUSCEPTIBILITY IN ANTISENSE OLIGONUCLEOTIDE TREATED USH1C MICE.

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LOCALLY ADMINISTERED LOVASTATIN-ENCAPSULATING NANOPARTICLES PROTECT AGAINST EXPERIMENTAL AUTOIMMUNE NEURITIS

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PARP-1 GOVERNS ALCOHOL-DEPENDENT BRAIN INFLAMMATORY SIGNALING AND NEURODEGENERATION

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EPIDERMAL GROWTH FACTOR PREVENTS AMYLOID-β INDUCED ANGIOGENESIS DEFICITS *IN VITRO* AND PREVENTS COGNITIVE DEFICITS *IN VIVO*

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EFFECT OF METHAMPHETAMINE SELF-ADMINISTRATION BY HIV-1 TRANSGENIC RATS ON STRIATAL DOPAMINERGIC MARKERS

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UTILIZING IPSC-DERIVED CORTICAL NEURONS HARBORING KNOWN EPILEPSY MUTATIONS TO ADVANCE GENE-SPECIFIC TREATMENTS

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PARKINSON'S DISEASE RELATED LRRK2- MEDIATED CELLULAR AND SYNAPTIC ALTERATIONS IN THE STRIATUM

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HDAC6 INHIBITION INDUCED A-TUBULIN ACETYLATION TRANSLOCATES GAS FROM LIPID-RAFTS: A NOVEL MECHANISM FOR ANTIDEPRESSANT ACTION

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D1

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Lake Forest College

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F2

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F3

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C. CONTE, J. PATEL, S. HERDEGEN, S. KAMAL, I. E. CALIN-JAGEMAN, R. CALIN-JAGEMAN
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F8

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Jacob W. Gray and Rachel A. Bergstrom
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G2

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G3

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G4

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G5

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THEME H. SENSORY AND MOTOR SYSTEMS

H1

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H2

AN INVESTIGATION OF APOPTOSIS IN INNER EAR HAIR CELLS USING JC-1 DYE

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H3

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H4

CHANGES IN THE EXTRACELLULAR MATRIX FOLLOWING ISCHEMIC STROKE IN THE RAT.

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H5

CORTICAL REORGANIZATION RELATED TO VOLUNTARY CONTROL OF THE PARETIC HAND IN CHRONIC STROKE FOLLOWING AN INTERVENTION USING A NOVEL ASSISTIVE SYSTEM: A PRELIMINARY REPORT

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H6

CRISTAE IN INNER EAR HAIR CELL MITOCHONDRIA ARE POLARIZED TOWARD CUTICULAR PLATE

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H7

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H8

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H9

MITOCHONDRIA NEAR RIBBON SYNAPSES IN INNER EAR HAIR CELLS

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H10

RECONSTRUCTION OF THE ODORANT RECEPTOR MAP IN THE OLFACTORY BULB OF AGED MICE

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H11

STRUCTURAL DIFFERENCES OF MITOCHONDRIA IN HAIR CELL EFFERENT BOUTONS AND ADJACENT TO STRIATED ORGANELLES USING EM TOMOGRAPHY

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POSTER ABSTRACTS

THEME A. COGNITION AND BEHAVIOR

A1

ASO THERAPY RESCUES DISRUPTIONS IN ORGANIZATION OF EXPLORATORY BEHAVIOR ASSOCIATED WITH USHER SYNDROME

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Usher syndrome is an autosomal recessive genetic disorder that is associated with impaired visual, auditory and vestibular function. The vestibular system contributes to spatial orientation by providing information for self-movement cue processing. Previous studies have demonstrated that the organization of exploratory behavior under dark conditions relies on self-movement cue processing. Degradation of this sensory input may influence exploratory behavioral organization. Exploration behavior is characterized by a series of progressions and stops along with the establishment of a home base. Recent work has demonstrated that antisense oligonucleotide (ASO) therapy can attenuate behavioral and electrophysiological deficits associated with a mouse model of Usher syndrome. The current study examines the effect of Usher syndrome and ASO therapy on the organization of exploratory behavior under dark and light conditions. Heterozygous and mutant Usher mice received an infusion of ASO or control at postnatal day five. Two months later, mouse exploratory behavior was recorded for 50 minutes during three consecutive dark sessions followed by three consecutive light sessions. Motion capture software was used to segment movement paths into stops and progressions. Usher syndrome mice exhibited disruptions in progressions and stops. ASO therapy attenuated these disruptions in exploratory behavior organization. These results demonstrate the potential of ASO therapy to ameliorate spatial orientation deficits associated with Usher syndrome. Further research is needed to assess the effectiveness of ASO therapy at different time points following treatment and to characterize the effects of ASO therapy on neural systems that mediate exploratory behavior organization. This study is funded by the NIU-RFMUS Collaborative Seed Grants.

A2

CREB OVEREXPRESSION IN DORSAL CA1 AMELIORATES MEMORY DEFICITS IN AGED RATS

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Humans and animals often display learning and memory impairments as they age, however the underlying mechanisms of these impairments are poorly understood. Identifying the molecular pathways that mediate these impairments will allow us to design therapeutics to prevent or reverse these deficits. Increasing activity of the transcription factor cAMP response element-binding protein (CREB) in young adult rodents has been shown to facilitate their behavioral performance and increase intrinsic cellular excitability – both are impaired in normal aged animals. To test if increasing CREB activity would ameliorate age-related cognitive deficits, we overexpressed CREB in CA1 of dorsal hippocampus using an adeno-associated viral vector. Young and aged rats both received CREB or control virus, then received Morris water maze training. CREB overexpression in aged animals ameliorated the deficits in long-term memory seen in control animals, while surprisingly; young animals were unaffected by CREB overexpression. Concurrently, cells overexpressing CREB in aged animals were found to have a reduced post-burst afterhyperpolarization i.e., increased excitability. These results indicate that dysfunction in CREB signaling may mediate age-related cognitive deficits. This work was supported by NIH R37 AG008796 and T32 AG020506, and the Glenn/AFAR Scholarship for Research in the Biology of Aging.

A3

EFFECTS OF LIGHT AND AMBIENT TEMPERATURE IN A DIURNAL RODENT, THE NILE GRASS RAT

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Changes in environmental conditions often result in changes in the display of circadian rhythmicity and locomotor activity levels of mammals. In previous experiments, day active (diurnal) grass rats (*Arvicanthis niloticus*) have been shown to switch to a night active (nocturnal) pattern of activity after the introduction of a running wheel. However, it is not yet known the mechanism by which animals switch from being diurnal to nocturnal. Here, we used grass rats to examine activity levels following manipulations of varying ambient temperatures and lighting intensities. Animals were singly housed with running wheels and data were collected in 12:12 light-dark (LD) conditions. First, we examined how a warmer ambient temperature during the day (25 degrees Celsius) and a cooler night (21 degrees Celsius) would affect wheel running activity. We found that 100% of grass rats in this condition were diurnal. The ambient temperature was then raised to a warmer condition (constant 32 degrees Celsius). Diurnality was still expressed by 100% of the subjects following the temperature increase, yet overall wheel running activity significantly decreased ($p < .05$). Next, we reduced the ambient temperature to a colder condition (constant 16 degrees Celsius). Again, grass rats maintained diurnal patterns of activity in cold conditions. Finally, we plan to adjust the room temperature back to a baseline temperature of 25 degrees Celsius, and dim the intensity of light in the environment. Altogether, we predict that changes in ambient temperatures will affect overall activity levels while

maintaining diurnality, whereas changes in lighting intensity will affect the display of diurnal activity patterns. Our results will allow us to predict how lighting and temperature maintain diurnal patterns, which is important in light of the growing evidence that humans that become night-active have significant health consequences. This work was supported by startup funds provided AJG by Hope College.

A4

EFFECTS OF OLIVARY PRETECTAL NUCLEUS (OPT) LESIONS ON BRAIN RESPONSES TO LIGHT IN DIURNAL GRASS RATS.

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The olivary pretectal nucleus (OPT) receives direct retinal input, exhibits light-induced Fos expression, and is involved in the pupillary light reflex (Gall et al., 2014; Trejo & Cicerone, 1984). We have recently shown that OPT lesions cause diurnal grass rats to decrease their activity in response to a light pulse (LP) given at Zeitgeber time (ZT) 22, opposite to controls. Therefore, the way grass rats respond to acute pulses of light (i.e., masking) is influenced by the OPT. The objective of the current study was to use Fos to examine brain areas through which the OPT might influence this masking effect of light in grass rats. We examined the effects of OPT lesions on the photic response in three retinorecipient brain areas, the suprachiasmatic nucleus (SCN), the ventrolateral geniculate nucleus (VLG), and dorsolateral geniculate nucleus (DLG). OPT lesioned and sham grass rats were either sacrificed at ZT23 at the end of a 1-h LP, or sacrificed at the same time without receiving a LP. We found that following the LP, both shams and animals with OPT lesions exhibited a significant increase in Fos expression in the SCN. In contrast, in the VLG, Fos was increased following a LP in shams, but not in lesioned animals. Finally, the DLG did not display increases in Fos in either controls or lesioned animals. Altogether, our results suggest that interconnections between the OPT, SCN, and VLG play a critical role in masking responses to light in grass rats. This study was funded by a National Institutes of Health (NIH) Ruth L. Kirschstein National Research Service Award (NRSA) from the National Institute of Neurological Disorders and Stroke (NINDS) (F32 NS083360-01; to A.J.G.), and from startup funds from Hope College to A.J.G.

A5

PHARMACEUTICAL MANIPULATION OF THE DOPAMINERGIC SYSTEM

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Dopamine plays a crucial role in governing complex social behaviors and motor function. Using the Zebrafish (*Danio rerio*) model, our goal is to better understand how manipulating cortical dopamine concentrations affects behavior. To manipulate the dopamine system, Apomorphine (APO, dopamine agonist) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, dopaminergic neurotoxin) were administered to separate groups of fish. Adult zebrafish were randomly selected and assigned to 1 of 3 groups: [control, MPTP (150 µM), and APO (150 µM)], and dosed for two minutes. Within each treatment group, groups of 3 fish were recorded in 300 mL of water in a novel tank. Distance (cm) and velocity (cm/sec) were calculated for each fish as a way of assessing motor function and social behavior. Nearest neighbor distance (NND) (cm) was also calculated as a measure of social behavior. After the administration of both APO and MPTP, there was an increase in the distance swam (Control M=73.7, SEM=2.9, MPTP M=77.9, SEM=3.1, APO M=77.2, SEM=5.2) and velocity of swimming (Control M=5.3, SEM=0.2, MPTP M=5.7, SEM=0.2, APO M=5.6, SEM=0.3). However, there was an increase in NND after MPTP (M=6.0, SEM=1.1) and a decrease after APO (M=5.1, SEM=0.4) when compared to control (M=5.4, SEM=0.6). Together these results suggest that while the motor system remains functional, there are changes in the social behavior. Larger distances were maintained between neighbors in the MPTP group, possibly signifying increased anxiety, however the decrease in the distance between neighbors after APO may indicate an increase in striking and/or chasing behavior. Further analysis is required to understand the effect of pharmaceuticals that manipulate cortical dopamine levels on the regulation of complex social behaviors. Based on our preliminary results, manipulation of the dopaminergic system through administration of both APO and MPTP has the ability to alter social behavior. The present findings help to characterize the connection between complex biological mechanisms, in this case the dopaminergic system, and its regulation of complex behaviors.

A6

THE RELATIONSHIP BETWEEN HEART-RATE VARIABILITY, SLEEP, RESILIENCE, AND BEHAVIORAL HEALTH SYMPTOMS IN A SAMPLE OF INTERNATIONAL CROSS-CULTURAL AID WORKERS

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International cross-cultural aid workers represent a unique cohort of people who expose themselves to extreme levels of adversity. Under these conditions, workers are vulnerable to trauma that can result in behavioral health concerns (e.g., depression or PTSD) that greatly affect their service. Therefore, it would be beneficial to gain a better understanding of the neurobiological mechanisms that support an adaptive response to extreme stress. Prior research by our group has demonstrated a link between autonomic function, interoception, behavioral health, and performance under stress, suggesting that individuals who perform well under severe stress process cognitive, emotional, and interoceptive information distinctively. Our goal is to apply this knowledge to international cross-cultural aid workers and to identify factors that influence resilience in order to inform the selection, training, and retention of cross-cultural workers.

We conducted a preliminary investigation by collecting heart-rate variability as a crude measure of autonomic function, and by administering questionnaires to men (n=7) and women (n=3) field workers who have experienced or witnessed high

amounts of traumatic events (e.g., rape, murder, natural disaster, bad accident, etc.). The questionnaires included the Connor-Davidson Resilience Scale (CD-RISC) and the Response to Stressful Experience Scale (RSES), the PTSD checklist for the Diagnostic and Statistical Manual of Mental Disorders 5 (PCL), the Pittsburg Sleep Quality Index (PSQI), and the Modified Mini-Screen. Our data show a Pearson Correlation of 0.77 (p=0.07) between the PTSD checklist and the LF/HF ratio, suggesting that as self-reported PTSD symptoms rise, HRV decreases. Our data also show a significant inverse relationship ($r = -0.90$, $p < 0.01$) between the PSQI and the RSES and a significant positive relationship ($r = 0.78$, $p = 0.04$) between the PSQI and the Mini-Screen. This indicates that better sleep quality is associated with less depressive symptoms and greater resilience. Furthermore, both the RSES ($r = -0.73$, $p = 0.04$) and the CD-RISC ($r = -0.83$, $p = 0.02$) showed significant inverse relationships to the Mini-Screen, suggesting that depressive symptoms decrease with increasing resiliency. These preliminary results from our pilot data successfully extend previous research in a unique sample, identifying heart rate variability and sleep as potential indices of performance under duress. Future studies will add direct measures of brain function collected while participants perform cognitive, emotional, and interoceptive tasks.

THEME B. DEVELOPMENT

B1

ADAMS AS POTENTIAL REGULATORS OF STEM CELL QUIESCENCE IN THE OLFACTORY EPITHELIUM

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Mammals have a limited capacity for neural regeneration. The olfactory epithelium (OE) is a unique tissue, in that it maintains a neural stem cell population throughout adulthood. Both horizontal and globose basal cells (HBCs and GBCs) give rise to new olfactory sensory neurons (OSNs). The OSNs generated in the OE are excitatory projection neurons which connect the OE to the olfactory bulb (OB) in the brain. HBCs adhere to the basal lamina where they self-renew at a low rate, unless activated by severe injury. GBCs are restricted to a cell-layer above the HBCs and proliferate more rapidly, replacing cells in the OE during regular turnover, as well as in response to injury. Whether HBCs or GBCs are the true neural stem cells of the OE has not been determined. Both populations are easily accessible in the nose. As more is learned about their basic regulation, they could be useful in many different medical and engineering applications. I examined three separate microarray studies, in the GEO database, to identify genes significantly up or down-regulated in the OE after damage. I identified members of a disintegrin and metalloprotease family (ADAMs) as differentially expressed in the OE between two and five days post-injury (olfactory bulbectomy). I predict these transmembrane proteins involved in cell adhesion and signal transduction are critical for maintenance and activation of HBCs in the OE. Southern and Western blot confirms the expression of ADAM 23, 21 and 4 in OE tissue. Immunohistochemistry staining tentatively shows localization of ADAM23 to more than one cell type. The relative changes in splice-variant and protein expression will be assessed during postnatal development and recovery from chemical (methimazole) lesion, using quantitative PCR and Western blot.

B2

EMBRYONIC FLOOR PLATE MICRODOMAINS AND IMPLICATIONS FOR DOPAMINERGIC NEURON SPECIFICATION

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Parkinson's Disease (PD) is a neurodegenerative disorder, characterized in part, by debilitating motor symptoms that result from the depletion of midbrain dopamine neurons (mDA) in the substantia nigra pars compacta (SNpc). Advancements in the use of stem cell based PD modeling and replacement therapies of DA neurons in diseased patients have shown quite promising results. However, due to the heterogenous non-DA cell composition after programming, a better understanding of the developmental lineage of these neurons is required. Fate mapping analysis indicates mDA neurons arise along the rostrocaudal axis during development from the floor plate, expressing the markers Lmx1a, and Foxa2, among many others. Prominent studies currently use LMX1A/FOXA2 as progenitor and mDA markers for screening in vitro stem cells towards PD research. Interestingly, further analysis indicates that although Foxa2 and Lmx1a are mDA progenitor markers, other non-DA progenitors also express these markers and develop adjacent to mDA neurons in the hypothalamus. Understanding proper mDA neurogenesis and their developmental boundaries will critically impact models of PD and future therapies which should be optimized towards a more homogenous production of human mDA neurons.

B3

MOLECULAR CHARACTERIZATION OF THE ROLE OF RNA-MEDIATED CHROMATIN REMODELING IN COFFIN SIRIS SYNDROME, AN INTELLECTUAL DISABILITY DISORDER

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Transcription-regulating long non-coding RNAs (lncRNAs) have the potential to control the site-specific expression of thousands of target genes. Previously, we showed that Evf2, the first described ultraconserved lncRNA, increases the association of transcriptional activators (DLX homeodomain proteins) with key DNA enhancers. Recently, we found that the Evf2-DLX1 ribonucleoprotein (RNP) contains the SWI/SNF-related chromatin remodeler Brahma-related gene 1 (BRG1, SMARCA4) in the developing mouse forebrain. Evf2 RNA directly interacts with BRG1 and inhibits BRG1 ATPase and chromatin remodeling activities. Interestingly, two of the mutations identified in patients with Coffin Siris Syndrome (CSS) localize to the BRG1 RNA binding domain (RBD). CSS is characterized by growth deficiency, intellectual disability, microcephaly, coarse facial features and nail defects. Despite

identification of CSS BRG1 mutations, how BRG1 is connected to intellectual disability is not known. Here we show that mutation of BRG1 at a site mutated in humans with CSS (Δ546) disrupts binding of BRG1 to Evf2 in vitro. These data suggest that an RNA binding mechanism may be the molecular basis for intellectual disability in CSS.

B4

VENTRAL CORD VC NEURONS ARE ABNORMAL IN THEIR DIFFERENTIATION IN HLH-3 LOSS OF FUNCTION HERMAPHRODITES

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A key question in neurodevelopment is "How do neurons acquire their identity?" As a model organism C. elegans is ideal to determine the mechanisms of neuronal specification and identity because of the invariant cell lineages in its development. Our goal is to characterize the function of the Asense-like protein, HLH-3, in C. elegans neurodevelopment. We are currently investigating functions for HLH-3 in neurons involved in sex-specific behaviors, including egg-laying. Our laboratory has previously published that HLH-3 is required for the terminal differentiation of the hermaphrodite specific neurons (HSNs) in the egg-laying circuitry, an event occurring past the embryonic developmental stage. hlh-3 loss of function hermaphrodites are egg-laying defective (Egl) in phenotype. Here we report that another cell type implicated in the egg-laying circuitry, the VC neurons, are also abnormal in their differentiation in hlh-3 (tm1688) hermaphrodites. The sex-specific VC neurons arise post-embryonically from the ectodermal like P cells (P3.aap-P8.aap) Three are anterior to the vulva, two flank the vulval opening, and one is posterior to the vulva. Although typically all VC neurons (1-6) are fully differentiated by the L4 larval stage we find that the majority of VC neurons of hlh-3 (tm1688) hermaphrodites are not by this stage. Whereas hlh-3 is necessary for VC differentiation in these lineages, the male-specific CA neurons arising from the same precursors do not appear to be affected; suggesting hlh-3 has a sex-specific role in these lineages.

THEME C. DISORDERS OF THE NERVOUS SYSTEM

C1

AAV9 GENE THERAPY SYNERGIZES WITH HEMATOPOIETIC REPLACEMENT TO PREVENT MAJOR NEUROLOGICAL DEFECTS IN A MOUSE MODEL OF KRABBE DISEASE

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Infantile Krabbe disease is a devastating genetic disorder, which causes progressive demyelination of the central and peripheral nervous system, neurosensory deficits, muscle atrophy, and early death. Krabbe disease is due to loss-of-function mutations in the gene encoding for the lysosomal enzyme Galactosylceramidase (GALC). This results in the toxic accumulation of one of its lipid substrates, galactosyl-sphingosine (or psychosine). Current therapy for patients afflicted with Krabbe is limited to Hematopoietic Stem Cell Transplantation (HSCT) from healthy donors, which has the ability to extend lifespan, but still results in many debilitating disabilities. In this study, we developed and optimized a gene therapy strategy using the adeno-associated virus serotype 9 (AAV9) vector to correct for the deficiency of GALC activity in combination with HSCT. Using the Twitcher mouse model of Krabbe disease, we show that AAV9 gene therapy restored GALC activity in CNS and PNS, thereby significantly reducing the accumulation of psychosine. Immunohistology demonstrated infection to target primarily into neurons and astrocytes. When combined with neonatal HSCT, AAV9 gene therapy resulted in nearly complete correction of the clinical phenotype and continued survival of affected mice by over 1000% of their expected lifespan. Histopathological analysis showed the reversal of demyelination, neuro-inflammation and gliosis, and neuropathy in treated mice. These results reveal the profound benefit of AAV9 gene therapy could have on human Krabbe's patients when used in conjunction with current therapies. This study is funded by awards to MSM from the NINDS (5F30NS090684) and to ERB from the NIH (R01NS065808 and R21NS087474) and the Legacy for Angels Foundation.

C2

ADVANTAGES OF SOLUBLE GUANYLYL CYLASE INHIBITORS FOR TREATING MOTOR DYSFUNCTION IN PARKINSON'S DISEASE

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L-DOPA is the gold standard for treating motor symptoms in Parkinson's disease (PD). However, repeated use and frequent escalations in dosage results in severe debilitating side effects termed L-DOPA–induced dyskinesias (LID). Here we compared the potential utility of a non-dopaminergic target to the therapeutic action of L-DOPA. One such target is the striatal soluble guanylyl cyclase (sGC) – cyclic GMP signaling pathway, which becomes abnormally upregulated following chronic dopamine depletion. We found that treatment with the sGC inhibitor ODQ (i.p., one week) was equally effective as L-DOPA in improving stepping behavior in 6-OHDA lesioned rats. These effects were dose-dependent, such that treatment with ODQ at 20 mg/kg elicited improvements in motor behavior equivalent to those observed with L-DOPA at 5 mg/kg. However, rats treated with L-DOPA developed severe LID after the fifth day of treatment. None of the rats treated with ODQ developed dyskinesias over the course of the seven-day treatment period. Interestingly, co-administration of ODQ enhanced the therapeutic effects of L-DOPA and significantly suppressed LID. Our findings indicate that inhibitors of sGC can be used to ameliorate motor deficits in PD or as an adjunct therapy to enhance the beneficial effects of L-DOPA and prevent the development of LID. Supported by

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C3

ANTISENSE OLIGONUCLEOTIDES FOR THE TREATMENT OF JUVENILE NEURONAL CEROID LIPOFUSCINOSIS.

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Juvenile Neuronal Ceroid Lipofuscinosis (JNCL) is a fatal, pediatric, neurodegenerative, lysosomal storage disease that is caused by the mutation of *CLN3*. Most cases of JNCL are caused by a deletion of *CLN3* exons 7 and 8. There is no effective therapy for JNCL and few options for correcting the defective gene expression associated with this $CLN3^{\Delta ex7/8}$ mutation. Here, we describe a new strategy to specifically recover $CLN3^{\Delta ex7/8}$ protein function. The deletion of exons 7 and 8 from *CLN3* results in a shift in the open reading frame of the mRNA, introducing a premature termination codon, which precludes full-length protein production. We *hypothesize* that correcting the reading frame of $CLN3^{\Delta ex7/8}$ mRNA will partially restore protein function. Removal of a number of different exons from the mRNA will reframe the transcript and produce a full-length CLN3 protein with an internal deletion. We corrected the $CLN3^{\Delta ex7/8}$ reading frame by inducing exon skipping during pre-mRNA splicing using antisense oligonucleotides (ASOs). We find that this frame-correcting approach produces a protein that partially reduces histopathological and phenotypic features of JNCL in $Cln3^{\Delta ex7/8}$ transgenic mice. Transgenic mice with exons 6, 7 and 8 deleted, mimicking the ASO effect, also show evidence of reduced pathology compared to $Cln3^{\Delta ex7/8}$ mice. Together, our results suggest that ASO-mediated reading-frame correction may be a promising therapeutic approach for Batten disease.

C4

CHARACTERIZATION OF A NOVEL MOUSE MODEL OF POST-TRAUMATIC HEADACHE

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Mild traumatic brain injury (mTBI) impacts approximately 1.3 million Americans per year, causing behavioral, cognitive, and emotional deficits. Of the many disabilities resulting from mTBI, post-traumatic headache (PTH) is the most common and long-lasting impairment. Often persisting for up to a year, PTH is most commonly associated with a migraine phenotype. To date, the mechanisms underlying the progression of mTBI to PTH have not been fully elucidated. We aim to develop a novel mouse model that reflects the relationship between mTBI and PTH by combining the closed head weight drop method and the nitroglycerin (NTG) chronic migraine model. NTG is a known human migraine trigger that also produces migraine-associated hyperalgesia in mice. In the mTBI groups, a 30 gram weight impacts the intact crania of anesthetized C57Bl6/J adult male mice. Sham groups undergo anesthesia, but are not impacted. After 2 weeks of recovery, mice are chronically treated with saline, 0.1 mg/kg NTG, or 10 mg/kg NTG over 5 test days. Basal and post-treatment mechanical thresholds are assessed using von Frey hair stimulation. Only the mTBI group developed a progressive and sustained basal hypersensitivity to the low dose of NTG, while the high dose of NTG produced hypersensitivity in both sham and mTBI groups. Both doses of NTG induced comparable acute (post-treatment) hyperalgesia in both groups, 2 hours after injection. Additionally, mTBI groups treated with either a low/high dose of NTG showed a longer recovery time in comparison to their sham counterparts. mTBI appears to produce an increased sensitivity to migraine-associated pain within the NTG model of chronic migraine. Future gene expression studies will explore the role of neuropeptides associated with migraine in this mouse model.

C5

CRYOPRESERVED DOPAMINE NEURONS DERIVED FROM HUMAN IPSCs REVERSE MOTOR DEFICITS IN ANIMAL MODELS OF PARKINSON'S DISEASE

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Parkinson's disease (PD) is characterized by the degeneration of dopamine (DA) neurons in the substantia nigra (SN) secondary to loss of striatal DAergic tone. Transplantation of midbrain DA neurons derived from human induced pluripotent stem cells (iPSC-mDA) offers a viable therapeutic. Cryopreservation of post-mitotic iPSC-mDA neurons reduces the need for manipulation in a clinical setting. In the present study, human blood samples were episomally reprogrammed into iPSCs and differentiated to mDA neurons via the floor-plate method. We show that these cryopreserved neurons have high freeze-thaw viability and exhibit a gene expression profile comparable to the human SN. *In vitro*, we show retention of mDA neuron lineage over 1 month by biochemical and histological analysis. Electrophysiological recordings show that iPSC-mDA neurons display spontaneous and evoked action potentials, as well as functional ion channels with channel-inhibitor response. To assess engraftment potential, iPSC-mDA neurons were transplanted into immunosuppressed Sprague-Dawley (SD) rats. Using human specific antigens, immunohistochemistry shows survival of transplanted iPSC-mDA neurons up to 6 weeks in both the striatum and SN of intact rats. To test their therapeutic value in a PD animal model, iPSC-mDA neurons were unilaterally transplanted in the striatum of 6-hydroxydopamine-lesioned immunosuppressed SD rats. Over 6 months, transplanted animals underwent rotation and cylinder behavioral testing and showed a reversal of motor asymmetry in apomorphine and amphetamine induced rotations only. Grafted neurons expressing mDA specific markers projected fibers from the graft to innervate the host striatum. Optical density measurements show a significant increase in tyrosine hydroxylase-ir (TH) fibers in the striatum of grafted rats when compared to vehicle controls. Stereological estimates show that 22.6% (101580 ± 25293) of grafted cells survive 6 months post-transplantation, and 34.5% (26081 ±4921) of the surviving cells are TH-ir. Using Ki-67 as a marker for proliferation, we found no replicating

cells. To evaluate survival in a more clinically relevant model, immunosuppressed cynomolgus macaques were transplanted with iPSC-mDA neurons bilaterally in the post-commissural putamen. Monkeys were sacrificed at 4 weeks and 3 months post-transplantation. Immunohistochemistry shows excellent graft survival as well as continued expression of DAergic markers. These data demonstrate the therapeutic potential of cryopreserved iPSC-mDA neurons for the treatment of PD. Funded by Rush Translational Sciences Consortium and Cellular Dynamics International.

C6

DELTA-TOCOTRIENOL PROTECTS OPTIC NERVE HEAD ASTROCYTES FROM OXIDATIVE INSULT

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Glaucoma and optic neuritis are multifactorial progressive ocular pathologies that are leading causes of visual impairment worldwide. They share several pathological hallmarks, incl. glial activation and extracellular matrix remodeling in the optic nerve head early during pathogenesis. Glioprotective strategies with the goal to preserve and/or restore the structural and functional viability of ONHA in order to slow glaucoma and related pathologies are thus of high clinical relevance. Delta-tocotrienol is a member of the vitamin E family, and a potent antioxidant. Despite its use as a nutritional supplement for a wide range of indications, including cancer and cardiovascular disease, the underlying molecular mechanisms of action of tocotrienols have yet to be fully elucidated. We herein measured the cytoprotective effects of delta-tocotrienol against oxidative stress-induced damage in primary adult rat optic nerve head astrocytes (ONHAs). ONHAs are the major glia cell type in the non-myelinated optic nerve, where they contribute to extracellular matrix synthesis and confer structural integrity to the optic nerve head. We utilized a previously validated set of standardized plate-reader assays to quantify the cytoprotective potential of delta-tocotrienol against *tert*-butyl hydroperoxide (*t*BHP)-induced oxidative stress. Delta-tocotrienol dose-dependently (0.05-50 μM) protected ONHAs from chemically-induced oxidative stress, as quantified by using lactate dehydrogenase (LDH) release and MTT reduction assays, established measures for apoptotic cell death and mitochondrial dysfunction. Pretreatment with 50 μM delta-tocotrienol shifted the concentrations to achieve half-maximal effects of *t*BHP by approximately 200 μM for LDH release and MTT reduction and was significantly more potent than the prototypic antioxidant, Trolox. This potent antioxidant effect of delta-tocotrienol is of high clinical relevance for studies involving vitamin E-mediated glioprotection and neuroprotection. To our knowledge, this is the first report of protective effects of tocotrienols in a preclinical model that mimics changes associated with glaucomatous optic neuropathies. This study was funded with support from the Dr. John P. and Therese E. Mulcahy Endowed Professorship in Ophthalmology (SK). This material is the result of work supported with resources and the use of facilities at the Edward Hines Jr. VA Hospital, Hines, IL. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

C7

EFFECTS OF CHRONIC ADMINISTRATION OF A D3 DOPAMINE RECEPTOR-PREFERRING AGONIST ON THE Akt/GSK3β PATHWAY IN STRIATAL BRAIN REGIONS

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Parkinson's disease (PD) is often treated with dopamine receptor agonists such as pramipexole (PPX). PPX has high affinity for D_2/D_3 receptors, but the signaling pathways that underpin the impulse control disorders (ICDs) – a debilitating side effect of dopamine agonist treatment – caused by PPX remain unclear. We previously demonstrated that acute administration of PPX alters signaling in the Akt/GSK3β pathway by decreasing phosphorylation of Akt and GSK3β in the ventral striatum/nucleus accumbens (NAc) of rats. The effects of chronic PPX administration on this pathway in a rat model of PD have yet to be determined. This is a relevant knowledge gap, as PPX is used as a long-term therapy in PD. As PD is a disease of the nigrostriatal system and PPX treatment affects brain regions associated with both ICDs – NAc -and motor behavior - the dorsolateral striatum (DLS) - it is important to evaluate nigrostriatal regions as well. We hypothesized that chronic administration of PPX would have the same effects as acute administration on the Akt/GSK3β pathway in the NAc, and we sought to study of the effects of chronic PPX on this pathway in both the NAc and the DLS.

To model PD in rats, we bilaterally injected the dopaminergic toxin, 6OHDA, into the DLS; (4μg/2μl). Injections of the ascorbic acid vehicle solution (2μl) served as sham controls. 21 days post-lesion, rats were implanted with subcutaneous osmotic minipumps which delivered PPX (1.2 mg/kg/day) or vehicle (saline) for 14 days. A forelimb adjusted step task was used to determine lesion-induced motor deficits, as well as efficacy of PPX administration. On the last day of PPX treatment, brain tissue was harvested for tyrosine hydroxylase (TH) immunohistochemistry or Western blot analyses. 6OHDA-lesioned rats showed profound stepping deficits that were reversed by PPX. Stereological cell counts of TH^+ cell bodies in the substantia nigra *pars compacta* (SNpc) were significantly lower in lesioned animals vs. sham controls; there was no effect of PPX on the number of TH^+ cell bodies. Western blotting revealed that pGSK3β /total GSK3β in the NAc and DLS did not differ significantly between treatment groups. These results indicate differences between the effect of acute and chronic PPX on the Akt/GSK3β pathway in the NAc, and suggest that Akt/GSK3β signaling in nigrostriatal regions do not underlie the motoric improvements and ICDs imparted by chronic PPX. This study is funded by a research award from NINDS (NS087559) to TCN and ALP.

C8

EFFECTS OF REPEATED CONCUSSIVE TRAUMATIC BRAIN INJURY (TBI) AT ACUTE AND CHRONIC TIMEPOINTS

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Traumatic brain injuries (TBI), particularly in milder forms, such as concussions that result from sports or combat, are becoming increasingly common. Oftentimes, these mild TBIs can result in cognitive and motor deficits. Furthermore, a single TBI increases vulnerability to a subsequent injury. Repeated mild TBIs are now understood to increase likelihood of developing a neurodegenerative disease, such as chronic traumatic encephalopathy, which is commonly found in the brains of injured athletes. However, the precise sequence of degenerative and regenerative responses remains unclear. To model the clinical course of repeated mild TBI, we have utilized a controlled cortical impactor to deliver a closed head injury to male Long-Evans rats. As the hippocampus is central to encoding memory and is known to support adult neurogenesis, we evaluated areas CA1, CA3, and the dorsal and ventral blades of the dentate gyrus. Brains were collected at acute and chronic time points to assess both the initial and long-term responses to impact. Coronal sections through the hippocampus were immunostained to detect mature neurons (NeuN), early neuroblasts (DCX), microglia (IBA1), and astrocytes (GFAP). Qualitative trends show neuronal cell loss in area CA1, the dorsal blade of the dentate gyrus, and reduced neuroblasts in the dorsal blade of the dentate gyrus. Additionally, volumetric data showed a decrease in hippocampal volume and an increase in ventricular size. Work in progress using stereological methods (*StereoInvestigator* software) includes estimation of cell populations (Optical Fractionator) and tissue volume (Cavalieri estimator). This study is funded by the RFUMS-Depaul Pilot Award.

C9

EPIGENETIC CONTROL OF CYTOKINE MRNA LEVELS AS A RESULT OF ENDOTOXIN TOLERANCE IS ALTERED IN HUMAN ADIPOCYTES TREATED CONCURRENTLY WITH ANTIPSYCHOTICS

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Schizophrenia is a highly variable and devastating mental illness which exhibits aberrations in both immune function and certain epigenetic marks. It has previously been shown that one of these repressive marks, dimethlyation of lysine 9 of histone 3 (H3K9me2) is globally elevated in peripheral blood mononuclear cells of schizophrenia patients. Furthermore, previous work in our lab has shown that antipsychotic treatment of a human adipocyte cell line (SW872) will increase global levels of both phosphorylated H3S10, and open chromatin mark which interferes with methylation of H3K9 via a methyl-phospho switch, and phosphorylated Heterochromatin Protein 1γ (HP1γ), which typically binds H3K9me2 and encourages the spread of heterochromatin but is thought to unbind upon phosphorylation. Utilizing the endotoxin tolerance paradigm, in which cells are subjected to lipopolysaccharide for long periods of time, undergo heterochromatinization at immune response promoters, and lose their immune response potency to further endotoxin insult, we are able to study the main players in immunity and epigenetics at the same time. Using chromatin immunoprecipitation (ChIP) for phospho-HP1γ, unphosphorylated HP1γ, and phospho-H3S10, we examined how these epigenetic marks change at the promoters of IL6, TNFα, KLF4, PPARγ, and IL-1β in SW872 cells in response to treatment with LPS, Risperdone, or concomitant treatment with both. We demonstrate that open chromatin marks significantly increase after short immune response-inducing LPS treatment, but decrease to at or below baseline values after 24 hour tolerance-inducing LPS treatment in all genes except KLF4 and PPARγ. Furthermore, treatment with Risperdone concurrently with LPS significantly rescues the open chromatin marking at these promoters in tolerized cells. These findings were then validated using qPCR in mRNA for these genes, demonstrating a functional consequence of these epigenetic changes. This study is funded by PHS grant (NIH) R01MH094358 (R.P.S.).

C10

EXAMINATION OF NEUROGENESIS AFTER STROKE AND ANTI-NOGO-A IMMUNOTHERAPY

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Ischemic stroke is a leading cause of adult disability worldwide with no approved pharmacological treatments to restore lost function. Our laboratory has shown that treatment with neutralizing antibodies against the well-known neurite outgrowth inhibitor protein Nogo-A promotes neuroplasticity and sensorimotor and cognitive recovery after cortical ischemia in adult and aged rats. As anti-Nogo-A immunotherapy stimulates growth in the adult brain, we investigated whether this treatment was able to enhance neurogenesis in the two major adult neurogenic niches, the subventricular zone (SVZ) and dentate gyrus (DG). Using bromodeoxyuridine injections and quantitative immunohistology *in vivo*, we determined that cellular proliferation in the SVZ and DG were not altered by treatment, nor was the total number of new neurons in the DG produced after stroke. Infusion of both control and anti-Nogo-A antibodies did, however, lead to hippocampal microgliosis. Neither Nogo-A gain of function nor Nogo-A neutralizing antibody treatment have shown an effect on SVZ-derived cell migration *in vitro*. We are currently using gene knockdown to examine the role of intracellular Nogo-A on the migration and morphogenesis of SVZ-derived neurons. This study is supported by the Department of Veterans Affairs and an American Heart Association predoctoral fellowship 15PRE24470136 (to DS).

C11

EXAMINING THE CONTRIBUTIONS OF α-SYNUCLEIN NITRATION AND C-TERMINAL TRUNCATIONS IN PARKINSON'S DISEASE USING YEAST MODELS

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Parkinson's disease (PD) is associated with the aggregation and misfolding of α-synuclein (a-Syn) within dying midbrain dopaminergic neurons. Notably, a-Syn is nitrated and truncated at its C-terminus in these dying neurons. Investigations *in vitro* and in cell culture demonstrate that truncated nitrated a-Syn forms are more aggregation prone and toxic to cells. However, organism-level evidence for C-terminal truncation and nitration on a-Syn's aggregation, membrane association, and toxic properties is lacking. In our first study, we hypothesized that nitration of at least of these nitration sites (or a combination of them) is key to cellular toxicity, aggregation and membrane association. The tyrosine residues on a-Syn that are nitrated are Y39, Y125, Y133 and Y136. We created point mutants that mimic (Y39C, Y125C, Y133C and Y136C) or block nitration (Y39F, Y125F, Y133F and Y136F) and characterized them in fission and budding yeast models. In budding yeast, nitration at Y39 influenced membrane localization, and nitration on Y133 had the most impact on toxicity. Fission yeast nitration on Y39 and Y125 affected toxicity the most and nitration on all four tyrosine residues influenced intracellular localization. Next, we evaluated the effects these mutants in two yeast strains that enhance (*cox5AΔ*) or reduce (*cox5BΔ*) nitrative stress. In both strains, a-Syn localization is altered and wild-type a-Syn is more toxic than either type of nitration mutants. In our second study, we hypothesized that larger truncations will lead to increased protein aggregation and toxicity because a-Syn's C-terminus governs solubility. We created and compared four C-terminally truncated versions (Syn-123, Syn-120, Syn-113, Syn-110) with the full length Syn-140, in a-Syn's wild-type and all six known familial PD mutant backgrounds (A30P, E46K, H50Q, G51D, A53E, and A53T). We now have evidence that for some familial mutations (A30P, E46K, and A53T), C-terminal truncations are similar to full-length protein in producing toxicity, but they reduce membrane association, unexpectedly a role of the C-terminus in membrane association. The location of GFP-tag on a-Syn influences how truncations affect membrane association. When completed, we expect that both studies will provide further insight on the influence of nitration and truncation variants of a-Syn and its role in PD.

C12

HIV-1-MEDIATED MPFC PYRAMIDAL NEURON HYPERACTIVITY IS ALLEVIATED BY COMBINED CHRONIC BLOCKADE OF L-TYPE Ca^{2+} CHANNELS AND NMDA RECEPTORS.

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HIV-1 infection induces neurological and neuropsychological deficits, which are associated with dysregulation of the medial prefrontal cortex (mPFC) and other vulnerable brain regions. Although over-activation of NMDA receptors is well described in the HIV infected brain, blocking NMDA receptors in clinical trials was not beneficial in reversing HIV-induced neuronal damage, which highlights the contribution of other pathways to this damage. In this study, we evaluated the impact of HIV in the mPFC and the therapeutic potential of targeting over-active voltage-gated L-type Ca^{2+} channels (L-channel) and NMDA receptors (NMDAR), using young HIV-1 transgenic (Tg) rats. Whole-cell patch-clamp recording was used to assess the membrane properties and voltage-sensitive Ca^{2+} potentials (Ca^{2+} influx) in mPFC pyramidal neurons. We found that neurons from HIV-1 Tg rats displayed reduced rheobase, spike amplitude and inwardly-rectifying K^+ influx, increased numbers of action potentials, and a trend of aberrant firing compared to those from non-Tg control rats. Neuronal hyper-excitation was associated with abnormally-enhanced Ca^{2+} influx (independent of NMDAR), which was eliminated by acute L-channel blockade. Combined chronic blockade of over-active L-channels and NMDARs with open-channel blockers abolished HIV effects on spiking, aberrant firing and Ca^{2+} potential half-amplitude duration, though not the reduced inward rectification. In contrast, individual chronic blockade of over-active L-channels or NMDARs did not alleviate HIV-induced mPFC hyper-excitability. These findings demonstrate that HIV alters mPFC neuronal activity by dysregulating membrane excitability and Ca^{2+} influx through the L-channels. This renders these neurons more susceptible and vulnerable to excitatory stimuli, and could contribute to HIV-associated neuropathogenesis. Combined targeting of over-active L-channels/NMDARs alleviates HIV-induced dysfunction of mPFC pyramidal neurons in young HIV-1 Tg rats, emphasizing a potential novel therapeutic strategy that may effectively decrease HIV-induced Ca^{2+} dysregulation in the mPFC.

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C13

IMMUNOREGULATORY AND MYELIN REPAIR THERAPIES IN T CELL-MEDIATED MOUSE MODELS OF MULTIPLE SCLEROSIS

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Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system characterized by demyelination and neurodegeneration in response to perivascular T-cell and mononuclear cell infiltration. Currently available disease modifying therapies, for reduction of frequency and severity of relapses, are global immunosuppressants acting through non-specific inhibition of T-cell activation/function and/or trafficking. These FDA-approved drugs have limited efficiency and are often associated with serious side effects. We have recently demonstrated an effective means of ameliorating disease in a mouse model of MS through tolerance induction in autoreactive T cells using i.v. infusion of 500nM poly(lactic-*co*-glycolic acid) nanoparticles coupled with or encapsulating myelin peptides (Ag-PLG NP) that effectively reduces disease burden in relapsing-remitting (R-EAE) and in chronic-progressive (C-EAE) mouse models of experimental autoimmune encephalomyelitis (EAE) by reducing inflammatory cell infiltration. Today, there are no FDA-approved therapies for enhancing myelination despite successful *in vitro* and *in vivo* pre-clinical testing of several molecules/compounds reported to promote oligodendrocyte differentiation/maturation. As autoimmunity and neurodegeneration underlie MS, effective disease modifying therapies need to both regulate the immune system and promote restoration of neuronal function, including remyelination. This research tests the hypothesis that remyelination can be more efficiently induced in mice in which the underlying autoimmune response is specifically regulated. We examined the effects of therapies employing drugs that promote myelin repair by stimulating oligodendrocyte progenitor cell expansion, homing and/or differentiation combined with nanoparticle tolerance-based immunoregulatory therapies on T cell-mediated EAE mouse models of multiple sclerosis. We examined clinical disease progression, behavioral outcomes, CNS immune and inflammatory responses, and flow cytometry-based enumeration of cells of the oligodendrocyte lineage. These pre-clinical trials may provide a novel and safe targeted approach that can be translated into effective disease modifying therapies for MS patients.

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C14

INHIBITION OF SOLUBLE GUANYLATE CYCLASE ALLEVIATES MIGRAINE-ASSOCIATED PAIN

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Migraine is an extraordinarily common brain disorder for which therapeutic options continue to be limited. The nitric oxide pathway has been heavily implicated in migraine, and the nitric oxide donor nitroglycerin (NTG) has been shown to reliably trigger migraine in humans. NTG stimulates soluble guanylate cyclase (sGC), the main NO receptor in the body, which increases production of cGMP. The guanylate cyclase pathway is of particular relevance to migraine as upregulation of cGMP by NTG or sildenafil (a phosphodiesterase 5 inhibitor) produces headache but no other type of pain. Previously we have shown that stimulating sGC produces a migraine-associated pain in mice, which was reversed by prototypic anti-migraine medications. The aim of this study is to determine the effectiveness of sGC inhibitors as novel anti-migraine therapies. C57bl6/J mice were treated acutely and chronically with either vehicle or RG2-12 prior to administration of NTG, vehicle, or the sGC stimulator VL-102. Basal and post-treatment mechanical thresholds were determined using von Frey hair stimulation. RG2-12 reversed acute hyperalgesia and basal hypersensitivity induced by both VL-102 and NTG. Acute treatment with RG2-12 also alleviated established hyperalgesia produced by chronic administration of NTG or VL-102. These results indicate that inhibition of soluble guanylate cyclase alleviates migraine-associated hyperalgesia in a mouse model of acute and chronic migraine. These data indicate that soluble guanylate cyclase inhibitors could be a promising therapeutic target for the treatment of migraine. This work was supported by NIH DA031243, the Department of Psychiatry UIC, and the UICentre

C15

MEMBERS OF CORTICOTROPIN RELEASING FACTOR (CRF) PEPTIDE FAMILY DIFFERENTLY MODULATE OXYTOCIN RELEASE IN THE BED NUCLEUS OF THE STRIA TERMINALIS (BNST)

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The neuropeptide oxytocin (OT) has been proven to play a key role in the regulation of social and anxiety-like behavior as well as stress-coping mechanisms. Previous experiments have indicated that OT neurons send oxytocinergic projections from the paraventricular nucleus of the hypothalamus (PVN) to the oval nucleus of the bed nucleus of the stria terminalis (BNSTov), a forebrain region critically involved in a long-duration fear response that resemble anxiety-like behavior. Importantly, these OT terminals in the BNSTov express corticotropin releasing factor (CRF) receptor type 2 (CRFR2), which suggests that CRFR2 might modulate OT release in the BNSTov. Here, we examined 1) whether OT is released in the BNSTov in response to an acute stress

and 2) whether OT release could be modulated by CRFR2. We employed microdialysis in freely-moving rats to determine if an acute stress and CRFR2 manipulation by a selective (Urocortin 3), non-selective (CRF) agonist; or antagonist (Astressin 2B), could modulate OT release. Our experiments demonstrate that acute stress does not induce significant OT release in the BNSTov and suggest that a specific mechanism exists in the BNSTov that prevents the acute stress-induced OT release. Further, we show that blocking CRFR2 by Astressin 2B delivered locally via reverse dialysis (retrodialysis), caused an instant and significant increase in the OT release in the BNSTov, while CRFR2 activation by Urocortin 3 caused a delayed and only moderate decrease in the OT release. Interestingly, a nonspecific CRFR2 agonist, CRF, did not have an immediate effect on the OT release, but instead caused a delayed and significant increase in the OT content in the BNSTov. This delay suggests a potential feedback mechanism via a postsynaptic CRFR1 activation, which is in agreement with our previously published findings that a reciprocal circuit exists between the neurons of the BNST and oxytocin neurons in the PVN. Furthermore, our data indicates that CRF (via CRFR1) and Urocortin 3 (via CRFR2) might exert opposite effects on OT release in the BNSTov, which further highlights differential roles of respective CRF peptide family members in modulation of anxiety and stress-coping mechanisms. Overall, our findings suggest a fine-tuned control of OT release by the members of the CRF peptide family and by the feedback loop between the BNSTov and PVN. Understanding how the PVN-BNSTov circuit modulates oxytocin release will provide a profound promise of oxytocin as a potential target for the treatment of stress and anxiety-related psychiatric disease. This work is supported by NIMH R00MH096746 grant and start-up funds of the *Chicago Medical School*, Rosalind Franklin University of Medicine and Science to JD.

C16

MODELING A SUBCONCUSSIVE IMPACT IN THE ADULT RAT

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A subconcussive impact is a milder form of brain injury that often goes undetected due to a lack of immediate concussion-like symptoms. However, multiple subconcussive impacts can produce behavioral deficits and cellular dysfunction. Subconcussive impacts have not been extensively examined in the TBI field. Specifically, the mechanisms of subconcussive impacts and their relationship to behavioral dysfunction are not fully understood. In order to further investigate these underlying mechanisms, we developed a clinically relevant closed head animal model of a subconcussive impact in adult rats using a Leica controlled cortical impact (CCI) device. Animals received either a single subconcussive injury or three subconcussive injuries administered 48 hours apart. Motor coordination (foot fault test) was tested at baseline, post-injury day (PID) 3, 7, 11, 21, and 27. No significant motor deficits were observed in either the single or repeat group at either time point. Object recognition was examined using the Novel Object task at PID 7 and 27. No significant memory deficits were observed in either group at either time point. No apparent gross pathology was observed on the surface of the brains for either group. In conclusion, we have developed a closed head injury model where one to three subconcussive impacts were not enough to produce any memory or motor deficits. Future studies will investigate a higher number of impacts to determine the threshold for behavioral symptoms. We will also perform histological examination of the tissue for markers of pathology.
This study is funded by DePaul University Research Council.

C17

MODULATION OF ETHANOL REWARD, ANXIETY, AND GENE EXPRESSION BY THE TRANSCRIPTIONAL REGULATOR LIM-DOMAIN ONLY 3 (LMO3)

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LMO3 is a transcriptional regulator that has previously been implicated in several alcohol-related phenotypes; notably, *Lmo3* knockout (Lmo3KO) mice exhibit increased binge-like ethanol consumption. To further characterize Lmo3KO mice, we tested for the rewarding properties of ethanol, using the conditioned place preference test, and ethanol-induced anxiolysis, using the elevated plus maze test. In both tasks, we found a sex by genotype interaction, wherein female Lmo3KO mice exhibited attenuated ethanol preference and ethanol-induced anxiolysis, and male Lmo3KO mice exhibited greater baseline anxiety. In order to explore the mechanism by which LMO3 is regulating these behaviors, we compared the expression of several alcohol-related genes (*Crh*, *Crhr1*, *Gabra1*, *Gabra4*, and *Gabrd*) between Lmo3KO and wildtype (WT) mice. Gene expression was examined in the nucleus accumbens (NAc), central nucleus of amygdala (CeA), and basolateral amygdala (BLA) using qPCR. Lmo3KO mice had greater *Gabra1* expression in the NAc, but reduced expression in the CeA. *Gabra4* expression was also increased in the BLA of Lmo3KO mice. A sex by genotype interaction was found for *Gabrd* – female Lmo3KO mice had significantly greater expression of *Gabrd* in the BLA than female WT mice. Finally, Lmo3KO mice had reduced expression of both *Crh* and *Crhr1* in the BLA, and reduced expression of *Crhr1* in the CeA. The dysregulated expression of GABA-A receptor subunits and the CRF system in the amygdala may account for the increased binge drinking in Lmo3KO mice, while changes in *Gabrd* expression in female Lmo3KO mice may drive the modulation of reward and altered anxiety-like behavior exhibited by these mice.
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C18

NEUROEPIGENETICS AND ALCOHOLISM

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Epigenetic mechanisms including DNA methylation and histone acetylation/methylation have been implicated in regulating gene expression and synaptic plasticity. Changes in epigenetic processes during brain development can lead to persistent effects on adult psychopathology. Here, we

examined the effects of adolescent alcohol exposure on brain epigenetic modifications and behavior phenotypes in adulthood. Rats were exposed to adolescent intermittent ethanol/n-saline (AIE/AIS) during post-natal days (PND) 28-41 with a 2-day on/off paradigm and epigenetic marks and related mechanisms in the amygdala and hippocampus as well as behavioral phenotypes such as anxiety and alcohol intake were measured in adulthood. Adolescent alcohol exposure produced a long-lasting impact on the epigenome by increasing DNA methyltransferase (DNMT) activity, histone deacetylase (HDAC) activity, HDAC2 and DNMT3b expression and by decreasing histone lysine demethylating enzyme LSD1 expression in the amygdala in adulthood. Neuropeptide Y (NPY), brain derived neurotrophic factor (BDNF) and activity regulated cytoskeleton-associated (Arc) protein expression, along with the expression of several other synaptic plasticity-associated genes, were decreased in amygdaloid structures of AIE adult rats as compared to AIS adult rats. Interestingly, chromatin was condensed at the NPY, Arc and BDNF exon IV gene promoters in the amygdala of AIE adult rats most likely due to an increase in DNMT and HDAC function, and a decrease in LSD1 and LSD1+8a expression. Treatment with DNMT or HDAC inhibitors attenuated AIE-induced anxiety-like and alcohol-drinking behaviors in adulthood, and also relaxed the chromatin around NPY, Arc and BDNF genes in the amygdala. In addition, hippocampal neurogenesis markers and BDNF expression were decreased by AIE in adulthood that was reversed by HDAC inhibitor treatment. These results suggest that AIE produces an enduring dysregulation in epigenetic processes in the amygdala and hippocampus, which may serve as a vulnerability factor for anxiety and alcoholism in adulthood.

C19

NON-CODING RNAS ARE ASSOCIATED WITH THE INFLAMMATORY MARKER IL6 AND ARE SENSITIVE TO EX-VIVO CHROMATIN REMODELING IN HUMAN PERIPHERAL BLOOD MONONUCLEAR CELLS

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It has become increasingly apparent that providing the code for protein is only one of a large number of functions of RNA in the eukaryote. Because non-coding RNAs (ncRNAs) are crucial for the fine tuning of gene expression networks during development and in adulthood, dysregulation of ncRNA expression has been implicated in the pathogenesis of neuropsychiatric disorders. Expression of these transcripts is under the control of a number of epigenetic mechanisms such as histone acetylation and methylation. In this study we measured the transcription of specific non-coding RNAs (AS1DHRS4, TMEVPG1, NRON, HERV-W env and HERV-W gag) in peripheral blood mononuclear cells (PBMCs) from a sample of healthy controls and subjects with schizophrenia. We demonstrate that the constitutive expression of TMEVPG1, NRON and both HERV-W transcripts are correlated with mRNA levels of the pro-inflammatory cytokine IL-6. Further, in an ex-vivo PBMC culture, application of the HDAC inhibitor valproic acid (VPA) induced significant increases in expression of AS1DHRS4, NRON and both HERV-W transcripts. However, we did not demonstrate a differential diagnostic effect in either the constitutive expression or response to HDAC inhibition for these selected ncRNAs in samples obtained from subjects with schizophrenia versus healthy controls. This study is funded by PHS grant (NIH) R01MH094358 (R.P.S.).

C20

PRESENILIN-DEPENDENT MODULATION OF AXODENDRITIC OUTGROWTH REQUIRES APP FUNCTION

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Presenilin 1 (PS1) is an essential component of the γ-secretase complex, the enzyme responsible for intramembraneous cleavage of amyloid precursor protein (APP) that generates β-amyloid peptides (Aβ) and APP intracellular domain (AICD). Mutations in PS1 lead to dominant inheritance of early onset familial Alzheimer's disease (FAD). Although there is a consensus that FAD-linked PS1 mutations affect toxic Aβ production, the importance of APP per se and other PS1-dependent substrates in the etiology of the disease has not been confirmed. Recently, we have observed that primary cortical neurons generated from PS1 knock-out ($PS1^{KO}$) and PS1 knock-in ($PS1^{KI}$) mice harboring FAD-linked PS1-M146V variant exhibit an increase of axodendritic outgrowth. These outcomes parallel a large and moderate increases of APP-CTF and DCC-CTF in brain lysates prepared from either $PS1^{KO}$ or $PS1^{KI}$ mice, respectively. Accordingly, these results are in support of a partial lost of function of γ-secretase activity in PS1 mutant. Strikingly, lack of APP expression in cortical neurons expressing PS1-M146V variant led to a decrease in both axonal and dendritic outgrowth; an effect that was not seen in neurons lacking DCC expression. These results indicate that APP is required for PS1-dependent change in neurite outgrowth associated with PS1 mutation. Treatment with γ-secretase inhibitor does not induce additional morphological change in $APP^{KO}PS1^{KI}$ supporting again the importance of APP in PS1-induced neurite outgrowth. Moreover, we observed that accumulation of APP-CTF through concomitant overexpression of APP full-length and γ-secretase inhibition or overexpression of membrane-tethered APP intracellular domain (mAICD) rescue axodendritic outgrowth in $PS1^{KI}$ neurons lacking APP expression. Taken together, our findings provide the first demonstration that a pathological loss of PS1 function lead to a gain of APP function. Our results also identify APP-CTF accumulation as a key player in axodendritic outgrowth. Because accumulation of APP-CTF at the membrane is an invariable outcome of therapeutic inhibition of γ-secretase aimed at reducing cerebral amyloid burden, our findings could have important implications in Alzheimer's disease treatment.

C21

REPEATED SOCIAL DEFEAT STRESS AFFECTS PERIPHERAL IMMUNE SYSTEM IN RATS: POSSIBLE LINK TO NEUROBEHAVIORAL ALTERATIONS IN CHRONIC STRESS DISORDERS.

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Psychological stress can induce depression and anxiety, and numerous studies implicate a role for the immune system in these effects. Repeated social defeat stress (RSDS) has been widely used as a model of chronic psychological stress in rodents, but its effects on the components of the peripheral immune system remain enigmatic. In the present study, adult male Sprague Dawley rats underwent RSDS by being exposed to an aggressor Long Evans rat for five consecutive days or control handling. On the third day after the last session, although the frequencies of CD4+ and CD8+ T-cells remain unchanged by RSDS as compared to the control group ($p > 0.05$), CD4+ T-cells show a significant reduction of the Th2-like cytokine profile, determined by the intracellular IL-4 staining ($p < 0.05$), without altering those of the CD8+ T-cells as analyzed by fluorescent activated cell sorting (FACS). Additionally, RSDS causes alteration of many different serum cytokines compared to the controls as measured by enzyme-linked immunosorbent assay (ELISA). Behavioral experiments show that RSDS induces increased anxiety-like behavior as evident by reduced central area exploration in the open-field (OF) test. Results from the elevated plus-maze (EPM) tests also support a similar trend of increased anxiety-like behavior after RSDS. In a separate group of experiments, peripheral immune-challenge with interleukin-1 also caused increased anxiety-like behaviors in OF and EPM tests. Taken together, this data suggest that RSDS tilts the balance of the Th1/Th2 cytokine profile within the CD4+ T-cells, changes the peripheral serum cytokine levels and also increases anxiety-like behavior in rats. The results have implications in understanding how chronic stress might alter T-cell cytokine signaling and modulate the peripheral immune system. Further exploration will test whether RSDS exerts effects on depressive and anxiety-like behavior in rodents by modulation of the immune system. This study is funded by grants from the National Institutes of Mental Health to JAR.

C22

TGF-B2 PERTURBATION OF THE KALLIKREIN-KININ SYSTEM IN HUMAN TRABECULAR MESHWORK CELLS

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In healthy eyes, intraocular pressure (IOP) is maintained through balanced production and outflow of aqueous humor (AH). Increased resistance to AH outflow is a major contributor of aberrant elevation of IOP. Transforming Growth Factor (TGF)-β2, a pro-fibrotic cytokine, is markedly elevated in AH of patients with POAG. The mechanism by which TGF-β2 promotes pathological elevation of IOP remains elusive, but may involve perturbation of the kallikrein-kinin system. Bradykinin (BK), a key mediator of the kinin system and a potent vasodilator, is produced locally within the eye. BK receptors subtypes have similarly been localized to ocular tissues. Activation of the BK B2-receptor lowers IOP in ocular hypertensive non-human primates. In contrast, porcine anterior segments chronically perfused with TGF-β2 exhibit a sustained increase in IOP. Here, we investigated the relationship between TGF-β2 and BK receptor expression and signaling in primary and transformed human trabecular meshwork (TM) cells. Quiescent TM cells expressed measurable levels of both B1 and B2 receptor mRNA as well as B2 protein. TM cells cultured in the presence of TGF-β2 exhibited a marked reduction in BK receptor expression in a time and dose dependent manner. siRNA-targeted disruption of the canonical (smad3) signaling pathway prevented TGF-β2 mediated attenuation of BK receptor mRNA and protein expression. In contrast, disrupting the non-canonical signaling pathway with exoenzyme C3 transferase had no effect on TGF-β2 mediated attenuation of BK receptor expression. TGF-β2 mediated decreases in BK mRNA content were not altered in the presence of actinomycin D, indicating that TGF-β2 does not affect BK mRNA stability. Together, these findings suggest that elevated content of TGF-β2 in the AH of POAG patients may elevate IOP, in part, by attenuating constitutive B2 receptor expression within the conventional outflow pathway. This work was supported by the Department of Veterans Affairs, the Illinois Society for the Prevention of Blindness, the Midwest Eye-Banks, Arthur J. Schmitt Foundation, and the Richard A. Peritt Charitable Foundation.

C23

THE PATHOLOGICAL ROLE OF REGULATORY AND γδ T LYMPHOCYTES IN INTRACTABLE PEDIATRIC EPILEPSY

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Rationale: Spontaneous seizures associated with epilepsy affect up to 1% of the world's population with more than half of the cases diagnosed during childhood. Disease prevalence and incidence are on the rise with one in 26 Americans being diagnosed with epilepsy over a lifetime. About one third of these patients develop drug-resistant epilepsy traditionally defined as therapeutic failure of at least 2 anticonvulsants, all of which only provide symptomatic seizure control without addressing the underlying pathophysiology. The pathogenesis and progression of epilepsy are poorly understood. In the past decade, increasing evidence suggests a link between brain inflammation and epileptogenesis. A number of commonly prescribed anticonvulsants have anti-inflammatory effects. Overall there are a lack of detailed human studies substantiating the contribution of blood-borne leukocytes in epilepsy development and progression to support the use of anti-inflammatory therapies.

Methods: To gain a better understanding of the immunopathogenesis of progression of epilepsy in an attempt

to develop more effective anti-epilepsy treatments that target the root cause of the disease, we performed detailed flow cytometric characterization of populations of brain-infiltrating as well as brain-resident immune cells on fresh surgically resected brain tissues. Patiens were children diagnosed with two leading causes of intractable epilepsies - focal cortical dysplasia (FCD2 ~50%) caused by malformations of cortical development and encephalomalacia (EM ~20%) due to brain injury.
Results: We demonstrate significant infiltration of the brain parenchyma by activated memory $CD4^+$ helper and $CD8^+$ cytotoxic T lymphocytes as well as blood-borne inflammatory monocytes. Moreover, we demonstrate for the first time that the γδ T lymphocytes are concentrated in the epileptogenic zone and their numbers positively correlate with seizure severity, whereas the numbers of brain-infiltrating regulatory T cells (Treg), that are specialized in dampening active immune responses, are inversely correlated with disease severity.
Conclusions: Our findings for the first time identify an important pathologic role for blood-derived leukocytes in epileptogenesis and provide the basis for the development of novel disease-modifying treatments for epilepsy, beyondcurrent symptomatic control of seizures,that target brain inflammation and restrict brain-infiltration of peripheral immune cells while avoiding the significant side effects of corticosteroids.
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C24

THE POTENTIAL THERAPEUTIC ROLE OF CONNEXIN MIMETIC PEPTIDE-43 IN TRAUMATIC BRAIN INJURY (TBI)

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Traumatic brain injury (TBI) is a serious public health concern accounting for a substantial sum of deaths and long-lasting neural deficits. Following TBI, a complex array of biochemical and neuroinflammatory cascades unfold, which can spread to distant areas of the brain relative to the focal point of the injury. The mechanisms of this spread of signalling molecules remains unclear. One hypothesis is that gap junctions aid in the quick dispersal. To determine the potential role of gap junctions in the spread of neuroinflammation and recovery post-TBI, A mini-osmotic pump situated at the brain surface was used to deliver either artificial cerebral spinal fluid (aCSF, n=8) or 5, 10, or 15 µmol/kg brain weight Cx43 mimetic peptide (CMP, n=9 each) in aCSF over a 24 hr period following injury. The pump remained in place until the rodent was killed 7 days post injury. Rats were analysed using behaviour testing and histological analysis. Significant sensorimotor deficits were observed between baseline and post-TBI time points; however, no significant difference was observed between treatment groups. An analysis of contusion size demonstrated no significant sparing of cells in treated animals, regardless of dose. The inflammatory response was investigated by measuring microglial activation (Iba-1) in areas medial and ventral to the contusion compared with comparable uninjured areas in the contralateral hemisphere. As anticipated, a significant increase in microglial activation was observed; however, this increase was not affected by treatment. A non-significant trend showed that groups receiving CMP treatment had worse outcomes in both behavioural and cellular analyses. Contrary to studies showing CMP benefits following spinal cord injury (SCI), this study did not demonstrate a potential therapeutic role for CMPs in TBI. This could potentially point to a different role for Gap junctions in TBI than in SCI, to different roles for the neuroinflammatory responses post injury, or may reflect issues to do with direct delivery of CMP to the site of injury. Future studies investigating i.p. delivery would be warranted.
This study is funded by a research grant awarded by the DePaul University Research Council.

C25

THERAPEUTIC CORRECTION OF APOER2 SPLICING IN ALZHEIMER'S DISEASE MICE USING ANTISENSE OLIGONUCLEOTIDES

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Apolipoprotein E receptor 2 (ApoER2) is an apolipoprotein E receptor involved in long-term potentiation, learning, and memory. Given its role in cognition and its association with the Alzheimer's disease (AD) risk gene, apoE, ApoER2 has been proposed to be involved in AD, though a role for the receptor in the disease is not clear. ApoER2 signaling requires amino acids encoded by alternatively spliced exon 19. Here, we report that the balance of ApoER2 exon 19 splicing is deregulated in postmortem brain tissue from AD patients and in a transgenic mouse model of AD. To test the role of deregulated ApoER2 splicing in AD, we designed an antisense oligonucleotide (ASO) that increases exon 19 splicing. Treatment of AD mice with a single dose of ASO corrected ApoER2 splicing for up to 6 months and improved synaptic function and learning and memory. These results reveal an association between ApoER2 isoform expression and AD, and provide preclinical evidence for the utility of ASOs as a therapeutic approach to mitigate Alzheimer's disease symptoms by improving ApoER2 exon 19 splicing. Future directions include assessment of other AD-related genes for targeting potential using ASOs.

C26

OXYTOCIN IN THE BNST REDUCES ACOUSTIC STARTLE RESPONSE – POSSIBLE ROLE OF PKCδ NEURONS

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Oxytocin (OT) is a hypothalamic neuropeptide that reduces stress response and has anxiolytic properties. While the neural circuitry underlying these effects remains largely unknown, the bed nucleus of stria terminalis (BNST) is a likely key component, because BNST expresses high levels of OT receptors and receives OT projections from the hypothalamic paraventricular nucleus (PVN).

To investigate the effects of OT in the BNST on anxiety-related behavior, we used an acoustic startle paradigm. Male Sprague-Dawley rats were tested for a baseline acoustic startle response, where they were exposed to 30 startle eliciting noise bursts. Based on their average acoustic startle response, animals were assigned into two treatment groups. On the following day, rats were tested for a baseline acoustic startle response, 10 min after bilateral infusion of either vehicle (0.5 µl) or OT (100 ng in 0.5 µl) into the BNST. Our results showed that the baseline acoustic startle response was significantly lower in OT-treated animals (294.60 ± 54.09) compared to the vehicle-treated animals (667.30 ± 119.61; $P < 0.05$ Bonferroni's post hoc test).

However, mechanisms underlying the anxiolytic properties of OT in the BNST are unknown. BNST comprises of GABA-ergic neurons that co-express various neuropeptides, including stress hormone, corticotropin-releasing factor (CRF). Therefore, we next employed an immunofluorescent approach combined with confocal microscopy using a marker for neuronal activation (c-Fos) to test whether OT interacts with different types of the BNST neurons. We infused OT into the BNST and analyzed brain sections for co-expression of c-Fos with neurons expressing Striatal Enriched Protein Tyrosine Phosphatase (STEP; a marker of CRF neurons), or Protein Kinase C δ (PKCδ; neuronal population distinct from CRF neurons). Double-immunofluorescence results demonstrated that c-Fos was expressed in a sub-population of the PKCδ-positive neurons in the oval nucleus of the BNST, but not STEP-positive neurons following OT infusion.

Our results show that OT in the BNST reduces acoustic startle response and this anxiolytic effect might be mediated by PKCδ-positive neurons in the oval nucleus.

C27

MILD SENSORINEURAL HEARING LOSS TRIGGERS AUDIOGENIC SEIZURE SUSCEPTIBILITY IN ANTISENSE OLIGONUCLEOTIDE TREATED USH1C MICE

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Type 1C Usher syndrome (Ush1c) is a genetic disorder characterized by deafness, vestibular defect and blindness. We have previously shown that an antisense oligonucleotide (ASO) that corrects the splicing defect associated with an Usher mutation in the Ush1C gene encoding harmonin can effectively improve vestibular and hearing deficits in a mouse model of the disease (Lentz, Jodelka et al. 2013). Here, we reported that ASO-treated Usher mice are susceptible to audiogenic seizures. This vulnerability to seizures can be mitigated by higher doses of ASO or by earlier dosing. These optimized treatment parameters also improve hearing associated with elevated functioning of the inner and outer hair cells of the cochlea, suggesting that suboptimal rescue of hearing could be the origin of the seizure susceptibility. Audiogenic seizure severity and susceptibility were lessened by inhibitors of specific metabotropic glutamate receptors, implicating aberrant calcium-signaling as a mediator of the aberrant response to noise associated with sub-optimal hearing rescue early in development.

C28

LOCALLY ADMINISTERED LOVASTATIN-ENCAPSULATING NANOPARTICLES PROTECT AGAINST EXPERIMENTAL AUTOIMMUNE NEURITIS

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Inflammatory peripheral neuropathies constitute one of the largest and least understood spectrums of neurologic disorders. Inclusive among these disorders is acute inflammatory demyelinating polyradiculopathy (AIDP), a debilitating autoimmune disease that affects the peripheral nervous system. Despite its overwhelming prevalence, treatment remains palliative and relies on the use of non-specific, immune-modulating therapies. While the mechanisms that govern disease onset and progression are not completely understood, trafficking of autoreactive leukocytes across the blood-nerve barrier and into peripheral nerves is an early pathological hallmark. Our group has reported that a short course of high-dose statin treatment therapeutically attenuates the clinical severity of an animal model of AIDP (experimental autoimmune neuritis, EAN) by restricting leukocyte migration. Despite these advancements, the clinical application of systemically-administered statins for the management of inflammatory disorders remains controversial. Nanotechnology-based drug delivery, however, represents a novel means by which to administer drugs that exhibit low bioavailability, high systemic toxicity, and poor water solubility, including statins. Copolymers of lactic and glycolic acid (PLGA) can be used to form injectable, biodegradable nanoparticles (NPs) that efficiently encapsulate hydrophobic compounds for controlled and sustained release. Here, we investigated the therapeutic potential of locally administered lovastatin-encapsulating NPs for the management of EAN. NPs were synthesized with an oil-in-water single emulsion and characterized with dynamic light scattering, a static dialysis assay, and high performance liquid chromatography. Compared to empty NPs, local administration of lovastatin-encapsulating NPs (25% w/w drug

loading) increased RhoB mRNA content *in vitro* in PNMEC cultures and *in vivo* when administered at the sciatic notch in healthy Lewis rats. A one-time, bilateral peri-sciatic injection of 25% w/w lovastatin-loaded NPs (20 mg) offered significant clinical and functional protection against the development of EAN. Preliminary data suggest that lovastatin-encapsulating NPs protect against EAN by locally disrupting leukocyte trafficking. The use of biodegradable lovastatin-encapsulating nanoparticles offers the advantage of a non-systemic, localized delivery strategy with which to better manage inflammatory peripheral nerve disorders.

C29

PARP-1 GOVERNS ALCOHOL-DEPENDENT BRAIN INFLAMMATORY SIGNALING AND NEURODEGENERATION

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Utilizing adult-age rat organotypic hippocampal-entorhinal cortical (HEC) slice cultures we explored the importance of poly [ADP-ribose] polymerase-1 (PARP-1) in alcohol's neuroinflammatory and neurodegenerative mechanisms. A key DNA repair enzyme that synthesizes ATP-derived poly ADP-ribose (PAR) polymers, PARP-1 nevertheless can promote neuronal death when overactivated (e.g., brain ischemia, seizures, trauma). We previously found that PARP-1 levels in HEC slices were increased by 4 days of neurotoxic alcohol binges (100 mM), with PARP inhibitor PJ-34 blocking the neurodamage. Here we show that three other PARP-1 inhibitors, olaparip, veliparib, and 4-aminobenzamide, were similarly neuroprotective. HEC slice results also reveal that phospholipase A2 (PLA2) isoforms—Ca^{+2}-dependent (cPLA2 IVA) and secreted (sPLA2 IIA)—known to be responsible for the neuroinflammatory arachidonic acid (AA; 20:4 ω6) cascade—have roles in binge alcohol's effects, since PLA2 inhibitors significantly reduce neurodegeneration. Results now demonstrating that PJ-34 and olaparib both abrogate alcohol's potentiation of cPLA2 and sPLA2 serve to connect the AA mobilization to PARP-1; however, PARP-1 inhibition does not reverse alcohol's suppression of Ca^{+2}-independent PLA2 (iPLA2 VIA), which might explain the observed loss of endogenous neuroprotective DHA (22:6 ω3). Additionally, indicating a dependence of a neuroinflammatory cytokine pathway on PARP-1 activity, alcohol's reported potentiation of the toll-like receptor-4 agonist, high mobility group box-1 (HMGB1), was inhibited by PJ-34. These pharmacological results link the key neuroinflammatory routes encompassing both phospholipids and cytokines with alcohol's neurotoxic activation of PARP-1. Supported by USPHS U01 AA018279 (MAC) and Loyola Res. Committee.

C30

EPIDERMAL GROWTH FACTOR PREVENTS AMYLOID-b INDUCED ANGIOGENESIS DEFICITS *IN VITRO* AND PREVENTS COGNITIVE DEFICITS *IN VIVO*

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Cerebrovascular (CV) dysfunction, previously an exclusionary criterion for the diagnosis of Alzheimer's disease (AD), is emerging as a critical component of AD pathogenesis. Indeed, AD risk factors and pathogenic pathways can exert detrimental effects on the CV in humans, AD-transgenic (Tg) mouse models, and *in vitro* systems. However, the topic of CV dysfunction in AD is controversial, with concerns centered on the extent of CV damage, the precise mechanisms responsible and the consequences for neuronal function. An important question is whether mediators of AD pathogenesis induce detrimental effects on CV length, which is dependent on vessel degeneration and/or changes in angiogenesis. Amyloid-b (Ab), particularly oligomeric Ab (oAb), is considered a major contributor to AD progression. Unfortunately, *in vitro* studies have not produced clear consensus on the role of oAb on vessel degeneration and angiogenesis, and work is surprisingly limited demonstrating the effects of oAb. Further, little is known regarding how angiogenic mediators, including key signaling molecules such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and fibroblast growth factor (FGF), interact with oAb to modulate brain endothelial cell (BEC) function. Thus, to address the discrepancies in the field, the current study aimed to definitively determine the effect of oAb on angiogenesis *in vitro*, utilizing single BEC cultures or triple cultures designed to mimic the microvascular unit (MVU: BECs, astrocytes and pericytes). Briefly, oAb (100nM-25nM), in multiple treatment paradigms, dose-dependently reduced angiogenesis and induced vessel disruption, as measured by vessel length and the number of meshes formed by BECs alone and by BECs within the MVU. Critically, EGF, not VEGF, rescued the oAb-induced deficits in angiogenesis across all paradigms. Building on the *in vitro* findings, we treated a novel AD-Tg mouse model expressing *APOE4,* the greatest genetic risk factor for AD, and overexpressing human Ab, with EGF (300mg/kg/week) from 6-8M, an age at which there is extensive Ab pathology, CV dysfunction and cognitive deficits. EGF treatment completely prevented the age-dependent decline in cognition as assessed by spontaneous alternation (Y-maze) and novel object recognition. Therefore, this proof of concept study demonstrates that targeting angiogenic pathways, particularly those involving EGF, is a potential therapeutic strategy for the treatment of AD and, more broadly, CV dysfunction. This study is also the first of its kind, demonstrating that treatment of a tractable AD-Tg mouse model with EGF rescues age and AD-induced cognitive deficits. This study is funded by lab startup funds awarded to Dr. Leon Tai.

C31

EFFECT OF METHAMPHETAMINE SELF-ADMINISTRATION BY HIV-1 TRANSGENIC RATS ON STRIATAL DOPAMINERGIC MARKERS

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The health profile of those infected with HIV has dramatically improved with modern day antiretroviral therapy. These drugs significantly reduce plasma viral load and prolong life. However, the brain remains a viral reservoir, and with the increased life span, HIV-associated neurological disorders (neuroAIDS) remain a relevant health concern. Basal ganglia dysfunction, particularly in the nigrostriatal dopaminergic system is observed in HIV/AIDS neuropathology. This has been associated with parkinsonian-like movement disorders. Methamphetamine (meth) abuse can also damage the nigrostriatal pathway. Data from the NIH suggests that 4.9% of people ages 12-25 years have used meth in their lifetime. Of these, many use meth recreationally without becoming dependent. There is a high incidence of recreational meth use in men who have sex with men (MSMs) including those that are HIV+. We are interested in determining if low dose use of meth is still sufficient to exaggerate dopaminergic neuropathology in HIV/AIDs. To study this comorbid condition, we implemented a rat model wherein young adult male HIV-1 transgenic (Tg) and non- transgenic (non-Tg) Fischer 344 rats self-administered meth (0.02-0.04mg/kg/0.05ml iv) 2hr/day for 21 days, at which time the average cumulative intake was only 4.5-5.2 mg/kg. Operant task controls were saline yoked. Brains were harvested 1 day following the last operant session. Brains were also taken from naïve Tg and non-Tg rats. Tyrosine hydroxylase (TH) was determined using immunohistochemistry and western blotting. Immunohistochemistry did not detect any changes in the substantia nigra or the striatum. In contrast, western blot assays revealed a reduction in striatal TH levels in Tg rats regardless of treatment. The present data indicates with the meth dose, self-administered by these rats, the stimulant does not exacerbate the effects of HIV-1 proteins on dopaminergic markers. However, an effect may be detected with longer withdrawal times, as we previously observed in meth self-administering Sprague Dawley rats (Kousik *et al*., *Euro J Neurosci* 40, 2014).

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C32

UTILIZING IPSC-DERIVED CORTICAL NEURONS HARBORING KNOWN EPILEPSY MUTATIONS TO ADVANCE GENE-SPECIFIC TREATMENTS

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Epilepsy is a neurological condition caused by disturbances in the electrical activity of the brain manifested via countless etiologies. It is estimated that 65 million individuals worldwide suffer from epilepsy with one-third of these individuals living with uncontrollable seizures because no known pharmacological treatment works for them. A portion of this population's disorder is the result of a single gene mutation within the sodium, potassium or inhibitory channels. Advances in personalized medicine offers hope not only for diagnosis but also treatment options for these individuals. Central to this vision is the induced pluripotent stem cell (iPSC) technology, which provides a platform to increase our understanding of how single-gene mutations result in disease states. This approach leverages human iPSC-derived cortical neurons, as a "disease-in-a-dish" model, to advance drug development and act as a springboard to discovering personalized medicines. Utilizing iPSC technology, we generated human cortical neurons carrying the SCN1A {knock-out}, KCNT1 {P924L}, or gamma 2{R43Q} single-gene mutations that result in Dravet syndrome, autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE) and Childhood Absence Epilepsy (CAE), respectively. The ability to engineer isogenic wild–type alleles into disease-associated alleles by genome editing human iPSC neurons provides unprecedented access to in vitro models of neurological disorders. Here we present anatomical data, via live cell imaging (neurite outgrowth), and functional data, via electrophysiology (multi-electrode array) or calcium flux, comparing human iPSC-derived wild-type vs. genome edited (SCN1A, KCNT1 or R43Q) cortical neurons. These data display hyper-active phenotypes that correlate to the epileptic genotypes and also show examples of selective pharmacology that can reverse these aberrant phenotypes. Collectively, our results illustrate how human iPSC-derived neurons can be leveraged in the personal medicine space.

C33

PARKINSON'S DISEASE RELATED LRRK2- MEDIATED CELLULAR AND SYNAPTIC ALTERATIONS IN THE STRIATUM

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Mutations in *LRRK2* represent a strong genetic risk for both hereditary and sporadic forms of Parkinson's disease (PD). However, there are still several fundamental aspects of LRRK2 function that remain unresolved at this time. 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. The function of LRRK2 in the striatum has remained relatively under-investigated; however, we recently showed that LRRK2 directs PKA signaling in SPNs. The pathogenic $LRRK2^{R1441C}$ mutation impairs the binding of PKA with LRRK2, leading to increased levels of PKA in the dendritic spines that, in turn, result in aberrant synaptic PKA signaling. The components of PKA enzyme in neurons are confined to sub-cellular compartments, ensuring for spatial and temporal regulations of PKA signaling which lead to specificity in fundamental striatal functions. Our data suggest that LRRK2 is strategically located in the dendritic shaft to organize signaling events in a spatiotemporal way. Therefore, we propose that increased synaptic PKA activity of $LRRK2^{R1441C}$ in SPNs stems from altered subcellular

compartmentalization of PKA. Furthermore, since PKA is a critical effector of dopamine receptors, our central hypothesis is that LRRK2-mediated deregulation of PKA activity results in aberrant dopaminergic and corticostriatal signaling in SPNs. In support of this idea, we provide evidence that *LRRK2*^{R1441C} mutation impacts dopaminergic signaling in SPNs. Specifically, SPNs harboring *LRRK2*^{R1441C} mutation show an abnormal elevation in PKA activity in response to dopamine receptor, Drd1, activation. In addition, *LRRK2*^{R1441C} SPNs show increased sensitivity to dopamine depletion as well as altered behavioral responses, suggesting a novel role of LRRK2 in dopaminergic signaling which in turn may direct the physiology of SPNs as well as the striatal related motor functions. Overall, our findings emphasize that LRRK2 contributes to glutamatergic synaptic functions by directing postsynaptic signaling events in the SPNs.

C34

HDAC6 INHIBITION INDUCED A-TUBULIN ACETYLATION TRANSLOCATES GAS FROM LIPID-RAFTS: A NOVEL MECHANISM FOR ANTIDEPRESSANT ACTION

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Histone deacetylase-6 (HDAC-6) enzymes involved in deacetylation of α-tubulin have been shown to be upregulated during neuropsychiatric conditions. HDAC6 knockout mice mimicked traditional antidepressant treatments. Nonetheless, a possible role for HDAC6 inhibitors in treatment of depression remains elusive. Previously we have shown that the treatment with monoamine based antidepressant drugs results in activation of G-protein subunit, Gαs, by facilitating movement out of membrane microdomains, (lipid-rafts), resulting in sustained cAMP production. Studies have also demonstrated interplay between tubulin and Gαs in lipid-rafts. Once out of lipid-raft domains, Gαs, couples with adenylyl cyclase-6 (AC-6). Although Gαs interacts directly with tubulin to modify microtubule dynamics, tubulin also acts as an anchor for Gαs in lipid rafts. Based on HDAC-6 roles in modifying α-tubulin acetylation and our data showing Gαs interactions with tubulin in lipid-raft domains, we hypothesize that acetylation of α-tubulin disrupts tubulin-Gαs anchoring, rendering Gαs free to activate AC-6 in non-raft domains. To test this, C6 glial cells were treated with HDAC-6 inhibitor, Tubastatin-A. Acetylation status of α-tubulin and localization of Gαs subunit in/out of lipid-raft membrane domains was studied. Chronic treatment with Tubastatin-A not only induced increased acetylation of a α-tubulin but also moved Gαs out of lipid-rafts, without changing total Gαs. Fluorescence Recovery After Photobleaching (FRAP) on C6 cells stably expressing Gαs-GFP, was conducted and cells pretreated with Tubastatin-A showed an “antidepressant signature”. Finally, brains from mice undergoing repeated swim stress were examined and these showed decreased acetylation of α-tubulin and translocation of Gαs subunits out of lipid-rafts relative to controls. These findings suggest HDAC6 inhibition resembles chronic antidepressant treatment. Therefore, compounds that decrease tubulin-Gαs interactions by increasing acetylation of a α-tubulin may show promise for antidepressant action.

C35

THREE EMERGING STORIES: ALPHA-SYNUCLEIN FAMILIAL MUTANT ANALYSIS IN YEAST MODELS M. MARSHALL, E. ONG, M. TEMBO, V. GEORGIEVA, N. KUKULKA, C. ALVARADO, M. MUNOZ, S. K. DEBBURMAN*Neuroscience Program and Biology Department, Lake Forest College, Lake Forest, IL 60045*

Parkinson’s disease (PD) is associated with the aggregation and misfolding of the protein alpha-synuclein in midbrain dopaminergic neurons. These dying neurons exhibit enhance nitrative stress, which may contribute to PD, while sumoylation of alpha-synuclein is hypothesized to be protective. The gene encoding for alpha-synuclein also is linked to six known point mutations that cause familial forms of PD. Three of them (A30P, E46K, and A53T) are now well studied and characterized in various models that indicate that each mutant’s distinct effect on cellular toxicity. When our lab made combination mutants of A30P, E46K, and A53T and characterized them in budding and fission yeast models, A30P demonstrated surprising dominance over E46K and A53T mutants in both models, giving new insight on the importance of A30P in alpha-synuclein’s conformation. Recently, three more familial mutants have been discovered (H50Q, G51D, and A53E). We have characterized their properties in yeast and found H50Q and A53E mutants to be toxic, bind membranes and aggregate while G51D is cytoplasmically diffused and non-toxic. To test the hypothesis that the new mutants are equally dominant in their pathological contributions, we characterized them in combination of each other. We found that G51D dominated over H50Q and A53E, reminiscent of the surprising A30P effects. To test whether nitrative stress regulates alpha-synuclein toxicity, we studied all six familial mutants in yeast strains altered for increased *(cox5aΔ)* and decreased *(cox5bΔ)* nitration. We found that increased nitrative stress enhances toxicity in all mutants except G51D, while decreased protects against toxicity in all mutants. Finally, we are testing the hypothesis that sumoylation regulates alpha-synuclein toxicity, by evaluating the familial mutants in yeast strains with diminished (*smt3*+) or excessive (*ulp1*) sumoylation. Preliminary evidence suggests that reduced sumoylation results in enhanced toxicity for mutations and alters early localization of alpha-synuclein. When completed, these three studies will add novel insight into how alpha-synuclein causes PD and the cellular environment that regulates this pathogenicity.

THEME D. HISTORY AND TEACHING OF NEUROSCIENCE

D1

BUILDING NEUROSCIENCE AT LAKE FOREST COLLEGE: INTEGRATION OF CURRICULUM WITH PUBLIC EDUCATION, K-5 OUTREACH, AND PEER LEARNING

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Since Lake Forest College's neuroscience major began in 2009, it has become one of the highest enrolled majors. With an early emphasis on creating a cohesive student centered community of scholars, the curriculum evolved to closely integrate three co-curricular goals: a focus on public education, K-5 outreach, and a peer learning community. In 2009, students formed Synapse, the neuroscience outreach organization, and in 2011, chartered *Nu Rho Psi,* the National Honor Society in Neuroscience. To achieve the first goal, these groups organize several public education opportunities: an annual Brain Awareness Week (BAW), an annual community seminar series featuring Chicago's best neuroscientists, and scientific conferences each semester that feature capstone academic work from multiple courses. During the BAW each fall, which attracts an attendance of over 1000, students from multiple courses showcase exhibits, teach-ins, labs, and presentations throughout the week, nationally noted speakers highlight interdisciplinary connections with neuroscience, and the annual Robert B. Glassman Brain, Mind, & Behavior Symposium spotlights faculty, alumni, and student research in neuroscience. Each fall, students also raise significant funds for a rare pediatric neurological disease (PMD), and they participate in Chicago's Annual Jones PMD Walk 'n Roll. Student groups achieve the second goal by collaborating with First-Year neuroscience courses each semester to conduct an outreach with local elementary schools to engage "How our Amazing Brain Works," which serves as a non-traditional final exam for those courses. Over 300 elementary school children have benefitted from this effort since 2009. Finally, the Neuroscience Program achieves the third goal by instituting a semester-length program of student peer teachers and mentors in introductory-level neuroscience courses. Advanced students from upper-level courses serve as Peer Teachers and they work with first-year students to master neuroscience content and academic skill sets linked with writing and research, while Peer Mentors focus on broader first-year college survival skills, such as project planning, time management, group collaboration, linked with completion of multiple group projects successfully over the length of a semester. The Lake Forest College Neuroscience Program's student-centered co-curricular emphasis supports a vibrant student scholar academic culture that has helped attract over 150 students to this discipline in a relatively short time, and it may serve as a model for institutions striving to achieve similar goals.

THEME E. HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

E1

HCN1 CHANNEL EXPRESSION IN THE BLA AND ANXIETY-RELATED BEHAVIOR

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The activity of pyramidal neurons in the basolateral nucleus of the amygdala (BLA) is predictive and consistent with the expression of anxiolytic- and anxiogenic-like behaviors in rats. Intra-BLA injections of Neuropeptide Y (NPY) reduce BLA output and are anxiolytic, whereas intra-BLA injections of Corticotropin Releasing Factor (CRF) increase BLA output and are anxiogenic. Previous studies from our laboratories demonstrated that both NPY and CRF act at the neuronal level by mediating the inhibition or enhancement, respectively, of the hyperpolarization activated, depolarizing conductance, the H current, carried by HCN channels (Geisbrecht et al., 2010). These studies, together with anatomical studies, indicated that it is likely that these actions of NPY and CRF result from bidirectional modulation of pyramidal cell HCN1 subunits as their final common pathway. Furthermore, repeated intra-BLA injections of NPY produce prolonged (weeks to months) behavioral stress resilience, as they markedly increase the time treated rats spend interacting in the social interaction (SI) test (Sajdyk et al., 2008). We now have data suggesting HCN1 expression is decreased in the BLA in NPY-induced stress resilience. Therefore, we hypothesize that the expression level of HCN1 in the BLA is important in mediating stress-related behavior.

To test this, we used a lentivirus expressing shRNA targeting mRNA for HCN1 to selectively reduce the expression of HCN1 in the BLA of male rats and stress-related behavior was assessed. Animals received injections (2 µL per side; 109 TU/mL concentration of virus) directly into the BLA of lentivirus expressing either shHCN1 or a scrambled (non-coding) shHCN1 sequence, or vehicle (saline) alone. Four weeks later, immunohistochemistry revealed significant reductions in HCN1 protein levels within the infected region. Social interaction was studied in all groups of injected animals at several times following the injections. As in chronically NPY-treated animals, SI times were increased in animals that received shHCN1-injections when compared to the other two control groups. All cohorts of animals were also tested in the elevated plus maze (EPM) test. Interestingly, knockdown of BLA HCN1 expression did not have an effect on the performance of these rats on the EPM.

These data reinforce our hypothesis that the H current plays a critical role in regulating BLA output, which in turn has significant consequences for regulation of behavioral responses to stress and on the expression of anxiety-related behaviors. This study is funded by R01 MH090297 (JHU, WFC).

E2

MOLECULAR MECHANISM OF AN ANCIENT MECHANISM OF EPIGENETIC TRANSCRIPTIONAL MEMORY

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Previous expression of genes can lead to mitotically heritable changes in their subnuclear positioning, interchromosomal clustering and chromatin structure by a conserved mechanism called epigenetic transcriptional memory. In yeast and human cells, this phenomenon requires interaction with nuclear pore proteins and leads to the recruitment of RNA polymerase II preinitiation complex (RNAPII PIC), leading to faster future reactivation. As a model for this conserved phenomenon, we have defined the molecular and cellular mechanism of *INO1* transcriptional memory. Active *INO1* interacts with the nuclear pore complex (NPC) and localizes at the nuclear periphery. Upon repression, *INO1* remains associated with the NPC at the periphery. Whereas targeting of active *INO1* requires two *cis*-acting DNA elements and the Put3 and Cbf1 transcription factors, retention at the nuclear periphery requires a distinct DNA element, the Memory Recruitment Sequence (MRS). We have identified a transcriptional repressor that 1) binds to the MRS specifically under memory conditions, 2) is necessary and sufficient for peripheral localization and 3) promotes recruitment of a remodeled form of the H3K4 methyltransferase COMPASS and the Cdk8+ form of Mediator. Remodeling of COMPASS removes the Cps40 module, blocking H3K4 trimethylation, but allowing H3K4 dimethylation. H3K4me2 recruits the SET3 complex, which plays an essential role in memory. Cdk8+ Mediator recruits RNAPII PIC but prevents association of the kinases that phosphorylate the CTD of RNAPII, blocking initiation. This mechanism is utilized by a number of yeast genes that are regulated by different stimuli as well as hundreds of human genes that are induced by interferon gamma. This suggests that memory employs control of transcriptional initiation, regulated by epigenetic inputs.

THEME F. NEURONAL EXCITABILITY, SYNAPSES AND GLIA

F1

ATP-INDUCED CHANGES IN INTRACELLULAR Ca^{2+} LEVELS AND EXTRACELLULAR H^+ CONCENTRATION FROM RETINAL MÜLLER (GLIAL) CELLS

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Adenosine 5'-triphosphate is believed to be co-released with neurotransmitters and can act as a signaling molecule via the activation of ATP-sensitive ionotropic and metabotropic receptors. In the present work, we examine changes in extracellular H^+ concentrations and intracellular Ca^{2+} rises triggered by ATP application onto isolated Müller cells and slices prepared from retinae of tiger salamanders. Recordings of H^+ concentration were obtained via the self-referencing technique and Ca^{2+} levels were imaged with the ratiometric Ca^{2+} dye Oregon Green. All recordings were performed with 1mM HEPES as the extracellular pH buffer. ATP causes a robust extracellular acidification from isolated Muller cells. This acidification is reduced in the presence of ATP receptor blockers suramin and PPADS, as well as in the presence of the anion transport blocker DIDS. ATP application also causes intracellular calcium rises in Müller cells. Both the calcium rise and the extracellular acidification are reduced when the reuptake of calcium into the ER is inhibited with thapsigargin and when the PLC-IP3 signaling is disrupted with U-73122 and 2-APB. Bath-applied ATP causes a robust extracellular acidification from retinal slices when the H^+-selective microelectrode is positioned in close proximity to the outer plexiform layer. Suramin and PPADS reduce the acidification measured from slices. ATP-induced extracellular acidification is also observed from Müller cells of other species, including human, rat and lamprey. This work emphasizes the role of ATP as an intercellular signaling agent in the retina, which can induce intracellular calcium rises in Müller glia, which in turn lead to robust changes in extracellular acidity. The fact that the ATP induced responses occur in Müller cells of a variety of species suggests a highly evolutionarily conserved response that is likely to play an important role in regulating responses of retinal neurons.

F2

CHARACTERIZATION OF A NEURON-ASTROCYTE CELL LINE CO-CULTURE SYSTEM FOR INVESTIGATING NEURITE GROWTH

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Central nervous system (CNS) injuries, including stroke and traumatic brain injury, are leading causes of disability and death worldwide in part due to the limited axon regeneration capacity of the CNS. Improved *in vitro* models, particularly those that are fast growing and readily modifiable by genetic and pharmacologic manipulations, are critical to further our understanding of the mechanisms inhibiting axon regeneration following CNS injury, and to develop high throughput screens for novel therapeutics. To address this need, our studies characterize co-cultures of N2a neuroblastoma cells, which can differentiate and extend neurites, with two complementary CNS astrocyte cell lines: A7 cells, which are axon growth permissive, and Neu7 cells, which are axon growth inhibitory. Previous studies suggests that axon growth differences between A7 and Neu7 cells are due to the density and chondroitin sulfate proteoglycan expression in their extracellular matrices. Consistent with these studies, we hypothesized that differentiated N2a neuroblastoma cells would show greater neurite growth in A7 co-cultures than Neu7 co-cultures. Our results suggest that (i) serum starvation induces N2a differentiation in a dose- and time-dependent manner, and (ii) differentiated N2a cells extend more and longer neurites when co-cultured with A7 cells than with Neu7 cells. Continued characterization of N2a-A7 and N2a-Neu7 co-cultures may provide efficient and complementary models for rapid identification of mechanisms underlying axon regeneration following CNS injury.

F3

CHARACTERIZATION OF REACTIVE ASTROCYTOSIS IN AXON GROWTH PERMISSIVE AND INHIBITORY ASTROCYTE CELL LINES

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In response to central nervous system (CNS) injury as a result of stroke, traumatic brain injury, viral encephalitis, multiple sclerosis, and other diseases, astrocytes undergo a series of progressive cellular and molecular changes referred to as reactive astrocytosis. These changes range from mild to severe hypertrophy, proliferation, and upregulation of glial fibrillary acid protein (GFAP) expression, with the most extreme cases resulting in formation of a persistent glial scar. The role of reactive astrocytosis in CNS injury remains debatable, with previous research suggesting that reactive astrocytosis may have beneficial effects, such as sequestering inflammation, and detrimental effects, such as inhibiting axon regeneration. To further our understanding of reactive astrocytosis, our studies characterize this process in two complementary CNS astrocyte cell lines: A7 cells, which are axon growth permissive, and Neu7 cells, which are axon growth inhibitory. Consistent with the role of reactive astrocytosis in inhibiting axon regeneration, we hypothesized that inhibitory Neu7 cells would be reactive under standard culture conditions and less susceptible to astrocytosis-inducing stimuli. Conversely, we hypothesized that permissive A7 cells would be more susceptible to astrocytosis-inducing stimuli. Our results suggest that exposure to a variety of stimuli, including potassium chloride, trypsin, and acidified media, produces different time- and dose-dependent increases in hypertrophy, proliferation, and GFAP expression in A7 and Neu7 cells. Continued characterization of reactive astrocytosis in A7 and Neu7 cells may provide uniquely complementary models for defining the role of astrocytes in CNS injury, including elucidation of novel therapeutic targets for diseases in which reactive astrocytosis is implicated.

F4

MEASUREMENT OF H+ FLUXES FROM CULTURED RAT CORTICAL ASTROCYTES USING SELF-REFERENCING H+-SELECTIVE MICROELECTRODES

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Glial cells are believed to play a key role in regulating extracellular levels of glutamate in the nervous system, transporting extracellular glutamate into the cytoplasm of the glial cells. This transport process is often associated with changes in extracellular levels of H+, which can by itself have a potent modulatory effect on neuronal excitability and synaptic transmitter release. In the present study, we have used self-referencing H+-selective microelectrodes to examine standing levels of extracellular H+ from quiescent cortical astrocytes cultured from rats, and have also examined changes in the level of extracellular H+ that occur upon addition of the neurotransmitter glutamate. Cultured astrocytes in a bicarbonate-based saline solution exhibit a standing acidic flux. When the normal 24 mM bicarbonate in the solution is replaced with 1 mM HEPES, a standing flux remains but is smaller in magnitude. The standing flux observed in the 1 mM HEPES condition remained when all of the extracellular sodium was replaced with choline. Application of glutamate induced a transient extracellular alkalinization, consistent with its transport into the glial cells. These results are the first to show extracellular H+ levels adjacent to quiescent glial cells and suggest the possibility that changes in extracellular H+ by glial cells may play a role in modulation of activity within the nervous system. This study is funded by National Science Foundation Grants 0924372 and 0924383.

F5

METABOTROPIC GLUTAMATE RECEPTOR 2 CONTROLS ELECTROTONIC ISOLATION OF STARBURST AMACRINE CELLS AND RESPONSES OF DIRECTION-SELECTIVE GANGLION CELLS

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Spatial compartmentalization of electrical signaling is crucial for the function of many neural circuits. In the mammalian retina, electrotonic isolation is thought to contribute to direction selectivity in the dendritic processes of starburst amacrine cells (SACs). These processes are strongly depolarized during visual stimuli that move centrifugally (from soma to distal tip) but not during stimuli moving centripetally. Precise GABAergic connectivity between individual SAC processes and direction-selective ganglion cells (DSGCs) enables DSGCs to fire action potentials during motion in their preferred direction, but not during motion in their anti-preferred (null) direction. Importantly, direction selectivity of SAC processes requires that depolarization in one process not propagate to other processes of the same SAC. Previous studies have theorized that this electrotonic isolation may arise from dendritic properties intrinsic to SACs such as ion channel distribution or dendritic diameter. Here, we identify a regulatory mechanism mediated by metabotropic glutamate receptor 2 (mGluR2) signaling that controls electronic isolation of SAC dendritic branches. We use a genetically encoded calcium sensor and patch-clamp electrophysiology to show that mGluR2 blockade increases propagation of electrical signals across SAC dendritic arbors, causing aberrant inhibition of DSGCs during motion in their preferred direction. Our results demonstrate that electrotonic isolation in this functionally-defined circuit plays a precise role in neural computation and may be dynamic and context-dependent. This study is funded by the National Eye Institute (R01EY024016 to WW and F30EY025958 to DK) and by a Roche/ARCS Fellowship award to DK.

F6

PERSISTENT TRANSCRIPTIONAL CORRELATES OF LONG-TERM SENSITIZATION TRAINING IN APLYISA CALIFORNICA.

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Sensitization is a ubiquitous form of non-associative memory. The long-term expression of sensitization memory depends in

part on persistent changes in gene expression. We used microarray and qPCR to enumerate the persistent transcriptional changes accompanying long-term sensitization of the tail-elicited siphon-withdrawal reflex in the marine mollusc *Aplysia californica*. Animals received unilateral long-term sensitization training. After behavioral confirmation of long-term memory 1 day after training, pleural ganglia were harvested, and gene expression was compared from the trained to untrained ganglia. Microarray analysis with 12 biological replicates shows strong regulation of over 500 transcripts. Using qPCR in an additional 10 samples we have validated over 30 of these transcripts and found a very strong correspondence between microarray and qPCR results. Overall, this work provides one of the most comprehensive analyses of the transcriptional correlates of long term memory. Analysis of the set of regulated transcripts shows that memory maintenance is accompanied by a complex array of gene expression changes which involves activation of key transcription factors, changes in the machinery of translation, extensive regulation of synaptic communication, and even alterations in transcripts related to neuronal excitability. This work helps shed light on the transcriptional networks that help sustain the expression of a long-term memory.

F7

TREATMENT WITH 670NM PHOTOBIOMODULATION REDUCES NFκB ACTIVITY IN A MODEL OF DIABETIC RETINOPATHY

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Purpose: Diabetic retinopathy (DR) is the most common complication of diabetes mellitus and a leading cause of blindness. The pathophysiology of diabetic retinopathy is complicated, involving inflammation, oxidative stress, elevated vascular endothelial growth factor (VEGF) and breakdown of the retinal vasculature. Current treatments for diabetic retinopathy antagonize the actions of VEGF and reduce vascular growth. These treatments are invasive and frequently ineffective. Irradiation with far-red to NIR light (photobiomodulation, [PBM]) has been shown to reduce oxidative stress and inflammation *in vitro* and *in vivo* and to attenuate the progression of DR. The transcription factor NF-κB is activated in response to inflammation and oxidative stress leading to the production of VEGF and ICAM. The purpose of the present study to test the hypothesis that 670 nm PBM will inhibit the activity of NF-κB and reduce the production of VEGF and ICAM.

Methods: Studies were conducted in a Müller glial cell culture model of DR. These cells have been shown to play a primary role in the progression of DR, due to a shift in their physiology from an anti-inflammatory to a pro-inflammatory state. Müller glial cells were grown in either low (5mM) or high (25mM) glucose to simulate normal or hyperglycemic conditions, respectively. Prior to treatment, cells being measured for NFκB activity were transfected with a luciferase and renilla plasmid. All cells receiving PBM therapy were treated with 670nm LED (180 sec at 25 mW/cm^2; 4.5 J/cm^2) for three days. Sham treated cells were handled in a similar manner for the same duration of time.

Results: NFκB activity was increased by 12% in Muller glial cells incubated in high glucose conditions compared to normal glucose conditions. High-glucose cultured Muller glial cells treated with 670 nm PBM exhibited a 50% decrease in activity.

Conclusion: These data support our hypothesis and suggest that activation of NFκB is a key feature of the Muller glial cell response to hyperglycemia and that 670 nm PBM attenuates this activation.

F8

XCT-MEDIATED AMPA RECEPTOR LOSS IN HIPPOCAMPAL CA3-CA1 REQUIRES MGLUR5

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Synapses in the mammalian brain are exposed to two biologically active pools of glutamate: 1) transient synaptic glutamate resulting from neuronal vesicular release and 2) ambient nonsynaptic glutamate released from both neurons and glia through a variety of molecular mechanisms. While the role of synaptic glutamate has been extensively studied, much of the function of nonsynaptic glutamate remains unknown. Several lines of evidence have shown that changes in nonsynaptic glutamate are linked to developmental, physiological, and behavioral defects in mammals. Approximately 60% of extracellular glutamate in the mouse hippocampus is released by the xCT transporter, a cystine-glutamate antiporter which is highly expressed and active on astrocytes surrounding CA1 pyramidal neurons. Mice lacking a functional xCT transporter (xCT$^{-/-}$) show both enhanced synaptic strength and increased AMPA receptor abundance at hippocampal CA3-CA1 synapses. Additionally, mutant xCT$^{-/-}$ miniature excitatory post-synaptic potentials (mEPSCs) are phenocopied by incubating control slices in glutamate-free solution. Here we show the effect of incubation in Group I metabotropic glutamate receptor (mGluR) antagonists on both control and xCT$^{-/-}$ slices and propose a possible mechanism by which extracellular glutamate acts through mGluR5 to modulate synaptic strength at hippocampal CA3-CA1 synapses.

F9

SIMULTANEOUS RECORDINGS FROM THE CALYX AND ENVELOPED HAIR CELL IN COMPLEX CALYCES OF THE POSTERIOR SEMICIRCULAR CANAL

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In vestibular epithelia, multiple hair cells (HCs) often converge onto a single primary afferent. In primitive vertebrates the HCs synapse onto simple bouton endings. With the advent of amniotes, the afferent complexity increases with the addition of expanded calyceal endings that envelop one or more HCs. Over the course of evolution there is an increased representation of these endings. However, the functional implications of the calyx remain obscure. Our experiments were designed to examine the synaptic and ionic basis of fast excitatory events and a slower modulation of inward, excitatory current in the calyx following depolarization of the hair cell. Simultaneous patch–electrode recordings from type I

HCs and their enveloping calyx were made with KF/KCl, dye–filled pipettes, in the epithelia of the posterior semicircular canal of the turtle, *Trachemys scripta elegans.* Both pre– and postsynaptic elements were examined in all pairwise combinations of current and voltage clamp, under conditions of ionic substitution, pharmacological block, and mechanical stimulation of the hair cell bundle. Steady–state and instantaneous I–V curves were constructed to analyze changes in conductance and driving force on the presynaptic HC, and the postsynaptic afferent terminal. Depolarization of HCs from a holding potential of –100 mV demonstrated a large, low voltage activated outward current from –90 mV, that was half–activated at –60 mV. Following depolarization, or mechanical stimulation of the HC ciliary bundle, large, rapid events were elicited in the calyx, that were consistent with conventional excitatory quantal transmission. With HC depolarization there was also a more graded response in the calyx. Both the rapid events and some of the graded response could be blocked by an AMPA receptor blocker CNQX. Calyceal endings held at –100 mV displayed a large inward current, and HC depolarization produced an additional inward current. Much of both the steady level and the HC evoked inward current could be blocked by ZD7288, suggesting that HCN channels in the calyx are also sensitive to the relative concentrations of monovalent ions. Measurement of the instantaneous I–V curve of the HC following prolonged depolarization demonstrated a shift in the reversal potential consistent with an elevation of $[K^+]$ at the basolateral pole from a nominal extracellular 4 mM to at least 16 mM. We conclude that at a minimum HC transmission to the calyx includes a delicate balance between AMPA mediated events, and depolarizing currents due to changes in monovalent ion concentration.

F10

CHANGES IN HILAR NETWORK PHYSIOLOGY AND CONNECTIVITY IN A MODEL OF TEMPORAL LOBE EPILEPSY

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Temporal lobe epilepsy (TLE) is typified by hippocampal hyperexcitability arising from altered activity and connectivity of hilar neurons. In animal models of TLE and human patients, network reorganization in the hilus leads to profound mossy cell death as well as mossy fiber sprouting and increased kainate receptor (KAR) expression in the dentate gyrus, which contribute to hyperexcitability. The "dormant basket cell" and "irritable mossy cell" hypotheses state that mossy cell death disinhibits the dentate gyrus or that remaining mossy cells after seizure-induced cell death become hyperexcitable. Hence changes in mossy cell excitability and in hilar synaptic connectivity are thought to contribute to pathological hilar hyperexcitability.We are examining physiological changes in the hilar circuit in the $Scn2a^{Q54}$ mouse, which reproduces the network-level reorganization and cell death seen in TLE. We hypothesize that, in this model, mossy cells will be hyperexcitable and that kainate receptor function will be altered at hilar synapses. To address these hypotheses, we are making loose-seal and whole-cell patch clamp recordings of mossy cells and granule neurons in acute slices from $Scn2a^{Q54}$ mice and wildtype (WT) littermates. Recordings are made after the onset of spontaneous seizures. We will examine the intrinsic physiology of mossy cells and kainate receptor function at mossy fiber – mossy cell and mossy cell – granule cell synapses. Our initial results demonstrate that mossy cell excitability is not increased in $Scn2a^{Q54}$ mice: spontaneous and maximum firing rate were not different between $Scn2a^{Q54}$ mice and WT littermates (spontaneous firing rate: 2.2 ± 0.9 Hz in $Scn2a^{Q54}$ and 1.8 ± 0.5 Hz in WT; maximum firing rate: 71.29 ± 11.89 Hz in $Scn2a^{Q54}$ and 44.43 ± 4.59 Hz in WT). In fact, mossy cell input resistance in $Scn2a^{Q54}$ mice was lower than in WT littermates, a change often associated with a decrease in excitability (182.04 ± 23.20 MW in $Scn2a^{Q54}$ and 300.64 ± 12.92 MW in WT; $P<0.005$). Hence our initial results suggest that mossy cells are not hyperexcitable in $Scn2a^{Q54}$ mice, which is inconsistent with the irritable mossy cell hypothesis. In addition, mossy cell number was not noticeably decreased in $Scn2a^{Q54}$ mice at this stage of disease progression. Ongoing experiments examine changes in synaptic strength and kainate receptor function at hilar synapses as well as correlate physiological changes with seizure frequency. This study will shed light on the cellular and synaptic alterations which underlie hilar network hyperexcitability, providing a framework by which future studies can target these pathological changes to alleviate seizures associated with TLE.

THEME G. NOVEL METHODS AND TECHNOLOGY DEVELOPMENT

G1

A TIMED BREEDING STRATEGY FOR PRIMARY NEURON CULTURES IN SMALL OR RESOURCE-LIMITED RESEARCH PROGRAMS

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Primary cortical neurons prepared from embryonic day 15 (E15) mouse pups are a robust model for basic neuroscience research at the undergraduate level, due in part to their abundance and ease of culturing. However, time and resource restrictions at small institutions or in small research programs make the relative uncertainty of "pair-and-hope" timed-breeding strategies a gamble that can, unfortunately, prevent the inclusion of such models into class activities and research programs. Here we present a standardized timed breeding and culture protocol that reliably produces timed-pregnant females on a set schedule. We take advantage of the Whitten effect, where females are housed with urine-soaked shavings from male cages for 4 days prior to mating to induce and synchronize estrus. Under our strategy, we observed a 41.6% pregnancy rate from induced females (n=12). Mucous plugs are regularly detected (80%) from total pregnancies confirmed (n=5) by significant weight gain as early as E8. The simple organization of such a reliable schedule for in-house production of timed-pregnant females provides routine opportunities for deep student engagement in the cellular neuroscience research process in class and in the research lab. Here we present such examples, including microscopy-,

protein-, and microfluidic-based projects providing the investigation of the cellular basis of neuron function.

G2

ADULT HUMAN BONE MARROW STEM CELL THERAPY FOLLOWING STROKE IN THE RAT CONTRIBUTES TO REWIRING SPECIFIC CORTICAL PATHWAYS

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Stroke is the leading causes of adult disability in the US, with more than 1 million survivors suffering from functional deficits resulting from stroke (Thom, et al., 2006). Ischemic stroke, resulting from lack of blood flow to the brain, leaves survivors with permanent neurological deficits for which no effective cure exists. The only current FDA approved treatment for stroke is during the acute stage, and many patients are unable to receive treatment in such a short time frame. A novel experimental approach that has tremendous potential to improve functional recovery after stroke includes stem cell transplantation. It has been previously shown that after middle cerebral artery stroke and intravenous and intracranial human adult bone marrow-derived stem cell (hABM-SC) therapy, motor pathways that originate in the uninjured, contralateral cortex sprout and become bilateral to help innervate areas that lost their connections due to the stroke (Andrews, et al., 2008). This neuroplasticity also correlates with increased contralateral forelimb function. We quantified the corticostriate fibers, commissural fibers, corticorubral fibers and corticospinal tract fibers. We found that neuroplasticity was present in and specific to both the corticurubral and corticospinal tracts, and absent in other pathways originating from the uninjured, contralateral cortex in the rat following a stroke and hABM-SC therapy.

G3

BIOPHYSICAL AND BIOCHEMICAL CUES ADDITIVELY AND SYNERGISTICALLY ENHANCE RATES OF AXONAL REGENERATION AND CONFER DIRECTIONALITY IN DORSAL ROOT GANGLION EXPLANTS

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Peripheral neuropathy can be the consequence of degenerative disease or traumatic injury. In either case, there is little that can be done to restore function to patients that have lost sensation and locomotion due to damaged peripheral nerves. Peripheral nerve regeneration does happen to some extent *in vivo* but this becomes less likely as the extent of the injury increases. In order to develop a means to mediate improved regeneration, we have investigated extracellular microenvironments in which biochemical and biophysical cues can be altered to optimize axonal regeneration. We have created a model using murine dorsal root ganglion (DRG) explants cultured on grooved topographic surfaces with feature sizes ranging from 400nm-4000nm. It is our hope that an optimal feature size will not only increase the rate of regeneration but also confer directionally to the extending neurites, thus increasing the efficiency of re-innervating a target organ. Additionally, we have investigated the effect of various neurotrophins (NGF, BDNF, GDNF, NT-3) in the presence of the specialized topographic surfaces. We hypothesize that there may be an additive or synergistic effect when preferential biochemical and biophysical cues are present simultaneously. Our results demonstrate that the DRG explants demonstrate enhanced directional growth on our larger sized topographical features, and that there is an additive effect in the presence of NGF and other combinations of soluble factors. Proceeding on this line of investigation may eventually lead to a biosynthetic implant that provides proper topographic and neurotrophic signaling to stave off the formation of scar tissue and enhance neuritogenesis in patients after injury. This project was funded by Midwestern University's Biomedical Sciences Program and the Midwestern University Multidisciplinary Award.

G4

VEGF-BASED NANOTHERAPY IN SPINOCEREBELLAR ATAXIA TYPE 1 (SCA1)

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Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant neurodegenerative disorder caused by the expansion of a polyglutamine (CAG) repeat in the protein Ataxin-1 (ATXN1). Clinically, patients exhibit severe ataxia, dysarthria and bulbar dysfunction. Pathologically, it is characterized by the neuronal loss of Purkinje cells in the cerebellar cortex, inferior olive and in the brainstem. Previously, we and others have found that mutant ATXN1 alters gene expressions well before the onset of other pathological and behavioral changes. We made the unexpected discovery that ATXN1 directly represses the expression of Vascular Endothelial Growth Factor (VEGF), an angiogenic cytokine that also has potent neurotrophic properties. As a result, SCA1 knock-in mice ($SCA1^{154Q/2Q}$; Q=glutamine) display abnormally low levels of VEGF in their cerebella. Delivery of recombinant VEGF into SCA1 mouse has been shown to improve SCA1 phenotypes, specifically the hallmark ataxia and the rescue of purkinje cells loss in the cerebellum. However due to several limitations of using recombinant VEGF (i.e. high manufacturing cost, biologically unstable with short half-life), in this study we have begun to explore the potential for using nanoparticles VEGF-mimetic peptide amphiphile (VEGF-PA) as an inexpensive alternative and innovative therapeutic agent for SCA1. Our preliminary data show that delivering VEGF-PA to late-symptomatic SCA1 knock-in mice can improve their behavioral and pathological phenotypes similar to what we observed with the delivery of recombinant VEGF. Given that that deficient VEGF activity has also been implicated in Parkinson disease, Huntington's disease, Alzheimer disease, and motor neuron disorders (i.e.

ALS and Spinal Bulbar Muscular Atrophy), our efforts will have the potential to revolutionize VEGF-based therapy for broad general application for neurodegenerative diseases. This work was funded by U.S. National Institutes of Health grant 1R01NS082351 and Louis A. Simpson & Kimberly K. Querrey Center for Regenerative Nanomedicine, Regenerative Nanomedicine Catalyst Award.

G5

DYNAMIC, MULTI-COLOR LABELING OF NEURAL CONNECTIONS IN DROSOPHILA

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Determining the pattern of activity of individual connections within a neural circuit could provide insights into the computation processes that are the basis of brain function. Here we demonstrate new strategies to label active synapses *in vivo* in *Drosophila*. First, we develop a powerful activity-dependent marker for synapses based on trans-synaptic complementation of GFP. Next, we create color variants, achieving activity-dependent, multi-color tagging of active synapses *in vivo*. Our system allows for the first time retrospective labelling of synapses (rather than whole neurons) based on their activity, in multiple colors, in the same animal. As individual synapses often act as computational units in the brain, our method will promote the design of experiments that are not possible using existing techniques. Moreover, our strategies are easily adaptable to circuit mapping in any genetic system.

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THEME H. SENSORY AND MOTOR SYSTEMS

H1

ADAPTIVE OPTICS REVEALS PHOTORECEPTOR DISRUPTION IN DIABETIC MACULAR ISCHEMIA

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Diabetic retinopathy (DR), an important microvascular complication of diabetes, is a leading cause of blindness in the United States. Diabetic macular ischemia (DMI) is a complication of DR, characterized by the occlusion and atrophy of retinal capillaries in the macula. The resulting retinal hypoxia leads to an upregulation of growth factors, which contribute to the onset and progression of diabetic macular edema and retinal neovascularization, which are major causes of vision loss in patients with DR. In some cases, however, ischemia becomes the predominant feature of the retinopathy, and profound and irreversible visual loss occurs out of proportion to that expected from any clinical findings. In this study, we used the RTVue-XR Avanti optical coherence tomography angiography (OCTA) to identify areas of capillary non-perfusion at the level of the deep capillary plexus (DCP), which supplies photoreceptors with 10-15% of their oxygen requirements. To assess photoreceptors in areas of DMI, we used an adaptive optics scanning laser ophthalmoscope (AOSLO), which allows for visualization of individual cone photoreceptor outer segments in the living human eye. We correlated our findings on AOSLO to those on spectral domain optical coherence tomography (SD-OCT), a clinical gold standard for following many retinal diseases. The SD-OCT device used for this study allows for simultaneous, co-registered infrared reflectance (IR) and SD-OCT imaging. Vascular landmarks were used to overlay the AOSLO montages and OCTA images to the IR image, allowing point-to-point correlation between SD-OCT, AOSLO and OCTA. This prospective observational study included seven eyes of seven patients diagnosed with DR. Four eyes showed evidence of DMI at the level of the deep capillary plexus (DCP) and three eyes with DR had normal DCP perfusion. We found that the areas of DCP non-perfusion in these four eyes tightly co-localized to photoreceptor disruption on AOSLO. In two of these eyes, these areas also co-localized to outer retinal disruption on SD-OCT. Three eyes with robust capillary perfusion of the DCP had normal photoreceptors on SD-OCT and AOSLO. In conclusion, using AOSLO and OCTA, this study shows that photoreceptor disruption corresponds to areas of capillary non-perfusion at the level of the DCP in patients with DMI. This observation, combined with our previous studies, is important in confirming the significant contribution of the DCP to oxygen requirements of photoreceptors in DMI, while highlighting the ability of AOSLO to detect subtle photoreceptor changes not always visible on SD-OCT.

H2

AN INVESTIGATION OF APOPTOSIS IN INNER EAR HAIR CELLS USING JC-1 DYE

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Apoptosis and cell reproduction are natural processes which occur in most animal cells. However, inner ear hair cells are unable to reproduce and lack the ability to fully recover from damage. Amingoglycosides are a class of antibiotics used to treat gram-negative bacterial infections. These powerful antibiotics also have severe side effects; specific aminoglycosides such as Streptomycin and Gentamicin are vestibulotoxic (Selimoglu, 2007) and can result in mitochondrial-related balance and deafness disorders, and eventually, hair cell death. There is a lack of vestibular mitochondrial studies in relation to apoptosis and by studying mitochondria within inner ear hair cells, light can be shed on this area. The overall goal of this study is to investigate the structural and functional properties of mitochondrial subclasses (based on size and location) within the hair cell, in relation to apoptosis. In this study, analysis of mitochondrial potential decay rates was performed on hair cells in vestibular tissue. JC-1, a ratiometric fluorescent probe (Keil et al., 2011), was used with an LSM 710 confocal microscope to record changes in mitochondrial potential among mitochondrial

subclasses between Type 1 and Type 2 hair cells. Fiji (ImageJ software) was used to measure relative intensities of JC-1 and to perform further analysis. Type II hair cells show greater mitochondrial potential decay rates than Type I hair cells. We also observed differences among mitochondrial subclasses. These differences indicate that specific mitochondria may be more susceptible to external effects and thus may trigger cellular apoptosis. These findings also serve as groundwork for comparison studies where we will investigate the mechanism by which aminoglycosides, particularly Gentamicin, act on specific subclasses of mitochondria and the greater process of inner ear hair cell apoptosis.

Keil et al. (2011) Pflugers Archiv 462: 693–708.
Selimoglu. (2007) Curr. Pharm. Des. 13: 119-26.

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H3

CAMKIIA MEDIATES HYPERALGESIA IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS AS A DOWNSTREAM OF IL-17

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Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. Pain is a common and severe symptom in MS. The mechanism for MS pain has not been well studied. We established an experimental autoimmune encephalomyelitis (EAE), a widely used animal model to study pathological mechanism of MS, in mice for the study. We found that spinal CaMKIIα activities were increased, correlating with the development of mechanical allodynia and thermal hyperalgesia, in EAE mice. Prophylactic and acute administration of KN93, an inhibitor of CaMKII, significantly reduced the clinical scores of EAE and attenuated mechanical allodynia and thermal hyperalgesia in EAE mice. Moreover, siRNA targeting CaMKIIα was effective in reversing established mechanical and thermal hypersensitivity in EAE mice. Furthermore, CaMKIIαT286A point-mutation mice showed significantly reduced signs of disease, evoked pain severity, and absence of spontaneous ongoing pain when compared with littermate wildtype mice. We also found that IL-17 is responsible for inducing but not maintaining mechanical and thermal hyperalgesia that is mediated by CaMKIIα signaling in EAE mice. Taken together, these data implicate a critical role of CaMKIIα as a cellular mechanism in pain and neuropathy in multiple sclerosis, and IL-17 may act as upstream of CaMKII in generation of pain.

H4

CHANGES IN THE EXTRACELLULAR MATRIX FOLLOWING ISCHEMIC STROKE IN THE RAT.

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Ischemic strokes are a severe central nervous system (CNS) injury which result in neuronal cell death and inflammation. Limited neuroplasticity is seen originated from the intact contralateral cortex following stroke. After CNS injury, chondroitin sulfate proteoglycans (CSPGs) have been shown to be inhibitory to neurite outgrowth. The CSPG neurocan is produced and secreted by astrocytes. After both stroke and spinal cord injury, the CSPG neurocan is upregulated in the CNS. After spinal cord injury, neurocan expression was increased at both the lesion site and areas distal to the lesion at the same time points as an increase in GFAP (a marker for activated astrocytes). The present study will investigate changes in astrocytes and neurocan expression in areas distal to the lesion after stroke. To characterize these changes in the present study, we examined the expression of neurocan and GFAP via western blot at 3, 7, 14 and 28 days post permanent middle cerebral artery occlusion in both the ipsilateral and contralateral cortex and in the cervical enlargement of the spinal cord. Results are forthcoming.

H5

CORTICAL REORGANIZATION RELATED TO VOLUNTARY CONTROL OF THE PARETIC HAND IN CHRONIC STROKE FOLLOWING AN INTERVENTION USING A NOVEL ASSISTIVE SYSTEM: A PRELIMINARY REPORT

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A large number of individuals with moderate to severe chronic stroke lack the ability to open their paretic hand effectively. This may be partially due to damage to the ipsilesional corticospinal tract and increased reliance on contralesional corticobulbospinal pathways, as previous evidence shows shifting of cortical activity to the contralesional hemisphere following stroke that can modulated by expression of synergistic movements. However, evidence for a successful intervention showing reorganization of cortical activity associated with post-stroke hand function recovery in this population is lacking. We used a newly developed electromyography (EMG)-triggered neuromuscular electrical stimulation (NMES) system — ReIn-Hand that enables this population to use the paretic hand to participate in a task-specific intervention. This allowed us to investigate whether a device assisted task-specific intervention will lead to a shift in cortical activity towards the ipsilesional sensorimotor areas to facilitate better control of voluntary hand opening.

Six individuals with moderate to severe chronic stroke participated in a 7-week intervention, 3 sessions per week. In each session, subjects used the paretic arm to perform 20-30 trials of tasks involving reaching, grasping, and releasing with the assistance of the ReIn-Hand. Passive range of motion, Box and Block, Semmes-Weinstein monofilament test, Nottingham Assessment, and grip strength were assessed before and after the intervention. Pre- and post-intervention, participants performed paretic hand opening with the arm resting on a haptic table or lifting up against 50% of maximum voluntary shoulder abduction force, while simultaneously measuring 160 channel electroencephalography (EEG). Cortical activity related to hand opening was reconstructed based on subject-specific head models. The reconstructed activity on sensorimotor areas was used to quantify a Laterality Index (LI).

Following the intervention, subjects showed improved manual dexterity, sensation, and grip strength. Furthermore, post-

intervention, subjects exhibited a significant shift in cortical activity related to paretic hand opening from the contralesional hemisphere to the ipsilesional hemisphere ($p<0.05$). These results suggest that using the ReIn-Hand system during functional reach/grasp movements is effective in improving voluntary hand control in individuals with moderate to severe stroke, as well as evoking cortical reorganization back to a more typical pattern seen in healthy individuals and well-recovered stroke subjects. This study is funded by NIDILRR - Field-Initiated Program 90IF0090-01-00.

H6

CRISTAE IN INNER EAR HAIR CELL MITOCHONDRIA ARE POLARIZED TOWARD CUTICULAR PLATE

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The main objective of this research is to study mitochondria in inner ear hair cells from a functional and structural perspective. Mitochondria are divided into three different sub-types according to size: large, medium, and small. Our focus is mitochondria near the cuticular plate (CP) in vestibular Type 1 hair cells. Since these mitochondria are adjacent to the CP, we also see rootlets in close proximity to them. In addition, we speculated that the side facing the CP has a significantly larger amount of cristae junctions (CJs) than the opposite side, a finding supported by our models of reconstructed mitochondria. CJs are direct interactions between the mitochondrial cristae and the the inner membrane. (Rabl et al. 2009) This suggests a polarization of CJs one side, so that can transport ATP and Ca^{2+} to points of interest, such as stereociliar rootlets and the CP (Perkins et al. 2010). We are also creating 3D tomograms, section by section, using IMOD software developed at the University of Colorado. We examined every section of the tomogram, and we accurately traced individual contours, that when meshed, give a very detailed structure of the mitochondria. Mitochondrial structures such as cristae, and inner membrane cristae junctions (CJs) are visible and easy to trace. By counting these CJs on either side of the mitochondria, we can determine their density relative to the CP. We have seen more inner membrane CJs on the side closer to CP and rootlets. Using the “get info” feature of the IMOD software, we are obtaining accurate measurements of the amount of inner membrane surface area. Interestingly, lamellar cristae in one model were seen to curve in the direction of the stereociliar rootlets. In the same model, three mitochondria combine to form a type of “super-mitochondrion” where CJs have higher electron density. Stereocilia are known to reform by reconstruction of their actin from tip to base using various myosin and rate regulating proteins (Naoz et al. 2008). We hypothesize that mitochondria are responsible for reconstitution of actin filaments in stereocilia using ATP (Naoz et al. 2008), as well as for maintaining the shape of the cuticular plate. The alignment of cristae between mitochondria may be able to increase ATP production. In conclusion, our results support the hypothesis that CJs are asymmetrical distributed in favor of structures requiring more ATP.

Naoz et al. (2008) Biophys J. 95: 5706–5718.
Perkins et al. (2010) J. Neurosci. 30: 1015-1026.
Rabl et al. (2009) J. Cell Biol. 185: 1047-1063.
Supported by NIH R21-DC013181 (AL) and P41-RR004050 (GP, ME).

H7

INVESTIGATING THE EFFECT OF NANO-SIZED TOPOGRAPHY AND EXTRACELLULAR MATRIX COATINGS ON NEURONAL REGENERATION

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Axonal growth is a key aspect of nerve regeneration, and is necessary to regain full function following a perpheral nerve lesion. Previous studies have shown that biophysical and biochemical cues are able to increase axonal growth. However, the growth is frequently uncontrolled and therefore unable to deliver the newly formed neurites to the desired tissue. The aim of this study is to use nano-sized topography to directionally control axonal growth, and to modify the components of the extracellular matrix to allow for the most extensive neurite regeneration. We hypothesize that the axons will use the topography as a biophysical signal and propagate parallel to them. Once an appropriate extracellular matrix is chosen, the synergistic biophysical and biochemical signals will lead to a longer effective axonal length. For the purposes of our study, we used *ex vivo* explants of cervical and thoracic mouse dorsal root ganglia (DRGs). The DRGs were harvested and cultured on anisotropic grooves. Groove widths ranging from 200nm to 2,000nm were used. A chemically identical flat surface was used as a control. Analysis of the explants showed that axons grow in a linear fashion along the 700 and 2,000nm grooves significantly more than all other conditions. This linear growth also significantly extended the average length of the axons on the 700 and 2,000nm plates. Upon further analysis, it was determined that DRGs cultured on the 700nm plate projected longer and more numerous axons than those cultured on the 2,000nm plate. Therefore, the 700nm grooved surface was selected to further study the effect of various extracellular matrix components on axonal growth. We can already assess differences in axonal growth behavior among the different matrices such as matrigel, osteopontin, and puramatrix. Currently, two different extracellular matrix coating procedures for matrigel are being compared. One method uses a spin-coater to distribute the matrix, the other relies on manual spreading of the matrigel. Differences in neurite growth depending on the coating procedure have been observed, some with additive effects when coated on topography. Additionally, DRGs cultured on surfaces void of any matrix coating are being investigated. In conclusion, these results may help us reveal general mechanisms responsible for axonal growth, and in the future can be applied toward novel treatments to directionally and biochemically enhance spontaneous nerve regeneration. This study is funded by the Midwestern University Biomedical Sciences Program, and the Midwestern University Multidisciplinary Award.

H8

LEARNING-RELATED PURKINJE CELL PHYSIOLOGY IN THE LARVAL ZEBRAFISH CEREBELLUM.

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Cerebellar learning is supported by plasticity at multiple synapses within the circuit. Purkinje cells receive excitatory synaptic inputs from parallel and climbing fibers, both of which are recruited during cerebellar learning and may undergo plasticity that supports the acquisition and retention of a learned movement. To detect plasticity at these synapses, we have made whole-cell, patch clamp recordings from Purkinje cells in larval zebrafish during cerebellum-dependent associative learning. In this task, a light (conditioned stimulus, CS) is paired with a mild electrical stimulus to the tail (unconditioned stimulus, US), which elicits fictive swimming (unconditioned response, UR). With repeated presentations of the CS and US, fictive swimming to the CS (conditioned response, CR) emerges. We have observed three distinct classes of Purkinje cell synaptic and spiking activity displayed during the CR. Multiple complex spiking cells (MCS, n = 12/30) show several complex spikes at the onset of the CR. Integrating EPSP cells (IE, n= 7/30) display parallel fiber EPSPs before the onset of the CR. These EPSPs summate, causing a long-lasting depolarization and simple spikes. Single complex spiking cells (SCS, n=11/30) display one complex spike at the onset of swimming, followed by either parallel fiber EPSPs and simple spikes or hyperpolarization that lasts several hundred milliseconds after the CR. Plasticity of the cellular response to the CS is evident in each group and progresses towards the synaptic and spiking activity observed during the CR. Also, the cellular response during the CR relates to the topographical location of Purkinje cells, with MCS cells in the medial half, IE cells in the middle, and SCS cells in the lateral half of the cerebellar hemisphere. To probe the contribution of Purkinje cells to the CR, we have used fish that express archaerhodopsin-3 in Purkinje cells, allowing us to preferentially suppress simple spikes during training. Optogenetic hyperpolarization of Purkinje cells impairs acquisition of the CR. Expression of the CR is also impaired by hyperpolarization, but only immediately following acquisition. Together, these results reveal synaptic plasticity during cerebellar learning, demonstrate that the physiological response of a Purkinje cell relates to its location within the cerebellum, and reveal the role of parallel fiber-driven simple spikes to the acquisition and expression of an associative cerebellar memory. This research is supported by: NIH R37-NS39395 (IMR), Brain Research Foundation (IMR, David L McLean), and NIH T32-MH067564 (TCH), and NIH F31-NS095476-01 (TCH).

H9

MITOCHONDRIA NEAR RIBBON SYNAPSES IN INNER EAR HAIR CELLS

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Mitochondria, generally referred to as the "powerhouses" of a cell, sustain life in eukaryotes by producing ATP. These structures, once thought to be bacterial symbionts, are now considered one of the most crucial organelles in the cell (Giezen, 2011). The mitochondrial inner compartment consists of two components, the inner membrane and the cristae. Recent EM tomography studies have shown us that these two membrane domains are connected by small tubular structures known as crista junctions (CJs). CJs "have been proposed to regulate the dynamic distribution of proteins, lipids, and soluble metabolites between mitochondrial subcompartments" (Zick et al. 2009). In our research, 3D models of mitochondria from vestibular hair cells were constructed from EM tomograms to understand the structural role of the cristae in neuronal activity at ribbon synapses. The cristae in the mitochondria serve as a site for a majority of the enzymes responsible for cellular respiration and ATP production, therefore playing an essential role in cellular activities, such as transmitting neuronal signals. A ribbon synapse is known to be a "'high capacity docking site' of synaptic vesicles that provide the fusion sites for 'active zones'" and they are known to have a large supply of "immobile synaptic vesicles rapidly available for exocytosis" (Schmitz et al. 1996). Synaptic ribbons are found in all hair cells. These synapses and the vesicles associated with them rapidly release neurotransmitters that carry messages between cells. These vesicles must be powered by an energy source such as ATP in order for them to transport and release neurotransmitters at the synaptic cleft. The objective of this study is to test the hypothesis that ribbon synapses require a large amount of energy to provide the power to transmit signals across synapses and that this energy is provided by mitochondria, which produce and contain large amounts of ATP. Cristae present in the mitochondrion, especially those in close proximity to synaptic ribbons, are oriented perpendicular to the ribbon and polarized towards the ribbon and its associated synaptic vesicles. By creating a 3D model of mitochondria near the synaptic ribbon, we have observed that multiple cristae in a single cell can provide the necessary energy. We have also noticed that the CJs are more predominant on the side adjacent to the synaptic ribbon in vestibular hair cells.

Van Der Giezen (2011) BioScience 61: 594-60.
Schmitz et al. (1996) J. Neurosci. 16: 7109-16.
Zick et al. (2009) Biochim. Biophys. Acta 1793: 5-19.

Supported by NIH R21-DC01381 (AL) and P41-RR004050 (GP, ME).

H10

RECONSTRUCTION OF THE ODORANT RECEPTOR MAP IN THE OLFACTORY BULB OF AGED MICE

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The olfactory system has been the subject of intense study because it is capable of lifelong regeneration at two levels. First, neural stem cells line the olfactory epithelium (OE) in the nose and give rise to olfactory sensory neurons (OSNs; responsible for the detection of odorants), which extend long axons to the olfactory bulb (OB). Second, neuroblasts in the subventricular zone in the brain migrate and differentiate into interneurons in the OB. Therefore, this system has been exploited to examine questions of neuroplasticity and neural circuit reconstruction. Previous research has mostly focused on the recovery of the peripheral olfactory system after injury [2], but factors such as age are often not considered. Our aim was therefore to examine how age affects the ability of regenerated OSNs to innervate their appropriate targets (glomeruli) in the brain following chemical ablation. To do this, we utilized mice aged 1-24 months that have been engineered to express a reporter or tag, namely taulacZ [1], in a specific subpopulation of OSNs that express olfactory receptor 17 (*olfr17*; commonly known as "P2" neurons). This tag allows the P2 neurons to be visualized using chromogenic and immunohistochemical techniques. The number glomeruli that were innervated by the regenerated neurons, the area of the OB occupied by P2-expressing neurons, and the total amount of chromogenic signal in the OB was quantified. The results of these experiments support previous findings in young mice that axon targeting is aberrant in aged mice following chemical ablation [2]. Because we have found that axonal path finding is dysregulated, we expect to see newly generated neurons innervating multiple — and, at times, incorrect — glomeruli, with some glomeruli being heterogeneously innervated by two different types of OSNs. Future clinical applications of stem cell use require that we not only induce proliferation to generate new neurons, but that we also ensure appropriate axon targeting and synaptic formation. Many neurodegenerative diseases disparately affect our aging population, making research on the effects of age on these processes essential. This research was made possible by the generous support of the Neuroscience Summer Fellowship and Mulcahy Scholarship provided by the Loyola Undergraduate Research Opportunities Program (LUROP) in the Center for Experiential Learning at Loyola University Chicago.

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H11

STRUCTURAL DIFFERENCES OF MITOCHONDRIA IN HAIR CELL EFFERENT BOUTONS AND ADJACENT TO STRIATED ORGANELLES USING EM TOMOGRAPHY

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Mitochondria are important organelles found in every cell of the body. The current depiction of a mitochondrion, containing an inner membrane (IM), outer membrane and cristae that increase the surface area of the IM has been the universally accepted model for decades. Although the basic function and structure of mitochondria have been studied, careful analysis of recent data gathered from electron microscopy has led to further investigation of structurally and functionally different subpopulations of mitochondria in the inner ear (Rabl et al., 2009; Zick et al., 2009). Using IMOD software, to reconstruct mitochondria located near different high energy-demanding intracellular components, key qualitative and quantitative data were obtained. Two objects of interest were efferent buttons, contacting vestibular Type I and Type II hair cells in the inner ear, and the striated organelle, found in the apicolateral region of hair cells. Two different types of crista morphology, tubular and lamellar, have been described in mitochondria. Efferent bouton mitochondria displayed tubular cristae as opposed to the lamellar cristae found in hair cell somatic mitochondria. In a recent study (Perkins et al. 2010), it was discovered that cristae interact with the IM at specific points, termed cristae junctions (CJs). They also found that there were more CJs on the sides of mitochondria adjacent to synapses than on the opposite side, thus mitochondria appeared to be polarized. This suggests that Ca^{2+} and ATP are directed towards the synapse. Qualitative information gathered from our 3D reconstructions suggests that cristae are polarized towards similar high-energy-demanding structures such as the hair cell striated organelle, dense core vesicles and synapses found in efferent boutons contacting afferent calyces. The exact correlation between CJ count and these high-energy-demanding structures is to be determined, however, our 3D reconstructions suggest there is a unique relationship between such structures, as well as the CJs of neighboring mitochondria.

Rabl et al. (2009) J. Cell Biol. 185: 1047-1063.
Zick et al. (2009) Biochim. Biophys. Acta. 1793: 5-19.
Perkins et al. (2010) J. Neurosci. 30: 1015-1026

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