# Fourth Annual Rutgers Brain Health Institute Symposium

Friday, November 30\(^{th}\), 2018

Nokia Bell Labs
Murray Hill, NJ 07974

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<td>10.45 AM – 10.55 AM</td>
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<td>11.00 AM – 11.10 AM</td>
<td><strong>Henri Antikainen</strong>&lt;br&gt;“Autophagy Induction Drives Neuroprotection After Traumatic Brain Injury by Inhibiting the Pro-Apoptotic TFEB/ATF4-Mediated Integrated Stress Response”</td>
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<td>11.15 AM – 12.15 PM</td>
<td><strong>Keynote: Dr. Richard Youle, PhD</strong>, Senior Investigator, National Institute of Neurological Disorders and Stroke, NIH.&lt;br&gt;“How PINK1- and Parkin-Mediated Mitophagy Prevents Neurodegeneration”</td>
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<td>2.40 PM – 2.50 PM</td>
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Mission Statement

The goal of the Brain Health Institute (BHI) is to develop neuroscience at Rutgers to become a highly translational and internationally preeminent research enterprise. New tools are transforming neuroscience, and these afford an unprecedented opportunity to create new treatments for central nervous system disorders. Neuroscience has been identified by Rutgers University as one of five signature areas for future focus and development. As part of this strategic plan, the BHI was established to become an internationally recognized center for basic, translational, and clinical research into the biological bases of human brain function and dysfunction. The BHI is the home for the overall Rutgers neuroscience initiative, and is a growing interdisciplinary institute consisting of more than 250 principal investigators with neuroscience laboratories across various campuses of Rutgers University and Rutgers Biomedical and Health Sciences. By supporting and coordinating neuroscience across all campuses, the BHI will unite Rutgers University’s dynamic and diverse neuroscience community toward common goals:

- To create research programs focused on the biological underpinnings of the central nervous system’s function and dysfunction.
- To develop treatments for these disorders using novel neuroscience tools.
- To establish a rich neuroscience resource in New Jersey that educates the public, clinicians, faculty, and students, as well as state, national, and international health officials.

BHI Strategic Plan

Initial focus for development of neuroscience via the BHI at Rutgers will be on four areas and associated disorders: Neurodevelopment, Neurodegeneration and Injury, Cognitive and Sensory Neuroscience, and Motivational and Affective Neuroscience. The selection of the focus areas was based on an analysis of strengths at Rutgers currently, as well as the recognition of prevalent nervous system disorders with a large need for novel treatments. A major goal will be to identify potential teams within these areas of focus, where targeted recruitments would have a significant impact on multi-investigator translational research.

A further area of focus for the Brain Health Institute will be to utilize new techniques in basic neuroscience to develop novel therapies for brain and spinal disorders. Over the past 7 years, developments in viral vector neurotransduction, optogenetics, and chemogenetics (designer receptors), among other areas, are revolutionizing neuroscience. These new methods have proven effective in altering brain function and dysfunction in highly specific ways in animal models, indicating that such methods may lead to a new generation of neurotherapeutics. Indeed, viral vectors are already being used in clinical trials to treat Alzheimer’s and Parkinson’s diseases by expressing growth factors to halt degeneration of neurons in the basal forebrain and midbrain. Similar viral vectors can be used to express opsins or designer receptors in a cell type-specific manner to allow control of selective populations of brain or spinal neurons with unprecedented specificity. This will allow new therapies, based upon knowledge from basic neuroscience research, with many fewer side effects compared to almost any current treatment. By studying different disorders in parallel, we can identify commonalities for the underpinnings of disease. The goal is to identify the genetic, environmental, and other aspects related to neuropathology and repair so that effective strategies can be developed for prevention and treatment.

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The Fourth Annual Rutger's Brain Health Institute Symposium

Friday, Nov 30th, 2018

Nokia Bell Labs, Murray Hill, NJ
SPEAKER ABSTRACTS
PINK1 and Parkin, both mutated in familial PD, normally work intimately together to initiate autophagy of impaired mitochondria. When mitochondria are damaged, Pink1 senses the damage and accumulates specifically on the outer membrane of damaged mitochondria where it phosphorylates ubiquitin chains. These phosphorylated ubiquitin chains on the outer mitochondrial membrane bind to cytosolic Parkin and activate Parkin’s E3 ubiquitin ligase activity yielding a feedback amplification loop that leads to autophagy of individual damaged mitochondria. Downstream of Parkin the machinery that mediates autophagosome recognition of damaged mitochondria links this pathway to genes mutated in ALS. Optineurin and the kinase TBK1, both mutated in familial ALS cases, participate in mitophagy in addition to NDP52. Optineurin and NDP52 bind to ubiquitin chains on mitochondria and also recruit autophagy machinery proteins, including the upstream kinase Ulk1 and the downstream autophagosome marker, LC3, to induce engulfment of the damaged mitochondria. Interestingly, in a murine model of mitochondrial damage, the product of the kinase PINK1 (phospho-S65 ubiquitin) is detected to increase in the cortex, representing a biomarker of PINK1 activity. Although mutations in Parkin and PINK1 in man lead to PD, mice lacking either or both genes have no PD related phenotypes. However, if mice are stressed, either by the exacerbation of mitochondria DNA mutation rates or by exercise, profound inflammatory phenotypes arise, several of which are linked to human PD patients. The inflammation appears to stem from mitochondrial DNA released into the cytosol when mitophagy does not clean up damaged mitochondria. Interestingly, preventing inflammation through the cGAS/STING pathway prevents neurodegeneration in a mouse model and suggests pharmaceutical treatment could potentially mitigate neurodegeneration.

Dr. Youle received an A.B. degree from Albion College and his Ph.D. degree from the University of South Carolina where he worked on the protein toxin ricin. He joined the Surgical Neurology Branch of NINDS in 1985 as a principal investigator where he has developed and moved into clinical trials new treatment strategies for brain tumors. Most recently his lab has discovered functions and interrelationships among proteins mutated in familial Parkinson’s disease. His current work focuses on molecular mechanisms of autophagy, mitochondrial quality control and neurodegenerative disorders. He has more than 200 published papers and has been awarded 26 patents. He currently serves as acting chief of the Surgical Neurology Branch and chief of the Biochemistry Section in NINDS. He is recipient of a mentor award from the Inventor’s Hall of Fame, NIH Director’s Awards in 1997 and 2011, and serves on the editorial boards of five journals and participates on numerous advisory panels.
Ronald P. Hart, PhD
Professor
Department of Cell Biology & Neuroscience
Rutgers-School of Arts and Sciences, New Brunswick

Interaction of Opioids and HIV in Developing Human Brain
Andrew Boreland1,2, Hsin-Ching Lin1, Zhiping Pang1, Arnold Rabson1, Peng Jiang2 and Ronald P. Hart2
1Child Heath Institute of New Jersey and 2Department of Cell Biology & Neuroscience, Rutgers University, New Brunswick, NJ

Even with successful combined antiretroviral therapy (cART), infection by Human Immunodeficiency Virus (HIV-1) persists in the population and is compounded by an overlapping crisis with drugs of abuse. The primary site of interaction between HIV pathology and opioid action is in the brain. On one hand, NeuroAIDS is a constellation of symptoms affecting cognitive, behavioral, and motor functions that has been particularly difficult to model in animal models because most animals are not infected by HIV. On the other hand, drug abuse, including opioids, exacerbates effects of HIV infection to produce long-term deficits in working memory and neuropathology, defined as HIV-associated neurocognitive disorder (HAND). Our goal is to recapitulate HIV infection in microglia derived from human induced pluripotent stem cells (iPSC) and to incorporate them into an iPSC-derived brain organoid model. This would mimic synaptic, immune and glial interactions in a 3D environment, uniquely enabling us to examine how these interactions are affected by drugs of abuse and HIV to mimic the current status of the HIV-infected population. Our studies will include cells containing variants of the mu-opioid receptor (MOR; encoded by the OPRM1 gene) and CRISPR/Cas9 gene-edited versions of this gene. We propose to develop this novel model to attack NeuroAIDS, HAND, and opioid use in in integrated stem cell model. Our immediate goal is to develop the technological base with which to ask hypothesis-driven questions about HIV-opioid interactions in specific cell types lacking or carrying the MOR receptor.

Candice Chavez, PhD
Post-doctoral Fellow (Laszlo Zaborszky’s lab),
CMBN, Rutgers- Newark

Striatal Activity During Auditory Learning and Habit Formation
P. Gombkoto1, D. Noofoory1, K. Bieszczad2, L. Zaborszky1;
1CMBN, Rutgers, The State Univ. of New Jersey, Newark, NJ; 2Psychology, Rutgers, The State Univ. of New Jersey, Piscataway, NJ.

The basal forebrain cholinergic (BFC) projection system plays a critical role in learning and memory processes including the induction of experience-dependent neural plasticity in the cerebral cortex. Our work using monosynaptic viral tracing of cholinergic projection cells that target the primary auditory cortex (A1) revealed that the BFC receives a large proportion of its input from the striatum. While it has been established that the striatum plays a role in learning, habit formation, and memory, it has not been considered in relation to the BFC-A1 circuit. We hypothesize that striatal cells that specifically project to the BFC-A1 circuit exert their influence differentially during early vs. late stages of auditory task performance. Using monosynaptic viral tracing with EnvA g-deleted rabies virus coding for channelrhodopsin (ChR2) in ChAT::Cre rats, we restricted ChR2 expression to cholinergic projection neurons that target A1 and their specific input cells within the striatum. This technique enabled selective optogenetic control over the striatal-BFC-A1 circuit allowing us to identify and determine striatal cell activity during an auditory-based behavioral task dependent on A1 plasticity. We recorded from the striatum and the basal forebrain throughout daily behavioral training sessions using a 64-channel 8-shank silicone optrode. The behavioral training consisted of an operant task where a pure tone stimulus (S+) signaled the availability to barpress for a water reward for water deprived rats. Preliminary data provide evidence for a diverse range of S+ tone driven activity in the striatum that suggests a changing profile of characteristic responses expressed early or late in training. These findings may show that the striatum dynamically alters its inputs to the auditory projecting BFC neurons as behavioral performance improves in auditory tasks.
Morgan H. James, PhD
Research Associate (Gary Aston-Jones lab)
Rutgers Brain Health Institute

The Orexin System as a Novel Target for the Treatment of Binge Eating Disorder

Gary Aston-Jones¹ & Nicholas T. Bello²
¹Brain Health Institute, ²Animal Sciences, SEBS, Rutgers-New Brunswick

Binge eating disorder (BED) is a major obstacle in the treatment of obesity, with 25-30% of obese individuals who seek medically-supervised weight loss having a diagnosis of BED. Unlike simple overeating, bingeing is accompanied by a sense of a “loss of control” over how much is eaten, characterized by a progressive escalation of intake of highly palatable food. In this way, many of the clinical characteristics of BED closely resemble symptoms of drug abuse disorders, pointing to possible commonalities in the neural circuitry underlying these disorders. The Aston-Jones laboratory was the first to identify a role for the hypothalamic orexin (hypocretin) system in drug reward and motivation, and subsequent studies in our lab have shown that compounds that block orexin signaling are highly effective at reducing drug seeking. In a collaborative project between the Aston-Jones and Bello laboratories (supported by the BHI Pilot Grant Scheme), we have shown that the orexin system underlies motivational changes that occur as a result of binge eating, specifically in obese animals. We show that binge eating is associated with an increase in the number of orexin neurons and that motivation for food following binge experience can be normalized by pretreatment with an orexin-1 receptor antagonist. Thus, the orexin system may be a potential novel target for pharmacotherapies designed to reduce food seeking in individuals with a history of BED. These findings are particularly timely given the recent FDA approval of the orexin receptor antagonist suvorexant (Belsomra™).

Jorge Serrador, PhD
Associate Professor
Department of Pharmacology, Physiology & Neuroscience
Rutgers-New Jersey Medical School

Neurovascular Coupling in Gulf War Illness

Glenn Wylie¹
¹Kessler Foundation, West Orange, NJ.

Gulf War Illness (GWI) affects the lives of approximately 25-32% of military personnel who were deployed to the first Gulf War (1990). This multi-symptom condition is characterized by fatigue, headache, and sleep disturbances. Cognitive impairment is also a prevalent symptom which has a substantial impact on daily living of Veterans with GWI. We have previously found that veterans with GWI demonstrate impaired cerebrovascular function. The goal of the current work is to examine how impaired cerebrovascular function may affect functional cerebral blood flow response during cognitive activation. Our secondary goal is to determine if we can improve cerebral vasodilation using dietary nitrate supplementation, in the form of beetroot juice, and will this improve cognitive function. Examining an initial group of 13 veterans with GWI we have found that they demonstrated impaired vasodilation to CO₂ in both the middle cerebral artery (+1.6±1.1 %/mmHg) and anterior cerebral artery (+1.5±1.6 %/mmHg) compared to vasoconstriction (-2.4±0.5 %/mmHg) and anterior cerebral artery (-3.5±1.2 %/mmHg). We are currently examining the relationship with cognitive function and preparing an MRI study to examine functional cerebral blood flow response both pre and following dietary nitrate supplementation. If effective this could provide a safe novel treatment for GWI.
Brain Markers Predicting Reading Recovery after Stroke

William Graves¹, Brian Yao², A.M. Barrett², Michael Germuska³
¹Psychology, RU-Newark, NJ; ²Kessler Foundation, NJ; ³University of Cardiff

Better understanding of cerebral blood flow (CBF) perfusion in stroke recovery can help inform decisions about optimal timing and targets of restorative treatments. In a preliminary study, we examined the relationship between cerebral perfusion and recovery from stroke-induced reading deficits. Left stroke patients were tested with a non-invasive CBF measure (Arterial Spin Labeling, ASL) < 5 weeks post-stroke, and a subset had follow up testing >3 months post-stroke. We measured blood flow perfusion within the left and right sides of the brain, in areas surrounding the lesion, and areas belonging to the reading network. Two hypotheses were tested. The first was that recovery of reading function depends on increased perfusion around the stroke lesion. This hypothesis was not supported by our findings. The second hypothesis was that increased perfusion of intact areas within the reading circuit is tightly coupled with recovery. Our findings are consistent with this hypothesis. We found that higher perfusion in the left reading network measured during the subacute stroke period predicted better reading ability and phonology competence in the subacute and chronic period. In contrast, perfusion of the right homologous regions was associated with decreased reading accuracy and phonology competence. In this talk I will discuss these findings and the broader implications of using ASL and perfusion fMRI to study stroke recovery.

Dopant-free Hydrogels with Intrinsic Photoluminescent, Injectable and Biodegradable Properties.

Peng Jiang¹
¹Department of Cell Biology and Neuroscience, Rutgers-New Brunswick, NJ

Photoluminescent hydrogels that function as both injectable scaffolds and fluorescent imaging probes hold great potential for therapeutics delivery and tissue engineering. Current fluorescent hydrogels are fabricated by either conjugating or doping a fluorescent dye, fluorescent protein, lanthanide chelate or quantum dot into polymeric hydrogel matrix. Their biomedical applications have been severely limited due to drawbacks such as photostability, carcinogenesis, and toxicity associated with the above-mentioned dopants. Here, we report a successful development of dopant-free photoluminescent hydrogels in situ formed by crosslinking of biocompatible polymer precursors, which can be synthesized by incorporating an amino acid to a citric acid based polyester oligomer followed by functionalization of multivalent crosslinking group through a convenient transesterification reaction using Candida Antarctica Lipase B (CALB) as a catalyst. We demonstrated that the newly developed hydrogels possess tunable degradation, intrinsic photoluminescence, mechanical properties, and exhibit sustained release of various molecular weight dextrans. In vivo study showed that the hydrogels formed in situ following subcutaneous injection exhibited excellent biocompatibility and emitted strong fluorescence under visible light excitation without the need of using any traditional organic dyes. Their in vivo degradation profiles were then depicted by non-invasively monitoring fluorescence intensity of the injected hydrogel implants. Our next step is to use the prepared photoluminescent hydrogel to encapsulate and deliver human neural stem cell for spinal cord injury repair and study the relationship between in vivo hydrogel degradation and nerve regeneration.
Parkinson’s Disease (PD), characterized by the accumulation of extracellular toxic oligomeric α-synuclein (αSYN), is one of the most common age-related neurodegenerative disorders, affecting an estimated population of seven to ten million worldwide. Microglia, the resident macrophages of the brain, are the first line of defense in the central nervous system and play a critical role in αSYN clearance and degradation. While the role of microglia in neurodegenerative pathologies is widely recognized, few therapeutic approaches have been designed to target both microglia activation and αSYN aggregation. To control αSYN trafficking and aggregation in microglia, we propose to use antioxidant nanoparticles (NPs) to aid the delivery of aggregation-inhibiting antioxidants, which would ameliorate ASYN aggregation, reduce microglia activation and potentially control neuroinflammation. NPs were formed via flash nanoprecipitation where hydrophobic core compound and amphiphilic shell molecule were kinetically assembled to form stable nanoparticle complex. Specifically, ferulic acid diacid with an adipic acid linker (FAA acid) and tannic acid (TA) were used as shell and core molecules to form FAA:TA NPs. Compared with control NPs (which have amphiphilic macromolecule shell and ferulic acid-based polymer in the core), FAA:TA NPs showed 3-fold stronger inhibitory effect on αSYN fibrilization with only 6 % increase in Thioflavin T fibrilization fluorescence intensity. In αSYN internalization experiments conducted in microglia, the amount of αSYN oligomer internalization decreased significantly upon treatment with FAA:TA NPs. The expression of CD36, a cell surface scavenger receptor involved in regulation of microglia activation upon αSYN exposure, was lowered, suggesting that the NPs’ efficacy in slowing down the initiation of inflammatory cascade of microglia. Reduction in reactive oxygen species in NP-treated microglia and in microglia-induced cytotoxicity in SH-SY5Y cells showed NPs ability to reduce neurotoxicity under extracellular aggregated αSYN exposure. This work could provide a promising nanotherapeutic method to target neurodegenerative diseases involving pathological protein aggregation.
Autophagy Induction Drives Neuroprotection After Traumatic Brain Injury by Inhibiting the Pro-apoptotic TFEB/ATF4-mediated Integrated Stress Response

Radek Dobrowolski¹; Haesun Kim¹; Steve Levison²
¹ Federated Department of Biological Sciences, Rutgers-Newark, NJ; ²Department of Pharmacology, Physiology and Neuroscience, RBHS-NJMS, Newark, NJ.

Traumatic brain injury (TBI), which in its most severe circumstances leads to neuronal cell death, is associated with an accumulation of both intracellular and extracellular aggregated proteins. Under normal conditions of homeostasis, autophagy is a regulatory surveillance process that monitors and degrades misfolded proteins, protein aggregates, and outdated organelles. This study examined the role of autophagy in modulating neuronal cell death following TBI. We report that Beclin1-mediated autophagy is capable of counterbalancing lysosomal inhibition resulting in increased autophagic flux driven by temporarily sequestering lysosomal substrates and reducing lysosomal load after TBI. In turn, restoration of autophagy protects from neuronal death by limiting the impact of the integrated stress response. The stress response pathway includes the activity of transcription factor EB (TFEB), which potentiates expression of activating transcription factor (ATF4) and pro-apoptotic C/EBP homologous protein (CHOP). These findings present a novel way to restore lysosomal function and show that restoration of autophagic function is neuroprotective by inhibiting pro-apoptotic stress pathways after TBI.
Mini Talks- Nokia Bell Labs

Marcus Weldon, PhD
President, Bell Labs and CTO, Nokia

“The Future of Human (sensory) Augmentation : A Bell Labs Perspective”

Shreyas Shah, PhD
Investigator, Physiological Communications

“Future of Human Sensing: Beyond Vital Signs to Biochemistry”

Dr. Mingde Zheng, PhD
Investigator, Physiological Communications

“Point-of-Care Bioelectrical Sensing”
POSTER ABSTRACTS
**Poster #1**
Effect of chronic corticosterone on instrumental behavior in mice

**Authors**
Andrew Dieterich, Mimi Phan, Benjamin Samuels

**PI Name:** Benjamin Samuels

It has been previously shown that chronic corticosterone (CORT) treatment in rodents impairs the acquisition of the instrumental response for food pellets, and lowers the breakpoint ratio in the progressive ratio test, a measure indicative of motivation. We used outcome devaluation, progressive ratio, and probabilistic reversal learning tests to assess the effect of chronic CORT on instrumental behavior. Outcome devaluation tests if goal-directed or habitual behavioral control mediates responding, while progressive ratio tests the willingness or motivation to expend effort to work for a reward. Probabilistic reversal learning examines behavioral flexibility and sensitivity to positive and negative feedback. In this study, adult male C57bl/6 mice were subdivided into CORT or Vehicle treatment-first, and instrumental acquisition training-first groups to assess the effect of CORT on instrumental learning using multiple behavioral tests. The CORT group showed impaired lever presses acquisition across training compared to the Vehicle group. We then compared responding between Vehicle and CORT-treated mice in multiple behavioral tests. In outcome devaluation, CORT mice failed to show sensitivity to the devalued condition in comparison to the valued condition. However, Vehicle mice only displayed a trend towards a reduction in responding for the devalued condition in the test. In the progressive ratio test, CORT reduced breakpoint ratio and active lever presses. In probabilistic reversal learning, CORT impaired completed reversals in training and test sessions. These results suggest that CORT impairs aspects of instrumental behavior learning and performance in mice.

*This work was supported by NIMH R01 MH112861 (BS).*

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**Poster #2**
Repeated mild traumatic brain injury in a mouse model: the effect of BDNF genetic polymorphisms on recovery and personalized treatment approaches

**Authors**
Anna Giarratana, Shavonne Teng, Cynthia Zheng, Smita Thakker-Varia, Janet Alder

**PI Name:** Janet Alder

Traumatic Brain Injury (TBI) is a serious and potentially life-threatening clinical problem. Clinicians have noticed that certain patients recover better after TBI. In this study, we sought to determine the effect of specific single nucleotide polymorphisms (SNPs) on recovery after TBI, and to investigate the underlying mechanisms that may be a factor. We have investigated cellular and behavioral outcomes in genetically engineered mice with the BDNF Val66Met polymorphism following repeated, mild TBI (rmTBI) in a lateral fluid percussion model. We have found that Met carriers have a larger injury volume as assessed by MRI and increased levels of neurodegeneration, apoptosis, p-tau, microglia, and gliosis in the cortex compared to Val carriers at 1 and/or 21 dpi. To gain insight into the mechanism of action of the cellular differences that we have seen, we used western blot analysis to investigate the levels of pro and mature BDNF after injury across the genotypes at 1 and 21 dpi, and found Met carriers have more proBDNF and less total BDNF than Val carriers. Therefore, we have concluded that the Met allele is a risk allele after rmTBI and have begun rescue experiments in injured mice by targeting the altered BDNF pathway using a BDNF overexpressing AAV vector. Using this method, we can rescue the increased astrogliosis seen after injury in the Met carriers back to Val carrier levels. This preliminary data offers promise that by targeting the BDNF pathway, we may be able to develop a personalized TBI therapy for Met carriers.

*Fellowship from the New Jersey Commission on Brain Injury Repair.*
Poster#3
Hyperhomocysteinemia causes cognitive impairment by hyper-activating mTOR and impairing autophagy via the inhibition of Phf8 histone demethylase in mice

Authors
Łukasz Witucki, Joanna Suszyńska-Zajczyk, Jacek Wróblewski, Robert K. Filipkowski, Hieronim Jakubowski

PI Name: Hieronim Jakubowski

Hyperhomocysteinemia (HHcy) is associated with neurodegeneration. The mechanistic target of rapamycin (mTOR) signaling/autophagy pathways and bleomycin hydrolase (Blmh) an Hcy-thiolactone-hydrolyzing enzyme are linked to neurodegeneration but underlying mechanisms are not fully understood. Our objective was to test a hypothesis that HHcy causes cognitive impairment via epigenetic effects on brain mTOR signaling/autophagy. HHcy was induced with 1% methionine in drinking water. Neurological phenotypes were assessed by using behavioral tests: Hind Limb, Beam Walk, Novel Object Recognition (NOR), and 8-arm Radial Maze (RAM). We generated a new Alzheimer’s disease (AD) model: Blmh⁻/⁻-5xFAD mice harboring APP/PSEN1 transgene with AD-causing mutations. Brain mTOR/autophagy pathways, Phf8 histone demethylase, and epigenetic marks on histones were quantified by Western blotting. HHcy mice exhibited significantly impaired activity, coordination in the Beam Walk, cognition in the NOR, and memory in the RAM tests. HHcy and Blmh inactivation significantly increased phosphorylated forms of mTOR and RPS6, decreased autophagy markers Beclin1, Atg5, Atg7, and LC3A/B. AMPK protein and its phosphorylated form, which directly inhibits mTOR and promotes autophagy, were significantly decreased. At the same time we observed significantly decreased histone demethylase Phf8 and increased Lys20 methylation in histone 4 (H4K20me1), which are involved in mTOR regulation. Epigenetic up-regulation of mTOR and down-regulation of autophagy, mediated by increased H4K20 methylation, contributes to the neurological deficits induced by HHcy in mice. Similar changes in the Phf8/H4K20Me1->mTOR->autophagy pathway induced by Blmh deficiency suggest the involvement of Hcy-thiolactone in epigenetic regulation of mTOR/autophagy.


Poster#4
Characterization and putative functions of differentially expressed circular RNAs in the post-stroke brain

Authors
Elaine Huang, Eric Ho

PI Name: Eric Ho

Strokes are the second leading cause of death worldwide. Understanding the roles of circular RNAs (circRNAs) in post-stroke neural repair can guide the development of novel therapeutics. circRNAs are a class of RNA molecules that are formed from back-splicing events. Not only are circRNAs highly enriched in brain tissue, but levels of circRNAs have been found to be significantly altered in the penumbra and core region post-stroke. Focal ischemia was induced in mice via intraluminal middle cerebral artery occlusion (MCAO) for 3 hours. Total RNA was harvested from tissues removed from penumbra and control regions for RNA-Seq analysis. Short reads were mapped to the mouse genome (mm10) by STAR and BWA. circRNAs were detected computationally by CIRCexplorer2 and CIRI2. Expression profiles of circRNAs from penumbra and control were compared using edgeR. Functional enrichment analysis using DAVID was performed on the host genes of circRNAs that exhibited a two-fold change or greater between the control and penumbra regions with p<0.05. Between the control and penumbra region, 745 differentially expressed circRNAs were detected from 624 genes. Based on the top five functional clusters generated by DAVID, these genes are involved with synaptic regions, kinase activity/phosphorylation, intracellular signaling, metal ion binding, and C2 calcium-dependent targeting. Conclusions: We have identified hundreds of differentially expressed circRNAs in penumbra versus control in mice. Since neuron stimulation has been a major post-stroke therapeutic strategy, future research on penumbra-enriched or depleted circRNAs may be key for the development of novel treatments.
Poster #5
Oxytocin neurons enable social transmission of maternal behavior
Authors
Ioana Carcea, Rumi Oyama, Dabiel Ramos, Joyce Mendoza, Maria Alvarado Torres, Harper Lethin, Robert C. Froemke

PI Name: Ioana Carcea

Maternal care is profoundly important for mammalian survival, and maternal behaviors can also be expressed by non-biological parents after experience with infants. One critical molecular signal for maternal behavior is oxytocin, released by hypothalamic paraventricular nucleus (PVN) and enabling plasticity within auditory cortex for recognizing infant vocalizations. To determine how these changes occur during natural experience, we continuously monitored home cage behavior of female virgin mice co-housed for days with an experienced mother and litter, synchronized with in vivo recordings from virgin PVN/oxytocin neurons. Mothers engaged virgins in maternal care by ensuring that virgins were in the nest, and demonstrated maternal behavior by self-generating pup retrieval episodes. These social interactions activated virgin PVN and gated behaviorally-relevant cortical plasticity for pup distress calls. Thus rodent maternal behavior can be learned by social transmission, and our results describe a mechanism for adapting the brains of new parents to infant needs via endogenous oxytocin.

Supported by NIMH, NARSAD

Poster #6
Maternal Exposure to Organophosphate Flame-Retardants and Anxiety-like Behavior
Authors
K. Wiersielis, S. Adams, A. Yasrebi, and T. Roepke

PI Name: Troy Roepke

Endocrine disrupting compounds (EDCs) are compounds found in our environment that interrupt typical endocrine function. A particular group of EDCs are flame-retardants due to their interaction with steroid and nuclear receptors in in vitro investigations. Humans are consistently exposed to flame-retardants daily as they are used in everyday items such as plastics, clothing, toys, and electronics. In the past, polybrominated diphenyl ethers have been used, however, since 2004, they have been replaced with organophosphate flame-retardants (OPFR) as the major flame-retardant chemical. The effects of maternal or developmental exposure to OPFR on behavior are currently underexplored. Yet, one such maternal exposure study in rodent models utilizing a commercial flame-retardant mixture containing OPFR reported significant differences in open arm entries on the elevated plus maze (EPM) in females (Patisaul et al., 2013, J Biochem Mol Toxicol). Here we evaluate anxiety-like behavior in the open field test (OFT), as well as, the EPM in male and female offspring that were maternally exposed to OPFR or oil controls. Males that were maternally-exposed to OPFRs had significantly reduced time of exploration in the center zone of the OFT, a marker of anxiogenic-like behavior, relative to their same-sex controls \( t(28) = 2.128, p = 0.042 \). No significant differences were found in center zone exploration time in maternally-exposed OPFR females relative to their oil controls \( t(25) = -1.018, p = 0.319 \). Interestingly, experimental females displayed anxiolytic-like behavior as evidenced by a decreased number of entries in the corners of the OFT, \( t(25) = 3.556, p = 0.002 \). In contrast, we saw no effect in experimental males on number of corner entries \( t(29) = -0.443, p = 0.661 \). We also assessed behavior in the EPM. Similar to outcomes in the OFT, maternally-exposed OPFR males had significantly reduced percent time in the open arms compared to same-sex controls \( t(28) = 2.096, p = 0.045 \). However, we did not see an effect in females on this measure \( t(25) = 0.579, p = 0.567 \). Our research illustrates that there are sex-dependent effects of OPFR exposure on exploratory behaviors in a mouse model as was previously found in a rat model. Future studies will evaluate other behavioral measures such as the Light/Dark box, social interactions, the effects of high-fat diets, and the receptor-mediated mechanisms underlying the sex differences.

Supported by R21ES027119
Poster#7
A transgenic mouse model of traumatic brain injury for evaluation of endogenous neural stem cell activity

Authors
Jeremy Anderson, Misaal Patel, Rebecca Risman, Sofia Castro-Pedrido, Quinn Wade, and Li Cai

Pl Name: Li Cai

Traumatic brain injury (TBI) causes temporary or permanent loss of memory, motor and cognitive function, and even death. Currently, there are no treatments to recover cells lost from the TBI. The adult brain harbors neural stem cells (NSCs) that may respond to injury and integrate into neural networks. Although the response of adult NSCs is typically insufficient to recover significant damage, an increased understanding of endogenous NSCs may be a potential to promote healing. The notch signaling pathway is highly involved in CNS development, neurogenesis, and injury response. Using a closed head injury (CHI) model in Notch1CR2-GFP transgenic mice, where Notch1-activated NSCs express GFP reporter, CHI was performed on 8-12 week old mice and brain tissue was analyzed 2 to 14 days post injury (dpi) to characterize the Notch1-activated NSCs. Compared to sham, Notch1-activated NSCs (GFP+ cells) in the hippocampus are significantly increased (p<0.05) at 2 dpi; these GFP+ cells proliferate in response to injury (PCNA and Ki67). Notch1-activated NSCs exhibit increased levels of NSC and progenitor cell markers (e.g., Nestin and DCX) at 2 dpi and lineage adoption markers (e.g., Tuj1, S100β and Olig2) at 14 dpi. These results demonstrate that Notch1CR2-GFP mouse is a useful tool that greatly facilitate cellular and molecular investigation of TBI. In addition, our findings support the potential of endogenous NSCs as a cell source for TBI therapeutics.

Supported by NJCSCR, Busch Biomedical Award

Poster#8
The role of Cytoplasmic FMRP Interacting Protein 1 in cocaine-addictive behaviors

Authors

Pl Name: Ozlem Gunal

Cytoplasmic FMR1-interacting protein (CYFIP)1 has been identified as a risk factor for several neuropsychiatric disorders including schizophrenia, intellectual disability, and autism in humans. We have previously shown that mice carrying a Cyfip1 mutation (Cyfip1±/−) show dysregulated synaptic plasticity and Rac1-dependent enhanced presynaptic function during development in the hippocampus. Structural and functional synaptic changes in the nucleus accumbens (NAc) are associated with addiction related behaviors such as cocaine seeking. New evidence on genetic risk factors can help elucidate the response to addictive drugs. To test our hypothesis that cocaine related behavioral responses and synaptic function in the NAc are affected when Cyfip1 levels are reduced, we performed open field tests and compared locomotor activity in control conditions and in response to cocaine by using an automated video tracking system. Wild type mice display an increase in locomotor response to the administration of cocaine (15mg/kg) in both genders, as expected. This response is blunted in all Cyfip1±/− mice and in male mice more than female. Preliminary data showing GluA1 immunolocalization in the NAc after cocaine injection indicate dysregulated GluA1 levels in Cyfip1±/− mice. Field EPSP recordings in the NAc show comparable post-tetanic potentiation between genotypes. These findings provide a novel cellular mechanism that may contribute to cocaine-induced behavioral alterations. Clarifying Cyfip1’s role in cocaine response, locomotor sensitization, and NAc plasticity, which is a previously unexamined target, may be relevant for a variety of disease-related genes with similar functions.
Poster #9
Computational Astrocyence: The computational role of astrocytic-neural interactions

Authors
Ioannis Polykretis, Vladimir Ivanov, Konstantinos Michmizos

PI Name: Konstantinos Michmizos

Astrocytes process and modulate neuronal activity but the underlying sub-cellular mechanisms for doing so remain elusive. To suggest possible functional roles for astrocytes at the network scale, we are developing biologically-constrained neural-astrocytic models. First, a 2D compartmental model, which preserves both the complex structure of astrocytes - consisting of functionally independent microdomains - and the spatial allocation of their sub-cellular organelles, exhibited four types of experimentally reported Ca2+ waves: a) fast, process-specific, b) delayed, microdomain-wide, c) medium- and large-range waves. The waves encoded the synchronous neuronal activity into their spatial extent and interacted with each other to modulate gliotransmitter release and introduce slow inward currents (SIC) in post-synaptic neurons, imposing synchronization. The SIC-induced Ca2+ influx triggered neuroplastic changes that were spatially restricted in the microdomain, providing a possible explanation for the recently reported formation of locally clustered functional groups of dendritic spines. Our model suggests a mechanism for discriminating active and inactive synapses via Ca2+ elevations and inducing selective synaptic modifications. This advocates the astrocytic microdomain as a fundamental learning unit in the brain. Second, a point process model suggested that astrocytes encode chaotic neuronal dynamics in their domains. The astrocytic model had homeostatically plastic receptors that detected synaptic activity and changed the frequency of Ca2+ oscillations. Interestingly, Ca2+ oscillation frequency increased with the chaotic neuronal activity. Overall, our computational models are used as test beds for verifying and further hypothesizing on the possible astrocytic mechanisms that affect brain function and dysfunction, including neuronal synchronization, plasticity and epileptiform activity.

Poster #10
Free Radical-Mediated Targeting of Therapeutic Factors for TBI

Authors
Emily DiMartini, Christopher Lowe, Keana Mirmajlesi, Adam Gormley, David Shreiber

PI Name: David Shreiber

Traumatic brain injury (TBI) begins with primary insult that causes acute and immediate physical injury to neurons that cannot be reversed. During the lengthy secondary injury, free radicals are produced by a number of mechanisms and contribute to the pathogenesis. We broadly proposed that these free radicals could be employed as a homing signal for targeting therapeutic delivery to the site of brain injury. Free radicals are a promising target because of their ability to initiate rapid polymerization. We hypothesized that free radicals produced during TBI could be used to initiate the crosslinking of acrylated polyethylene glycol (PEG) molecules. Then, a neurotrophic factor can be coupled to the polymer backbone and accumulate at the TBI site. Previous work in our lab has demonstrated the reactivity of acrylated PEGs with physiologically relevant radicals though reactive oxygen species (ROS) and reactive nitrogen species (RNS) assays. Building on previous results, we sought to characterize the crosslinking kinetics and its implications in immobilizing our polymer networks within tissue mimics. We found that crosslinking efficiency and immobilization potential varied with polymer chain length, which suggests that a tunable platform can be achieved. Additionally, the reaction of these functionalized PEGs with free radicals protected cortical neurons from the damaging effects of oxidative stress in vitro. Together these results provide promising proof-of-concept for using free radicals as a means of specifically targeting and sustaining nearly endless therapeutic payloads to improve functional outcomes following TBI. Future work will focus on delivering brain derived neurotrophic factor as the payload.

Supported by NIH-UMDNJ Biotechnology Training Program (NIH T32 GM008339)
New Jersey Commission on Brain Injury Research Pilot Research Grant (CBIR16PIL015)
TechAdvance (FP10535)
Poster #11
The absence of p75NTR in granule cell precursors of the cerebellum increase cell proliferation and anxiety levels

Authors
Zanin JP, Shiflett MW, Li Y, Verpeut J, Wang SSH, Santhakumar V and Friedman WJ

PI Name: Wilma Friedman

The external granule layer (EGL) of the cerebellum is a transient proliferative layer were the granule cell precursor (GCP) undergoes clonal expansion to originate the granule neurons. Besides its role in balance and posture, recent functional and anatomical evidence has demonstrated that the cerebellum is also required for cognitive tasks such as reward anticipation and anxiety.

The p75 neurotrophin receptor (p75NTR) is expressed in the EGL. Previously, we demonstrated that the absence of p75NTR promotes a delay in GCP cell cycle exit, producing an abnormally large cerebellum that persisted into adulthood, with motor consequences.

In the present work, we observed that the absence of p75NTR increases the cell cycle speed of the GCP and this mechanism involves RhoA. We also demonstrated, that deleting p75NTR specifically from the EGL, induced an increase in Purkinje cell fairness properties, most likely due to an excess excitatory input. Finally, the network alteration observed promotes an increase in anxiety levels in these animals.

Our results suggest that p75NTR must be spatiotemporally regulated during cerebellar development. The absence of p75NTR in the EGL promotes a deregulation in cell cycle affecting neuronal network that ultimately leads to increase anxiety in adult animals.

Poster #12
The gastrin-releasing peptide (Grp) gene may link processing of signals related to stress and fear memory

Authors

PI Name: Gleb P. Shumyatsky

Unraveling the specificity of sensory information processing will significantly improve our understanding of how brain works. One of the approaches towards this goal is to dissect at the molecular level region-restricted neural networks. Earlier we identified the gastrin-releasing peptide (Grp) gene, as enriched in the neural circuitry of learned fear (Shumyatsky et al., Cell 2002). When the principal neurons fire, they release GRP, which binds the GRP receptor (GRPR) located on inhibitory interneurons, leading to interneuron’s excitation and release of GABA. This in turn inhibits excitatory principal cells, providing an inhibitory feedback loop. The lack of the GRPR leads to greater and more persistent long-term fear memory in the GRPR knockout (KO) mice. In the current study, using our recently developed GPR KO mice, we find that the GRP may be involved in processing of stress-related memory of fear. The GRP KO line displayed increased long-term contextual and cued fear memory but normal anxiety and pain sensitivity. Mildly stressed GRP KO mice showed increased freezing and its slower extinction in the stress-enhanced fear learning (SEFL) paradigm. To identify relevant genes, we are currently investigating transcriptional profile of GRP-KO mice. We also perform visualization of the GRP neural circuitry using retrograde AAV-based tracing and staining with EGFP, which is knocked-in in the Grp gene locus. This study raises intriguing possibility that the GRP can be a molecular target suitable for alleviating the persistence of traumatic memories.

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Poster #13
Obesity propensity differentially influences morphine withdrawal behaviors in male mice

Authors
Xinyi Li, Dushyant Kshatriya, Gina Giunta, and Nicholas T. Bello

PI Name: Nicholas T. Bello

Individual differences contribute to the varying susceptibility for weight gain and opioid use. The divergence and convergence nature of these individual susceptibilities has not been examined. Therefore, the objective of this study was to determine the influence of obesity propensity on morphine withdrawal behaviors. Obese-prone (OP) and obese resistant (OR) male C57BL/6J mice were identified on an 8-weeks high-fat diet (45% Fat). Following identification, OP and OR mice were fed a 5-weeks control diet (10% Fat) and randomized to receive 7-day (twice daily) injections of saline or escalating doses of morphine (20-100 mg/kg/day, i.p.). Following a 7-day withdrawal period, open field exploration test, elevated plus maze, and pre-pulse inhibition were performed on three succeeding days. During the dosing and withdrawal period, morphine administration resulted in a significant decrease in % body weight change in both OP and OR mice. Following the 7-days withdrawal period, open field exploration test revealed a greater number of line crossings in morphine-treated OR mice in comparison to saline-treated OR mice (p<0.05). No effects were observed in elevated plus maze. Morphine-treated OP mice displayed attenuated pre-pulse inhibition. With a 74 dB pre-pulse intensity, morphine-treated OP mice exhibited lower % pre-pulse inhibition in comparison to morphine-treated OR mice (p<0.05). In response to 90 dB pre-pulse intensity, % pre-pulse inhibition exhibited by morphine-treated OP mice were lower than that of saline controls and morphine-treated OR mice (p<0.05). Individual differences culminating in the spectrum of lean and obese phenotypes may contribute to differences in morphine withdrawal.

The project was supported by NJ06180 from the National Institute of Food and Agriculture of the U.S. Department of Agriculture.

Poster #14
Gαq sensitizes TRPM8 to inhibition by PI(4,5)P2 depletion upon receptor activation

Authors:
Luyu Liu, Yevgen Yudin, Chifei Kang, Natalia Shirokova, Tibor Rohacs

PI Name: Tibor Rohacs

Activation of G-protein coupled receptors (GPCRs) was proposed to inhibit the cold and menthol sensitive Transient Receptor Potential Melastatin 8 (TRPM8) channels via direct binding of Gαq to the channel. It is well documented that TRPM8 requires the plasma membrane phospholipid phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2 or PIP2] for activity. It was claimed however that a decrease in cellular levels of this lipid does not contribute to channel inhibition upon receptor activation. Here we show that supplementing the whole cell patch pipette with PI(4,5)P2 reduced inhibition of TRPM8 by activation of Gαq-coupled receptors in mouse dorsal root ganglion (DRG) neurons. Activation of the same receptors induced Phospholipase C (PLC) activation and decreased plasma membrane PI(4,5)P2 levels in these neurons. PI(4,5)P2 also reduced inhibition of TRPM8 by activation of heterologously expressed Gqq-coupled muscarinic M1 receptors. Co-expression of a constitutively active Gαq protein that does not couple to PLC inhibited TRPM8 activity, and in cells expressing this protein decreasing PI(4,5)P2 levels using a voltage sensitive 5’-phosphatase induced a stronger inhibition of TRPM8 activity than in control cells. Our data indicate that PI(4,5)P2 depletion plays an important role in TRPM8 inhibition upon GPCR activation, and Gαq inhibits the channel by reducing its apparent affinity for PI(4,5)P2 and thus sensitizes the channel to inhibition by decreasing PI(4,5)P2 levels.

Supported by NS055159 & GM093290 (TR) and HL141170 (NS)
**Poster #15**  
Pro-inflammatory Cytokine Modulation Following Chronic Fentanyl Self-administration in Rats  

**Authors**  
Angela Dao, Alexander Kusnecov, Mark West  

**PI Name:** Mark West  

Opiate abuse is associated with an increased prevalence of blood borne viruses and opportunistic infections due to specific immunomodulatory effects of opioid drugs that can influence this susceptibility in a dose-dependent manner. Fentanyl, a synthetic opioid painkiller 50-200 times more potent than morphine, is a μ-opioid receptor (MOR) agonist and known to have strong immunosuppressive effects, specifically inhibiting cells of the innate immune system and pro-inflammatory cytokine production as well as impairing a successful immune response. In a rat model, we will examine the effects of voluntary chronic, long-access fentanyl self-administration (SA) on in vivo cytokine production and immunomodulation in response to the endotoxin lipopolysaccharide (LPS). The specific cytokines of interest are IL-1β, TNF-α, and IL-6, which are the most prominent neuromodulatory cytokines associated with inflammation. LPS readily induces a vigorous, full-scale systemic inflammatory response resulting in increased expression of these pro-inflammatory cytokines in control rats. Preliminary results indicate that this response is suppressed during withdrawal from fentanyl SA. The results of this study may show for the first time that chronic fentanyl SA significantly suppresses the in vivo cytokine response to endotoxin challenge with possible implication for opiate relapse.

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**Poster #16**  
The Function of TSC in CNS Myelination  

**Authors**  
Angelina V. Evangelou, Jennifer N. Bourne, Wendy B. Macklin & Teresa L. Wood  

**PI Name:** Teresa L. Wood  

A number of investigators in the field of myelin biology have provided evidence that the mechanistic target of rapamycin (mTOR) has an important role in oligodendrocyte development and CNS myelination. The Wood laboratory previously demonstrated that deleting mTOR from the oligodendrocyte lineage leads to hypomyelination in the spinal cord (Wahl et al., 2014). In contrast, other groups have upregulated the mTOR pathway in the oligodendrocyte lineage by deleting Tuberous Sclerosis Complex (TSC), the negative upstream regulator of mTOR. Surprisingly, these studies showed that mice with constitutive activation of the mTOR pathway display a hypomyelination phenotype, instead of hypermyelination as originally predicted (Lebrun-Julien et al., 2014; Carson et al., 2015; Jiang et al., 2016). However, in these prior reports, the deletion of TSC was introduced early in development, during specification or differentiation of the oligodendrocyte cell lineage. Thus, myelination independent of differentiation was not evaluated. The goal of this study is to assess how myelin production is altered when mTOR signaling is upregulated exclusively in the mature oligodendrocyte population, so that the differentiation process remains unperturbed. We have generated an inducible conditional knock-out mouse model for Tsc1 and induced deletion specifically at postnatal day (PND) 7-10, at the peak of oligodendrocyte differentiation. Electron microscopy analysis at PND 25 showed normal myelin thickness indicating no effect of TSC1 loss on developmental myelination. Surprisingly, myelin thickness was decreased at PND 49. Ongoing analyses are designed to define the mechanism underlying this defect in myelin maintenance in Tsc1 cKO spinal cord.

This work is supported by R01 NS082203 & R37 NS082203 awarded to TLW and WBM
Poster #17
Brain Imaging at Rutgers University Molecular Imaging Center (RUMIC)

Authors
Derek Adler (Manager), & Edward Yurkow (Director)

PI Name: Derek Adler

Rutgers University Molecular Imaging Center (RUMIC), Rutgers University Biomedical Research Cores, 41 Gordon Road (Suite D), Livingston Campus, Piscataway NJ

The Rutgers University Molecular Imaging Center (RUMIC), located on the Livingston Campus, provides a non-invasive approach to study various biological and disease models in living systems and ex vivo organs. Our comprehensive imaging modalities for the basic sciences include: MRI, PET/CT, microCT, Optical/X-ray Imaging and High-Resolution Ultrasound Technologies. The facility allows researchers to generate multiple, spatially resolved anatomical, functional, and molecular-level readouts from a single study. Image reconstruction, 3D display and quantitative image analysis are also available. The Center provides animal holding facilities for serial imaging, anesthesia, surgery and veterinary care. In addition to consultation and experimental services, the Center offers periodic training and conducts research to improve existing imaging technologies. Our mission is to empower Rutgers users by promoting independent utilization of the facility and to provide imaging resources to external organizations. Images generated at the Center for various cancer investigators at Rutgers University are highlighted. This poster displays examples of the various brain scans conducted for researchers at Rutgers University.

Poster #18
Brain-on-a-chip for Traumatic Brain Injury Drug Discovery

Authors
Anton Omelchenko, Anil Shriraro, Atul Bhattiprolu, Jeff Zahn, Rene Schloss, Nada Boustany, Martin Yarmush, and Bonnie L. Firestein

PI Name: Bonnie Firestein

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in the world and there is no treatment available for TBI-induced cell damage in the brain. Diffuse axonal injury (DAI), a common TBI pathology, results from severe axonal strain following primary insult. The requirement for histological analysis makes it difficult to elucidate the etiology and progression of DAI in vivo. Alternatively, in vitro cell culture models of DAI lack the structure, function, and physiology of brain tissue which complicates clinical therapeutics translation. To address these limitations, we developed a microfluidic platform to model DAI in vitro and to evaluate possible therapeutics. Our platform uses microchannels to confine axonal tracts protruding from organotypic brain slices located in separated compartments. Pressurization of a cavity beneath the microchannels is used to induce stretch/strain injury. As mitochondrial dysfunction and calcium overload are involved in axonal injury, we hypothesized that inhibition of mitochondrial fission and of the reverse-mode of the sodium-calcium exchanger via pharmacological treatment with dynasore and SN-6, respectively, may decrease injury pathologies following injury. Our results show that stretch injury significant increases the size and number of focal axonal swellings (FAS). Treatment with 80μM dynasore or 10μM SN-6 before injury prevents increase in size of FAS while treatment with dynasore, but not SN-6, attenuates increased number of FAS. Our platform aims to provide a high-throughput system for screening potential therapeutics for DAI, and to allow for monitoring of axons and axonal subcellular structures before and after stress/strain injury.

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**Poster #19**
Survival of and Altered γ-Secretase Activity in a Psen1<sup>L435F/L435F</sup> Knock-in Rat Model of AD

**Authors**
Marc Tambini and Luciano D'Adamio

**PI Name:** Luciano D'Adamio

Familial forms of AD (FAD) are caused by mutations in Amyloid Precursor Protein (APP), whose processing can result in the formation of amyloid beta (Aβ), or by mutations in Presenilin 1/2 (PSEN1/2), which comprise in part the γ-secretase complex that cleaves Aβ from fragments of APP. Psen1-knockout (Psen1-KO) mice and knock-in (KI) mice with homozygous FAD-associated L435F mutations (Psen1<sup>L/L</sup>) are embryonic and perinatally lethal, precluding a more rigorous examination of the effect of AD-causing Psen1 mutations on neurodegeneration. Given the better suitability of rats as a model organism, with regards to surgical interventions and behavior testing, we generated a rat KI model of the Psen1<sup>L</sup> mutation. We find that, unexpectedly and in contrast to Psen1<sup>L/L</sup> mice, Psen1<sup>L/L</sup> rats survive into adulthood despite loss of γ-secretase activity as measured by cleavage of APP-CTFs. The survival of these rats affords the opportunity to examine the effect of homozygous Psen1 AD mutations on neurodegeneration.

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**Poster #20**
The Selective mGluR Group I Agonist, 2-Chloro-5-hydroxyphenylglycine (CHPG), Enhances BDNF and Myelination in the Cuprizone Model and Improves Clinical Signs in Experimental Autoimmune Encephalomyelitis

**Authors**
Kyle Saitta, Talia Planas, Lauren Lercher, Yangyang Huang, April DeStefano, Althea Stillman, Ashish Patel, W. Geoff McAuliffe, Cheryl Dreyfus

**PI Name:** Cheryl Dreyfus

Previous studies indicated that injection of metabotropic glutamate receptor (mGluR) agonists into the cuprizone-lesioned corpus callosum reverses deficits in myelin proteins through the action of astrocyte-derived BDNF. Recent studies that used the more clinically relevant peripheral injection of the mGluR agonist CHPG determined that reversals in BDNF and myelin protein deficits in the cuprizone model are elicited through Group I mGluRs. Furthermore, 2 weeks of treatment results in elevation of BDNF and myelin proteins as well as a reversal in myelin deficits. When the selective mGluR-5 antagonist MPEP was injected directly into the lesion site prior to peripheral injection of CHPG, elevations in BDNF and myelin proteins induced by CHPG were blocked by MPEP, suggesting that mGluR-5 mediates actions of CHPG and that CHPG injected peripherally acts within the lesion site. To determine if CHPG is effective in a second demyelinating model that includes an immune component, experimental autoimmune encephalomyelitis (EAE) was elicited and CHPG was injected every other day either prior to the appearance of clinical signs of disease or after disease onset. CHPG prevented disease progression, reversed clinical signs and increased BDNF and myelin proteins. To determine which cells are responsible for these effects, several cell types were analyzed for the presence of mGluR-5. mGluR-5 co-localizes with astrocytes and rarely co-localizes with microglia. Overall, these data suggest that CHPG is effective in two mouse models of demyelination and may be a therapeutic approach for demyelinating diseases.

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**Poster #21**

Regulation of Piezo2 Currents by Gi-protein Coupled Receptors

**Authors**

John S Del Rosario, Tibor Rohacs

**PI Name:** Tibor Rohacs

Mechanotransduction is a critical biological process for organisms to discriminate between environmental cues. However, little is known about the molecular and cellular components that contribute to its regulation. Piezo2 channels have been identified as key channels responsible for mechanosensation. These channels are expressed in Dorsal Root Ganglion (DRG) neurons and genetic mutations in these channels have been shown to impair physiological processes such as light touch, proprioception and balance in humans and mice. Activation of the Gq-coupled bradykinin beta 2 receptor (BDKRB2) have been shown to enhance Piezo2 currents, involving a PKC and cAMP-dependent mechanism. However, whether Gi-coupled receptors in DRG neurons play a role in the regulation of Piezo2 channels is still unexplored. Electrophysiological experiments in our lab show that activation Gi-protein coupled receptors potentiate Piezo2 currents in DRG neurons and heterologous systems. This potentiation is inhibited by blocking Gβγ using the C-terminal domain of beta adrenergic kinase (βARKct). In addition, inhibition of Gβγ-downstream kinases such as mitogen-activated protein kinase (MAPK) or phosphoinositide 3-kinase (PI3K) also abolish the potentiation of Piezo2 currents by Gi-protein coupled receptors implying an indirect effect of Gβγ on Piezo2 channels. Furthermore, behavioral experiments to assess touch sensitivity show that activation of the Gi-coupled GABA_B receptors enhances mechanosensitivity in female mice, but not in male mice thus suggesting a sexual dimorphism in mice mechanosensitivity. We aim to investigate GPCR signaling in the regulation of mechanoreceptors and dissect specific molecules and proteins that can potentially serve as a basis for the development of new drug targets for the treatment of mechanical-pain.

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**Poster #22**

Cellular Deficits in a Combined Model of Blast and Blunt Traumatic Brain Injury

**Authors**

Aswati Aravind, Julianna Kosty, Venkata Kakulavarapu, Maciej Skotak, Eren Alay, Namas Chandra, Bryan Pfister

**PI Name:** Bryan Pfister

Traumatic Brain injury (TBI) in military personnel occur both due to exposure to blast overpressure waves and focal blunt impacts during falls or motor vehicle accidents. While blast waves cause a diffuse pressure loading to the brain, a blunt impact is more focal to the site of impact. This difference in loading is, however, not taken into consideration when reporting clinical outcome. While single and repetitive models of blast or blunt are currently under investigation, a combination of blast and blunt impact has yet to characterized. Our hypothesis is that a blast exposure, while not necessarily leading to a diagnosable injury, will predispose the brain to greater injury upon a second blunt impact to the head. Here, we present a model of combined blast and blunt impact and a comparison of the neuronal loss caused by the single and combined impacts. Neurondegeneration was observed in the ipsilateral hippocampal regions of blunt and combined impact animals while no neurdeneration was observed in the blast and sham animals. Neuronal counts for the degenerated hilar neurons indicated significantly higher neurodegeneration (p<0.05) in the combined impact animals when compared to shams or single impact animals. A preliminary study with n=2 for neuronal survival at a long term time point of 34 days post impact showed a decrease in neuronal survival in both the single and combined impact animals with increased neuronal loss in the combined impact cohort. Thus, the blast impact seems to condition the brain to increased neuronal deficits on a subsequent blunt impact.

*This work was supported by the New Jersey Commission on Brain Injury Research grant CBIR16PIL021.*
**Poster #23**

Microglia/macrophage Pannexin-1 channels promote neuroinflammation and blood brain barrier leakage after traumatic brain injury.

**Authors**
Joon Ho Seo, Miloni Dalal, Frances Calderon, Jorge Contreras

**PI Name:** Jorge Contreras

Neuroinflammation is a major component of secondary damage after brain injury. Activation of inflammatory cells at the injury site causes release of pro-inflammatory cytokines and chemokines, which mediate recruitment of microglia and leukocytes to the injury site. ATP release during the secondary injury has been shown to be pro-inflammatory. Recently, Pannexin-1 (Panx1) channel proteins have been identified as an important conduit for ATP release. Our previous work has shown that pharmacological inhibition of Panx1 channels promotes tissue protection and reduces inflammation at the site of injury using controlled cortical impact (CCI) model of TBI. While it is evident that Panx1 channels drive propagation of inflammation, the cell types responsible for the Panx1 signaling that leads to enhanced of brain vascular permeability and infiltration of immune cells after brain injury are unknown. Because it has been shown that ATP release and migration of microglia are mediated by Panx1 channels in vitro, we generated conditional knockout mice to examine the potential actions of microglial/monocyte Panx1 after CCI. In this study, we report that cell specific deletion of Panx1 reduces expression of pro-inflammatory cytokines and immune cell infiltration after CCI. Additionally, using MRI and western blot, we show that microglial Panx1 promote tissue damage and blood brain barrier leakage at the injury site. Finally, we show that the conditional knockout mice show improved motor function after CCI. Collectively, these data indicate that targeting Panx1 channels in microglia may serve as an effective therapeutic approach to reduce brain damage and improve outcome after TBI.

**Poster #24**

Tet dioxygenase regulates neural development by modifying mRNA ribocytosine

**Authors**
Hiep Tran, Badri Nath Singh, Neha Changela, Ethan Chiang, Joe Kramer, Ruth Steward

**PI Name:** Ruth Steward

The Tet enzyme converts 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) in DNA resulting in C demethylation, thereby regulating gene expression. Recent work in our lab showed that Tet can also regulate the 5-hydroxymethylribocytosine (5hmrC) mark in RNA, especially in mRNAs of neuronal genes. We found that loss of Tet causes abnormal axon patterns in the optic lobes. Also, a CRISPR-induced C598A mutation in the Tet DNA binding domain showed a specific brain phenotype, loss of the alpha lobes in the mushroom body, a structure in the fruit fly brain responsible for learning and memory. We have identified potential Tet target genes which function in mushroom body development and axon guidance. Further study of these genes will help us elucidate how Tet regulates neural development through modifying ribocytosine in neuronal mRNAs. Our work addresses the question of how genes required in neural development are regulated through an epitranscriptomic mechanism.

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**Poster #25**  
Novel ROCK inhibitor reduces rod axon retraction during retinal detachment

**Authors**  
Éva Halász, Ilene Sugino, Marco A. Zarbin, Ellen Townes-Anderson

**PI Name:** Ellen Townes-Anderson

Retinal detachment causes retraction of rod photoreceptor axons from the outer plexiform layer (OPL), resulting in synaptic disjunction. Our previous work demonstrated that activation of RhoA-ROCK signaling plays a pivotal role in axon retraction. Inhibition of this pathway using Rho kinase (ROCK) inhibitors decreased synaptic disruption; however, the required dosages were high. Here we test whether AR-13503, a more potent ROCK inhibitor, recently FDA-approved, can prevent synaptic breakage. Retinal detachments were made in pigs by subretinal injection of balanced salt solution (BSS). One eye was treated with drug and the other served as control. Two hours after detachment eyes were harvested and fixed for histological examination by immunocytochemistry and confocal microscopy. Labeled synaptic vesicles (SV2) normally localize in the OPL. After detachment labeling occurs also in the outer nuclear layer (ONL) indicating axon retraction. Retraction was quantified by image analysis of SV2 labeling in the ONL and analyzed by a paired t-test. Subretinal injection of AR-13503 (0.5 µM) reduced synaptic breakage by 63.7% compared to untreated detachments (n=3 pigs, p<0.001). With an intravitreal injection of AR-13503, a more clinically relevant procedure, there was a 40.2 % decrease in retraction between the detached areas (n=3 pigs, p=0.029). AR-13503 decreased rod-bipolar synaptic disjunction after retinal detachment at more than a thousand-times lower concentration than previously tested ROCK inhibitors. In addition to its potency, this drug has a longer half-life and greater specificity, and therefore is a better candidate for therapeutic procedures to reduce synaptic disjunction after retinal detachment.

Supported by NIH Grant EY021542, Aerie Pharmaceuticals

**Poster #26**  
Cerebral Hemorrhage Initiated Perivascular Inflammation and Neurodegeneration in Fluid Percussion Animal Model

**Authors**  
Xiaotang Ma

**PI Name:** James Haorah

Traumatic brain injury (TBI) is a major health problem for over 3.17 million people in the US, attracting increasing public attentions. Understanding the underlying mechanism of TBI is becoming urgent to better diagnose and treat the disease. Using the fluid percussion injury rat model, we investigated the footprint of neuroinflammation and neurodegeneration in the present studies. We observed an increase hemorrhagic lesions and infarct volume in the injured brain with increment of pressure. To correlate this extent of injury, we examined the bio-distribution of fluorescent tracer (FITCl=d2000) after post-injury injection of the tracer through intracisterna magna. Surprisingly, the bio-distribution of the tracer was specifically diminished at the site of injury compared with non-injured side or the sham controls, suggesting that coagulation at the hemorrhagic site could have blocked the movement of the tracer. Immunohistochemical observation of coagulation factor XII expression and necrotic cell death in and around the impact site confirmed the blockade of the tracer bio-distribution at the injured side of the brain. Different biomarkers, including tight junction proteins, immune cells accumulation and neuronal death demonstrated blood brain barrier disruption, neuroinflammation and neurodegeneration surrounding impact site. Altogether, these results suggest that instant focal hemorrhagic injury resulting from rupturing the brain vessels causes onsite perivascular inflammation and neurodegeneration due to thrombosis. Understanding the multiple processes occurring after TBI is crucial to develop neuroprotective and regenerative therapeutics to ameliorate the short and long-term consequences of TBI.
Poster #27
The penta-EF hand protein PDCD6 interacts with cell adhesion molecule CHL1 depending on Ca^{2+}

Authors
Helen Baixia Hao, Thomas Theis, Gabriele Loers, Sanjana Arsha, Jeeyong Shin, Wise Young and Melitta Schachner

Pl Name: Wise Young and Melitta Schachner

The close homolog of L1 (CHL1) is a member of the L1 family of cell adhesion molecules (CAMs). The protein is expressed predominantly in various kinds of neurons and to a lesser degree in glial cells in vivo. CHL1 has been implicated in the nervous system development and synaptic plasticity. It also promotes elongation of neurites and survival of neurons in vitro. Here, we identified programmed cell death protein 6 (PDCD6) as a novel binding partner of CHL1 intracellular domain (ICD). Co-immunoprecipitation with the lysate of 3-day-old mouse brain or primary cultured cerebellar granule cells suggest an association of PDCD6 with CHL1. Pull-down assay with purified His-CHL1-ICD also showed the interaction between PDCD6 and CHL1-ICD in vitro. As PDCD6 is a calcium-binding protein belonging to the penta-EF hand protein family, our results also suggest that the association of these two proteins is Ca^{2+} dependent. In addition, CHL1 and PDCD6 showed nice co-localization in the cerebellum and brain stem of 3-day-old and 6-month-old mouse brains. The interaction of CHL1 and PDCD6 was further demonstrated by proximity ligation assay in the cerebellum and brain stem at these two development stages. The co-localization and the signal of proximity ligation assay was also observed in cultured cerebellar granule cells. Our present study demonstrates that PDCD6 binds to CHL1-ICD depending on Ca^{2+}. The function of their interaction in the survival and neurite outgrowth of cerebellar granule cells will be investigated in future studies.

Supported by The Li Ka Shing Foundation (to M.S.) at Shantou University Medical College

Poster #28
Astroglial TFEB as a regulator of protein homeostasis in the brain

Authors
Henri Antikainen, Haesun Kim, Radek Dobrowolski

Pl Name: Radek Dobrowolski

Transcription factor EB (TFEB) is a central regulator of lysosomal biogenesis and autophagy that responds to nutrient signaling and cellular stress. We have previously described an Alzheimer’s disease-like phenotype with neuronal death and aggregating toxic proteins such as beta-amyloid and phospho-tau in TFEB fl/fl-nestin cre mice, which lack TFEB in neuronal progenitor cells. In this mouse line, three different mature cell lineages are affected by the genetic manipulation: neurons, oligodendrocytes and astrocytes. In the current study, we are examining the effects of TFEB loss in each of these cell types and their contributions to the disease-like phenotype. Oligodendrocytes do not appear to be affected by the loss of TFEB, as seen by their retained myelination capability in TFEB fl/fl-nestin cre mice. Astrocytes are more reactive in TFEB fl/fl-nestin cre in the corpus callosum, striatum and cortical layers. In these regions, also microglia exhibit increased reactivity, despite not being directly affected by the genetic manipulation. The microglia could be triggered by stimuli in the environment caused by the loss of TFEB, or by altered astroglia-to-microglia signaling. We will use astrocyte-specific TFEB knockout mice and knockdown primary cell culture to address whether the loss of TFEB increases astrocyte reactivity and pro-inflammatory signaling directly, and to assess what the contribution of TFEB loss in astrocytes is to the disease-like phenotype in the brain.
Poster #29
VPA exposure at postnatal day 7 results in abnormalities in behavior and dendritic morphology

Authors

PL Name: Alexander Kusnecov
Valproic acid (VPA) is a GABAergic anticonvulsant, and if taken during pregnancy may increase the risk of autism in offspring. In animal models, prenatal VPA exposure results in postnatal behavioral and anatomical deficits similar to human autism. However, few studies have examined the effect of VPA during the first week of postnatal development, which is roughly analogous to the third trimester in humans in terms of brain development. In the present study, mice were administered 300 mg/kg of VPA at postnatal day 7 (P7). Mouse pups displayed deficits in surface righting, a test of motor development, 24 hours after VPA treatment, with partial recovery 48 hours after VPA treatment. Furthermore, mice treated at P7 with VPA showed dendritic spine abnormalities at postnatal day 30 (P30) in both the prefrontal cortex and primary auditory cortex. Lastly, there were no differences in the elevated plus maze test between VPA- and saline-treated mice. As both developmental delays and dendritic spine abnormalities have been associated with autism in humans, P7 treatment with VPA may be a viable animal model of autism. However, further tests need to be conducted to determine if the behavioral profile caused by early postnatal VPA-treatment aligns with symptoms of autism.

Poster #30
Effects of Small Compounds on Structure of Amyloid-β_{1-42} Monomer

Authors
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PL Name: Cristiano Dias
Alzheimer’s disease is associated with fibrillar deposits of Amyloid-β, an intrinsically disordered peptide. Molecular structure and aggregation rate of Aβ are observed to be significantly dependent on the properties of its aqueous environment. For example, NaCl is shown to accelerate Aβ fibril formation whereas 4-Aminophenol (4AP) and Inositol have been shown to reduce its aggregation rate. Despite many studies to investigate the effects of small molecules on aggregation of Aβ, its atomic interactions with small molecules which mediate various structures and behavior of this peptide, are not well understood. To investigate Aβ molecular structures and to understand how Aβ properties are affected by compounds, we performed extensive Replica Exchange Molecular Dynamics (REMD) simulations on Aβ_{1-42} monomer with explicit solvent and small molecules. Our research reveals that each molecule affects different regions of Aβ_{1-42} and the peptide adopts distinguished structures compared to control system. Specifically, we observe that NaCl increases contact among residues K16-E22 and V38-I41, 4AP increases K16-E22 and N27-G37 contacts and Inositol mainly disrupts the intrapeptide contacts. Effects of compounds on structural and physical properties of Aβ_{1-42} monomer will also be discussed.
Poster #31
Helium-ion microscopy imaging of formalin-fixed uncoated samples of brain and nerve tissue

Authors
Hussein Hijazi, Mengjun Li, Antonio Merolli, Joachim Kohn, Leonard Feldman, Torgny Gustafsson

Pl Name: Leonard Feldman

Scanning Helium-ion Microscopy (HIM) uses impinging helium ions instead of electrons as in a conventional Scanning Electron Microscopy (SEM). In HIM, the ion emission originates via field ionization from a tungsten (W) tip and is adjusted to correspond to emission from a single W atom. The extracted ions are accelerated down the column of the microscope in the same fashion as in SEM. However, the high resolution and high depth of field is related to a combination of a small beam (~ 0.5 nm), the high brightness, the small opening angle and the ion-beam materials interaction. The secondary electron yield is much higher than in SEM, giving the images a better signal-to-noise ratio. More importantly, there is no need for metal coating of the samples; this enables the direct investigation of delicate surface features that may be obscured by the metal coating required in SEM. We have started imaging samples of brain and sciatic nerve explanted from rat and rabbit. Tissue were retrieved without perfusion and fixed in Formalin. Samples should be ideally prepared in thick sections shaped like cubes of 1 mm side but larger samples can be acquired to be placed in circular holder of 20 mm in diameter. Dehydration in a graded ethanol series is performed prior to placing under vacuum overnight. Myelinated fibers in the white matter and in the sciatic nerve show the more physiological appearance of the myelin sheath as a swollen wrap around the axon. Round oligodendrocyte cell body morphology in the brain is well preserved.

Poster #32
Multilayer Implantable Intracortical Microelectrode Probe to Improve Recording Potential

Authors
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Pl Name: Jeffrey D. Zahn

Brain–computer interfaces (BCIs) can be used to help patients with paralysis to restore some movement functions by recording movement-related neural signals, and then decoding them to control signals to drive external prosthetic devices. Extracting neural activities of high quality from the brain is crucial in the functioning of BCIs. Of all recording approaches, intracortical neural probes have been identified as having the highest signal to noise ratio (SNR) and spatial resolution to encode fine motor intent. However, due to its invasiveness, this approach suffers from chronic instability, as the tissue inflammation around the implantation site tends to induce an immune cascade and subsequent gliosis, which eventually isolates the implanted probe from nearby neurons, leading to degradation of the recorded signal quality. The hypothesis that smaller, more compliant probes produce less damage to brain tissue and thus elicit a weaker reactive tissue response has propelled researchers to utilize softer polymer materials as probe substrates while attempting to scale down the probe footprint. However, small footprints of the probe shank limit the number of recording channels that can be supported by each probe shank, if the conventional approach of patterning all electrodes on a single layer is adopted. As such, the probes might be unsuitable for human prosthetic use. We present a novel strategy of scaling up the number of recording sites without proportionally increasing the size, specifically the width of the probe, by layering recording electrodes vertically on multilaminate Parylene support layers.

This work is supported by New Jersey Commission on Spinal Cord Research Award #CSCR12IRG001 and Award #CSC16IRG007.
Poster #33
The role of p75NTR in inducing axonal degeneration after injury

Authors
Laura E. Montroull and Wilma J. Friedman

PI Name: Wilma J. Friedman

Expression of p75NTR is induced in numerous Central Nervous System (CNS) neurons after damage in the adult brain and has been shown to regulate neuronal cell death in several injury models. While the neuropathological consequences of TBI are heterogeneous, diffuse axonal injury is ubiquitous at all severity levels, leading to deficits in connectivity that may or may not recover over time. p75NTR has been widely studied in the Peripheral Nervous System in various injury and cell-death paradigms, as well as in developmental axonal pruning and degeneration. However, the role of this receptor in mediating axonal degeneration after TBI remains unclear. To determine the role of p75NTR in this process we performed in vivo and in vitro experiments. We subjected adult mice to mild traumatic injury using lateral fluid percussion brain (LFP) injury model. We found that one day after LFP, p75NTR is upregulated in axons and this increase is maintained 3 days after the injury. The co-localization of p75NTR with βAPP, suggests that those axons are degenerating. To understand the mechanisms of p75NTR in mediating axonal degeneration, we are using a variety of in vitro approaches including an in vitro model of axonal stretch injury to examine axon-specific signaling mechanisms.

This work was funded by the New Jersey Commission for Brain Injury Research

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Poster #34
p75NTR regulates proliferation of neural stem cells in the SVZ of the developing rat brain

Authors
Subhashini Joshi and Wilma J. Friedman

PI Name: Wilma J. Friedman

During development, a small population of subventricular zone (SVZ) neural stem cells (NSC) express the common neurotrophin receptor p75NTR. In this study we show that p75NTR is expressed in Nestin positive, proliferating NSCs throughout postnatal development of rats. The aim of this project is to determine the role of p75NTR in SVZ NSCs in the developing brain. Immunostaining for p75NTR shows a distinct localization of cells to the dorsolateral part of the SVZ extending into the Rostral Migratory Stream (RMS) towards the olfactory bulb. Studies in adult mice report p75NTR to be required for migration of cells from the SVZ to the olfactory bulb via the RMS, however, in developing rats p75NTR cells colocalize with markers of proliferation (Ki67) in both the SVZ and the RMS and not markers of migration (DCX). Additionally, an enriched population of p75NTR cells isolated from the SVZ of WT rats forms larger neurospheres in vitro compared to cells obtained from KO animals. These results indicate that p75NTR is regulating proliferation of NSCs during development. Further studies will aim at determining the molecular mechanisms involved in the regulation of this population of cells.
Poster #35
Modulation of PP2A Methylation and Activity by Oxidative Stress

Authors
Hye-Jin Park, S. Zhang, K. L. Huber, R. Yan, Jie Zhang, M. Grudniewska, I. Jung, J. B. Stock, M M Mouradian

PI Name: M M Mouradian

The formation of pathologic aggregates of hyperphosphorylated, misfolded a-synuclein and tau is a common feature in a-synucleinopathies and tauopathies, respectively. Our recent postmortem brain studies of Parkinson’s disease, Dementia with Lewy Bodies, Alzheimer’s disease and Progressive Supranuclear Palsy revealed that dysregulation of the phosphatase that dephosphorylates these two proteins, protein phosphatase 2A (PP2A), is a common feature among these disorders. The PP2A isoform that dephosphorylates a-synuclein and tau is B55alpha containing, and its assembly and activity are tightly regulated by reversible carboxyl methylation of the C subunit. In a-synucleinopathies and tauopathies, we found an imbalance in the expression levels of the two PP2A modulating enzymes that control its methylation, namely leucine carboxyl methyltransferase (LMCT-1) and protein phosphatase methylesterase (PME-1), creating conditions that favor inactivation of PP2A. However, the mechanism underlying dysregulation of PP2A methylation and its decreased activity in neurodegenerative diseases is not fully understood. Another common feature among these disorders is oxidative stress. Therefore, here we sought to address whether oxidative stress contributes to the altered state of PP2A methylation and the expression of its methylation modulating enzymes. Challenging human neuroblastoma SH-SY5Y cells with hydrogen peroxide resulted in significant changes in the expression levels of both LCMT-1 and PME-1, associated with demethylation of PP2A. Through changes in the methylation status of PP2A, its activity is also significantly reduced under conditions of oxidative stress. These findings support a role for oxidative stress in modulating PP2A activity, and consequently, the accumulation of hyperphosphorylated protein aggregates in neurodegenerative diseases.

Poster #36
Ethanol Withdrawal Drives Depression-Like Behaviors by Activating Neurons in the Rostromedial Tegmental Nucleus

Authors
Rao Fu, Wanhong Zuo, Nimisha Shiwalkar, Xuejun Chen, Alex Bekker, Jiang-Hong Ye

PI Name: Jiang-Hong Ye

Rostromedial tegmental nucleus (RMTg) GABA neurons exert a primary inhibitory drive onto midbrain dopamine neurons. RMTg is excited by a variety of aversive stimuli. We investigated whether the RMTg-ventral tegmental area (VTA) circuit participates in the aversive consequence of ethanol withdrawal. Experiments were performed in adult male Long-Evans rats at 48-hour withdrawal from chronic (12 weeks) ethanol drinking in the intermittent schedule. These rats displayed a clear anhedonia and depression-like behavior measured with the sucrose preference test and forced swimming test. This aberrant behavior was accompanied by a substantial increase in cFos expression in the RMTg neurons that project to the VTA identified by the combination of immunohistochemistry and retrograde tracing techniques. Ex vivo electrophysiological data showed that chemogenetic inactivation of RMTg neurons reduced GABA release to, and accelerated the spontaneous firings of putative dopamine neurons in the VTA. Additional studies showed that the anhedonia and depression-like behavior was mitigated by pharmacological or chemogenetic inhibition of RMTg neurons. Using functional contralateral disconnection procedure, we further showed that the depression-like behaviors were rescued by unilateral RMTg inactivation combined with activation of contralateral but not ipsilateral nucleus accumbens (Acb) shell D1 and D2 receptors, indicating the integrity of RMTg-VTA-Acb pathway in one hemisphere is sufficient to elicit the depression-like behavior during ethanol-withdrawal. Overall, the present results reveal a key role for RMTg projection to the VTA in the depression-like behavior in animals withdrawn from chronic ethanol administration and suggest that the RMTg could be a potential therapeutic target for alcoholics.

Supported by NIH grants AA021657 and AA022292.
**Poster #37**

Dissecting the specificity of Semaphorin 3A-PlexinA4 signaling that controls cortical dendrite elaboration and axon guidance events *in vivo*.

**Authors**

Victor Danelon, Ron Goldner, Edward Martinez, Irena Gokhman, Kimberly Wang Avraham Yaron, Tracy S. Tran.

**PI Name:** Tracy S. Tran

The proper wiring of the nervous system during development is regulated by extracellular cues and their ability to induce diverse cellular responses through activation of receptors on the surface of developing neurons. Semaphorin (Sema)3A signaling through the Neuropilin-1/Plexin (Plxn)A4 receptor complex had been demonstrated to promote basal dendrite arborization of cortical pyramidal neurons, and PNS axons both in vitro and in vivo. How the same ligand-receptor pair achieved these distinct cellular processes are largely unknown. We previously suggested that diverse responses elicited by Sema3A signaling could be found at the receptor level, within the cytoplasmic domains of PlxnA4. Here we generated a new PlxnA4 mouse line where the conserved triplet basic amino acids KRK, in the cytoplasmic domain of the receptor, were changed to AAA. We found that this KRK-motif is required for Sema3A induced dendritic elaboration of cortical neurons both in vitro and in vivo. In contrast this motif is dispensable for growth cone collapse and axon repulsion of DRG sensory neurons and the formation of the anterior commissure, which is absent in the PlxnA4 null mutants. Furthermore, we show that the RhoGEF Farp2, which we demonstrated to bind the KRK motif of PlexinA4, is also required for dendritic arborization but not for inhibitory axon guidance events. Moreover, the downstream target of Farp2, Rac1 GTPase, is required for Sema3A-induced dendrite elaboration. Collectively, results from our study provide new insights on the mechanisms that allow the same ligand-receptor pair signaling to trigger distinct cellular responses in different neuronal cell types.

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**Poster #38**

Innovative drugs to modulate drug clearance from the brain via cerebrospinal fluid pathways

**Authors**

M. Dessi, C.M. Wood, J.C.Sy

**PI Name:** Jay C. Sy

A localized delivery of therapeutics into the brain is a unique challenge in the treatment of brain cancers and neural diseases. Drug exposure in the brain is affected by the continuous circulation and efflux of Cerebrospinal Fluid (CSF) secreted at the choroid plexus. In this study, we hypothesize that the ability to modulate the CSF production can affect the local drug exposure and distribution profile in the brain. In order to efficiently test this hypothesis, we use two drugs as potential CSF-modulatory agents that could change the pharmacokinetics of small molecule tracers in the brain. Our findings highlight the ability of the drugs to locally tailor the CSF dynamics and control the drug delivery into the brain. These results foster the development of an in vitro model to screen CSF modulating drugs in order to identify more effective therapeutics and decrease the gap between the in vitro and vivo models.

The results pave the way for the possible use of ACZ and VRPL as CSF-modulatory agents, providing insights on the design of novel therapeutic strategies to tailor the CSF clearance in the treatments of brain pathologies.

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Poster #39
Cryo-electron Tomography Reveals Structural Morphology of Transmissive PolyQ Species and Their Critical Interactions with Extracellular Vesicles

Authors
Xuyuan Kuang, Paul Castellano, Uttara Hardikar, Jennifer Jiang, Zhiyong Bai, Zik Tan, Wei Dai

PI Name: Wei Dai

Huntington’s Disease (HD) and eight other human neurodegenerative diseases are associated with proteins containing expanded polyglutamine (polyQ) sequences, affecting ~200,000 individuals in the United States. These inherited disorders, nearly all of which are invariably fatal, share similar polyQ-associated pathologies involving protein misfolding and aggregation. During disease progression, polyQ aggregates can spread from affected cells to their neighbors, where they act as template to recruit homotypic proteins into aggregates leading to cell death throughout the central nervous system. We recently demonstrated that both synthetic polyQ40 peptides and cerebrospinal fluid (CSF) from HD patients can induce protein aggregation in cells. HD patient CSF exhibits a ~105-fold higher seeding efficiency versus synthetic polyQ40 peptides. This finding suggested that seeding activity depends on the presence of polyQ-sequences but is modulated by factors present in biofluids or the extracellular matrix. Moreover, comparably high seeding efficiency has been observed in conditioned medium from PC12 cells expressing expanded polyQ tract mHTT proteins. Correlative light and electron microscopy and cryo-electron tomography revealed interaction of polyQ oligomers with extracellular vesicles (EVs) in the conditioned medium. Based on functional studies that showed polyQ seeds combined with preformed liposomes dramatically increased seeding efficiency, we concluded that cell-derived EVs directly complex with polyQ seeds and thereby potentiate polyQ seeding by coupling polyQ entry with physiologic membrane traffic events. Given the well-documented role of EVs in cell-to-cell communication, we believe that understanding their role in polyQ disease pathogenesis may ultimately lead to identification of potential new targets for polyQ disease intervention.

Supported by Busch Biomedical Grant

Poster #40
Decisions about time localized to circuits within temporal and prefrontal cortices

Authors
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PI Name: Tracey J. Shors, Laleh Najafizadeh

We are constantly estimating time in our everyday lives but neuroscientists know very little about the neural mechanisms through which the brain estimates time – and where in the brain they occur. In this study, we identified neural activity in select cortical regions which may predict characteristics of subjective time estimation. Participants (n=10; 3 repeated) completed a modified temporal bisection task during which they were presented with one of two visual stimuli on a computer screen. Participants were asked to decide whether the stimulus was short (400 ms) or long (1600 ms) by pressing a keyboard button. EEG recordings were analyzed using i) temporal segmentation to detect state transitions in the brain, ii) functional connectivity analysis to spatially locate functional networks on the cortex, and iii) temporarily-informed Boolean matrix factorization, which allowed us to recognize regions of these networks that are most involved in time estimation. We found that these regions are located predominantly in the temporal or frontal lobes (and in the right hemisphere) compared to the parietal or occipital lobes. Moreover, time-locked activity was most evident around the geometric mean, about 800 ms. The time-locked activity at the geometric mean is particularly intriguing given this activity is not an obvious response to the stimuli or the behavior and thus must reflect some internal calculation of time. These data identify a putative cortical circuit within the temporal and frontal cortices engaged in temporal decision making, along with a potential marker of internal calculations used in those decisions.

Supported by Brain Health Institute, Rutgers University
Poster #41
Leukemia Inhibitory Factor Deficiency Dis-inhibits Progenitor Cell Proliferation Following TBI

Authors
Michelle Frondelli, and Steven W. Levison

PI Name: Steven W. Levison

Traumatic brain injury is a significant problem that affects about 500,000 children each year. As cell proliferation is required for brain development, we investigated how a head injury would affect the progenitors of the subventricular zone (SVZ) and subgranular zone (SGZ). Leukemia inhibitory factor (LIF) is a required component of the neural stem cell niche and is an injury-induced cytokine that influences neurogenesis and gliogenesis. Therefore, we evaluated proliferative responses of SVZ and SGZ progenitors during recovery from a closed head injury (CHI) in wild type (WT) and LIF haplodeficient (LIF-H) mice. CHI’s were performed on postnatal day 20 males and female mice. Stereological counting methods were used to quantify the numbers of Ki67+ cells in the SVZ and SGZ and sections were immunolabeled for glutathione S-transferase-mu (GST-mu) as an index of astrocyte development and Olig2 for oligodendrocyte development. Ki-67 staining revealed ~60% increase in proliferating cells in the SVZ with little change in the SGZ at 48h of recovery in the WT animals relative to sham. By contrast there was a ~350% increase in Ki-67+ cells in the SVZ and a ~15% decrease in proliferating cells in the SGZ in the injured LIF-H mice, relative to sham. Minimal overlap of Olig2/Ki-67 staining suggests that newly generated cells post injury, are not oligodendrocytes. The increased numbers of GST-mu+ SVZ cells in the injured WT mice suggests that more astrocytes are being produced post injury, whereas fewer are being generated in the LIF-H injured mice. Altogether, these data support the view that when levels of LIF are decreased, there is an expansion of the progenitor population, possibly at the expense of the stem cell population.

This research has been funded by NJ Commission on Brain Injury Research

Poster #42
Elevation of TRPV 1 function in the lateral habenula mediates aversive behaviors in alcohol-withdrawn rats

Authors
Rao Fu, Wanhong Zuo, Nimisha Shiwalkar, Xuejun Chen, Alex Bekker, Jiang-Hong Ye

PI Name: Jiang-Hong Ye

Recent rat studies indicate that alcohol withdrawal can trigger a negative emotional state including anxiety- and depressive-like behaviors and hyperalgesia, as well as elevated glutamatergic transmission and activity in the lateral habenula (LHb) neurons. TRPV1, a vanilloid receptor expressed in the habenula, is involved in pain, alcohol dependence, and glutamatergic transmission. We, therefore, hypothesized that LHb TRPV1 contributes to the changes in both the behavioral phenotypes and the LHb activity in alcohol-withdrawn rats. Adult male Long-Evans rats randomly assigned into the alcohol and water (Naïve) groups, were trained to consume either alcohol or water-only using an intermittent-access two-bottle-choice procedure. Slice electrophysiology was used to measure spontaneous excitatory postsynaptic currents (sEPSCs) and firing of LHb neurons. We found the basal frequency of sEPSCs and firing of LHb neurons at alcohol-withdrawn rats were significantly increased. The TRPV1 antagonist capsazepine (10 µM) induced a stronger inhibition on sEPSCs and firing in Withdrawn rats than Naïve rats. By contrast, the TRPV1 agonist capsaicin (3 µM) produced a weaker potentiation in Withdrawn than Naïve rats. Conversely, capsaicin’s actions in Naïve but not in Withdrawn rats were significantly attenuated by the pretreatment of TRPV1 endogenous agonist N-Oleoyldopamine. In Withdrawn rats, intra-LHb infusion of TRPV1 antagonists attenuated hyperalgesia, and anxiety-like behaviors, decreased alcohol consumption upon resuming drinking and elicited a conditioned place preference. Overall, enhanced TRPV1 function may contribute to increased glutamatergic transmission and activity of LHb neurons, resulting in the aberrant behaviors during ethanol withdrawal.

The work was supported by NIH grants AA021657 and AA022292
Altered resting-state functional connectivity in collegiate athletes with episodic binge drinking

Authors
Nicola de Souza, S. Gohel, J. Buckman, N. Viagas, T. Porfido, & Carrie Esopenko

PI Name: Carrie Esopenko

Collegiate athletes report more occasions of binge drinking (BD) than non-athletes. However, few studies have examined if BD is associated with altered resting-state functional connectivity (rsFC) in collegiate athletes. The objective was to determine if differences in rsFC exist based on BD history in collegiate athletes. Forty-eight collegiate athletes (56% female; age: M = 19.30 years) completed self-report questionnaires assessing the number of BD occasions in the past year. Participants also completed resting-state functional magnetic resonance imaging (rsfMRI) to examine rsFC. RsFC in the salience, default mode (DM), and left and right frontoparietal (LFP, RFP) networks was compared between low-risk users (LRU; n=21), who either did not drink or reported no occasions of binging, and higher-risk users (HRU; n=27), who reported at least one binge episode in the last year. We found increased connectivity between the salience network and the DM, LFP, and RFP networks for HRU relative to LRU. Specifically, the right insula exhibited higher rsFC to posterior regions of these networks. Further, we found reduced connectivity of HRU within the DM and between the DM and RFP networks. These results suggest that alterations in rsFC associated with limited episodes of BD can occur even in healthy collegiate athletes. It is unclear, however, whether these alterations are associated with other factors such as exposure to head trauma and mental health history. As such, future research is needed to examine alterations in rsFC in collegiate athletes with greater variability in BD and account for other factors known to affect rsFC.

This work was supported by SHP Intramural Research Grant

Assessing Long Term Spinal Cord Structure Changes using Diffusion Tensor Imaging in Patients with Incomplete Traumatic Spinal Cord Injury

Authors
Hannah Ovadia, Sarah Wood, Zhiguo Jiang, Gail Forrest, Steven Kirshblum, Bing Yao

PI Name: Bing Yao

The challenges of spinal cord injury (SCI) extend far beyond physical damage; patients face severe disability, difficulty functioning, and expensive treatments. The questionnaires and exams used to measure recovery have several shortcomings, including variability across examiners and difficulty detecting changes. The goal of this study was to test whether nerve fiber structural changes in the spinal cord could be detected using diffusion tensor imaging (DTI).

SCI patients (n=4) and matched controls (n=4) were scanned five times over a six-month period (baseline, 2-week, 1-month, 3-month, and 6-month time points). MRI Images were acquired of the cervical and thoracic spinal cord (C1 – T12). Mean values of fractional anisotropy (FA), axial diffusivity (AD), apparent diffusion coefficient (ADC), and radial diffusivity (RD) were calculated and compared between groups. Patients additionally completed the Spinal Cord Independence Measure (SCIM; a measure of functional ability) at each visit.

Paired T-tests revealed significant differences between SCI patients and their matched controls for all DTI parameters, except RD (p < 0.01). Mean values were lower among patients for each parameter at every time point. SCIM scores additionally improved over time (p < 0.05), with higher scores at the six month period than at baseline (p < 0.05; mean = 81.24 and 69.0, respectively). However, DTI indices did not show significant correlation with SCIM totals.

These findings support the hypothesis that DTI can detect the reduced nerve fiber structure quality in SCI. It could also potentially provide different neurophysiological information than traditional self-reports.

This work was supported by NS085456 and NJ Commission on Spinal Cord Research CSCR15ERG013
**Poster #45**
Ventromedial hypothalamus (VMH) neurons which express neuronal nitric oxide synthase (nNOS) project to the lateral hypothalamus

**Authors**
Beatrice Trias, Pallabi Sarkar, Hamad Wajid, Vanessa Routh

**PI Name:** Vanessa Routh

A functional relationship with regard to energy balance exists between the lateral hypothalamus (LH) and the ventromedial hypothalamus (VMH). However, the neuronal phenotype underlying the anatomical connection between these nuclei is not known. The VMH possesses glucose-inhibited (GI) neurons. We have shown that VMH GI neurons are critical for restoring euglycemia after insulin-induced hypoglycemia. This suggests that VMH GI neurons are important regulators of glucose homeostasis. The cellular fuel sensor, AMP-activated protein kinase (AMPK) mediates glucose sensing in VMH GI neurons. VMH AMPK also modulates energy homeostasis via connections to the LH orexin neurons. Thus, VMH GI neurons may play a role in this pathway as well. VMH GI neurons express nitric oxide synthase (nNOS). Therefore, we hypothesize that VMH nNOS neurons project to the LH. This hypothesis was tested by injecting retrobeads (retrograde tracer) into the LH of orexin GFP+ mice and determining whether the retrobeads were co-localized with VMH nNOS expressing neurons. Mice were sacrificed by transcardial perfusion followed by fixation with 4% paraformaldehyde one week post-surgery. The brains were extracted and cryosectioned through the VMH. Immunohistochemistry was used to detect VMH nNOS expressing cells co-localized with retrobeads. Retrobeads were observed throughout the 3 main VMH subdivisions: ventrolateral, dorsomedial, and central. nNOS expressing cell bodies which were labelled with retrobeads were observed predominantly in the ventrolateral and dorsomedial VMH. These data suggest that VMH nNOS expressing neurons project to the LH. Furthermore, VMH GI neurons may play a role in the regulation of energy balance via this pathway.

*Supported by 1R01-DK10367*

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**Poster #46**
Neuronal nitric oxide synthase (nNOS) neurons in the ventromedial hypothalamic nucleus (VMH) express bone morphogenic protein receptor 1a

**Authors**
Hamad Wajid, Pallabi Sarkar, Kevin B. Knapp, Vishwendra Patel and Vanessa H. Routh

**PI Name:** Vanessa Routh

The VMH regulates 4 distinct aspects of glucose and energy homeostasis: hepatic glucose production, the counter-regulatory response to hypoglycemia (CRR), brown adipose thermogenesis/white adipose browning and peripheral insulin sensitivity. The cellular fuel sensor AMP-activated protein kinase (AMPK) plays a key role in the first 3 of these processes. VMH AMPK activation increases blood glucose by increasing hepatic gluconeogenesis and stimulating the CRR. Conversely, VMH AMPK activation inhibits brown fat thermogenesis and white fat browning leading to decreased energy expenditure and weight gain. Estrogen promotes weight loss by inhibiting VMH AMPK. Bone morphogenetic protein 8B (BMP8B) mediates estrogen's thermogenic effect. VMH glucose-inhibited (GI) neurons require AMPK-induced activation of neuronal nitric oxide synthase (nNOS) for activation in low glucose. Estrogen inhibits VMH nNOS-GI neurons. These data suggest that estrogen's thermogenic effect is due, in part, to inhibition of VMH nNOS-GI neurons. We hypothesize that BMP8B mediates the inhibitory effect of estrogen on GI neurons. We used immunohistochemistry to determine whether nNOS and the BMP8B receptor, BMPR1a, co-localize in the VMH. We observed intense immunoreactivity of nNOS in both dorsomedial (dm) and ventrolateral (vl) VMH. The vlVMH had large, clearly-defined nNOS+ cell bodies and a robust expression of BMPR1a. We observed a larger percentage of cells that were BMPR+ (50.6±4.3% of total) compared to nNOS+ cells (39.6±3%). Of these, BMPR1a and nNOS co-localization was observed in 31.6±4.5% of total vlVMH cells. The co-localization of nNOS and BMPR1a is consistent with the hypothesis that BMP8B mediates the effect of estrogen on VMH nNOS-GI neurons.

*Supported by 1R01-DK10367*
Poster #47
A Novel Dynamic Functional Connectivity-Based Method for Early Classification of EEG Recordings

Authors
Ali Haddad, Foroogh Shamsi, and Laleh Najafizadeh

PI Name: Laleh Najafizadeh

The development of Brain Computer Interfaces (BCIs) involves tradeoffs between the required acquisition time for performing the classification, and the classification accuracy. A feature extraction/classification algorithm capable of decoding different classes of tasks with high accuracy using short recording intervals is of great interest. This work presents a new algorithm for the early classification of EEG signals associated with tongue-hand movement execution and imagery tasks. A new feature extraction method based on dynamic functional connectivity graphs is presented. First, EEG recordings, after being spatially decorrelated, are segmented using the source-informed segmentation algorithm into sequences of intervals during which functional networks sustain their connectivity. Next, functional networks during each segment are localized and their corresponding graphs are constructed, taking into account the connection weight of each pair of nodes. Finally, common spatial patterns (CSP) analysis is applied to estimate the most discriminatory classification features. These features are then passed to a Long Short Term Memory (LSTM) neural network. Experimental results show that an average accuracy of about 80% is achieved using the first 500 msec of EEG data, which is notably shorter than the interval needed for most existing methods.

Supported by DARPA, Siemens

Poster #48
Effects of Chronic Social Stress on a Neurodevelopmental Disorder Mouse Model

Authors
Mimi Phan, Nikita Jadav, Tonia Liu, Raaga Rambhatla, Christine Yohn, Benjamin Samuels, Emanuel DiCicco-Bloom

PI Name: Emanuel DiCicco-Bloom

Autism spectrum disorders (ASD) are pervasive neurodevelopmental disorders characterized by impairments in social interaction and communication and the presence of repetitive or stereotyped behaviors. Compounding these challenges are findings indicating that adults with ASD experienced more stressful life events, greater perceived stress, and increased comorbidity with anxiety disorder and depression. Stress exposure contributes to multiple disorders, and chronic stress is a major risk factor for mood disorders. However, it remains unknown whether adult exposure to stress can exacerbate the neurobiological and behavioral phenotypes associated with ASD. We used Engrailed-2 knockout (En2-KO) mice that exhibited ASD-related behaviors and abnormalities in monoaminergic neural circuitry to determine whether chronic exposure to stressful social interactions exacerbates 1) negative valence behavioral phenotypes and the neuroendocrine response to stress and 2) monoaminergic neural circuit abnormalities in En2-KO mice. En2 genetic polymorphisms are associated with ASD in humans. En2-KO mice display social abnormalities and cognitive deficits. Altered monoaminergic signaling in the forebrain is associated with mood disorders and their treatments, suggesting an overlap in the circuitry underlying ASD and mood disorders. Our data indicate that: 1) exposure to acute stressors such as forced swim and restraint lead to a greater elevation of corticosterone levels in the En2-KO than in the WT mice and 2) exposure to a 10-day Social Defeat Stress paradigm exacerbated negative valence behaviors in En2-KO mice, in tasks such as the open field and social interaction tests. Findings suggest genotype-x-environment interaction between En2 and chronic exposure to stress can exacerbate behavioral and neurobiological phenotypes.
Poster #49
Label-free Tracking of Mitochondria in Neurons

Authors
Mohammad Naser, Rene Schloss, Bonnie Firestein, Nada Boustany

PI Name: Nada Boustany

Abnormal mitochondrial morphology and dysfunction have been associated with diseases such as Alzheimer’s, Parkinson’s, Amyotrophic lateral sclerosis (ALS) as well as Traumatic Brain Injury (TBI). Such discoveries have motivated researchers toward the development of mitochondria-targeted therapy. This in turn necessitates an accurate assessment of mitochondrial dynamics. Traditional mitochondria targeted dyes or mitochondria-targeted fluorescent proteins affect mitochondrial metabolism and dynamics adversely. In this work, we investigate how we can quantify mitochondrial dynamics in neurons without the use of fluorescent dyes. For this purpose we used a Fourier filtering based label-free technique to image neurons under glutamate induced injury. Our goal is to assess the severity of the chemical insult on mitochondrial morphology and function using the label-free technique. This technique doesn’t use any exogenous marker and hence can be used to develop alternatives to the label-based assays and potentially provide a method for rapid drug-screening. Techniques developed in this project can ultimately help to develop and test mitochondria-targeted neuroprotective therapies.

Supported by partially supported by Grant CBIR14PIL005 from the New Jersey Commission on Brain Injury Research and NSF grant CBET1512170

Poster #50
Molecular mechanisms of myelin degeneration following mild traumatic brain injury

Authors
Alexandra A. Adams, Bryan J. Pfister, and Haesun A. Kim

PI Name: Haesun A Kim

Traumatic brain injury (TBI) is one of the leading causes of hospitalization and death in the United States. The effects of TBI on myelin remain largely uncharacterized. Recent animal studies indicate that mild TBI (mTBI) induces primary demyelination. Importantly, myelin loss in the brain has been shown to leave previously myelinated axons more vulnerable to degeneration after secondary injuries. Axons are known to release excessive amounts of glutamate following injury. Our recent in vitro study demonstrates that neurons distal to the site of injury remain hyperexcitable for up to one hour after injury. Previous studies have suggested that NMDAR mediated calcium entry in oligodendrocytes (OL) may play a role in myelin damage after CNS injury. We hypothesize that glutamate release from hyperexcited axons activates glutamate mediated calcium dependent signaling in OLs that disrupts myelin homeostasis.

Using an in vitro stretch-injury device combined with a neuron-OL co-culture system, we show that injury to neurons results in intracellular calcium increases in non-injured neighboring OLs, suggesting the occurrence of an injury induced neuron to OL signaling event. Further, NMDA treatment in mature OL monoculture induces downregulation of myelin basic protein expression, which is attenuated with inhibition of the ERK pathway. In vivo, we show that mild fluid percussion type injury in mice increases ERK activity in Olig2+ cells within white matter tracts without subsequent death of CC1+ cells. Our findings suggest that neuronal hyperexcitability and aberrant glutamate release may initiate calcium mediated ERK activation in the OL that results in loss of myelin.

This work was supported by grants from the New Jersey Commission on Brain Injury Research (CBIR11PJ012) and the Rutgers Initiative for Multidisciplinary Research Teams (IMRT) to H.A.K
**Poster #51**
Single Cell RNA Sequencing of Immortalized Multipotent Otic Progenitors

**Authors**
Jihyun Kim, Joseph Fantuzo, Zhichao Song, Azadeh Jadali, and Kelvin Y. Kwan

**PI Name:** Kelvin Y. Kwan

The inner ear is responsible for hearing and balance. The cochlea is the auditory organ that is responsible for hearing complex sounds. Spiral ganglion neurons (SGNs) are the primary auditory neurons. SGNs relay neural signals from the cochlea to the cochlear nucleus and it is essential for the auditory circuit. Improper development or damage to SGNs results in cell death and causes hearing loss. Use of otic progenitors to replace damaged SGNs is a potential avenue for regeneration. Understanding the molecular changes in otic progenitors as they differentiate into neurons will accelerate efforts for regeneration. To understand this process, immortalized multipotent otic progenitors (iMOPs) were employed for single cell RNA sequencing (scRNA-seq). iMOP cells are clonal cell lines derived from developing murine otic progenitors. Under the appropriate culture conditions, iMOPs can differentiate into cells with bipolar neuronal morphology and fire action potentials. Even though iMOP cultures contain over 90% neuronal β-tubulin (TUBB3) expressing cells, the cultures are heterogeneous because they contain cells at different stages of neuronal differentiation. scRNA-seq provided an unbiased classification of distinct populations of differentiating cells by employing dimensionality reduction methods for clustering. Analysis revealed at least three distinct cell populations during iMOP neuronal differentiation, which are neuroblasts, intermediate neural progenitors, and neurons. The transcriptome changes between distinct cell populations predicted two possible neuronal differentiation trajectories from an otic progenitor into a neuron. Validation of the transcriptome changes using stranded RNA-seq and fluorescence in situ hybridization provided additional insight into the molecular mechanisms that underlie neuronal differentiation.

*This work was supported by NIH R01 DC015000; NIH R01 DC016612*

**Poster #52**
Alginate Encapsulated Mesenchymal Stromal Cells as a Treatment for Traumatic Brain Injury

**Authors**
Xiomara I. Perez, Elisheva Strauss, Rene S. Schloss, Martin L Yarmush

**PI Name:** Martin L. Yarmush

Traumatic Brain Injury (TBI) is a leading cause of disability and death worldwide, characterized by initial blunt trauma which leads to inflammation, and neuron damage and death. While available therapies treat post-TBI inflammation, few promote neuroregeneration and functional restoration. Mesenchymal stromal cells (MSC) are a potential treatment option due to their innate ability to both reduce inflammation and promote tissue regeneration. Our group has previously encapsulated MSC in alginate (eMSC) as a way to provide positional control after transplantation. Furthermore, eMSC have been shown to have superior neuroinflammatory-modulatory effects relative to free MSC. However, we have not yet evaluated the effect of MSC on promoting injured neuron functional recovery. Thus, these studies were designed to develop an in vitro neuronal injury model to evaluate the therapeutic efficacy of MSC. Briefly, E18 rat cortical neurons were isolated, seeded on poly-d-lysine (PDL) coated plates and injured on day in vitro (DIV) 18 with hydrogen peroxide (H2O2) followed by complete neurobasal media washes. Viability was determined via Calcein, Ethidium and DAPI staining at 0 and 24 hours post-injury. Our results indicated that dosing with 200μm and 100μm H2O2 led to significantly lower viability at 0 hours. However, after 24 hours there was no significant difference in viability in groups treated with μ. Therefore, future studies will utilize 100μm H2O2 to injure neurons, followed by treatment with free MSC and eMSC. During the course of these studies, other injury models, such as glutamate toxicity, as well as neuroregenerative therapies, will be compared.

*This work was supported by NIH T32 GM008339; (NSF) CBET 1512170; NASA NJ Space Grant Consortium*
**Poster #53**

Novel organoid and chimeric mouse brain models to study human iPSC-derived microglia

**Authors**

Ranjie Xu, Andrew Boreland, Peng Jiang

**PI Name:** Peng Jiang

As the resident macrophage of the central nervous system, microglia play critical roles in maintenance of CNS homeostasis and regulation of diverse aspects of neuronal function. Increasing evidence indicates that dysfunction of microglia contributes to neurodevelopmental and neurodegenerative diseases, such as schizophrenia and Alzheimer’s disease. However, most of the previous studies on microglia largely relied on rodent microglia, because of the scarcity of available functional human brain tissue and primary microglia cultured from human brain tissue. Recent transcriptomic studies have clearly demonstrated that a number of immune genes, not identified as part of the mouse microglial signature, were abundantly expressed in human microglia. Moreover, limited overlap was observed in microglial genes regulated during aging and neurodegeneration between mice and humans, indicating that human and mouse microglia age differently in health and disease. These argue for the development of species-specific research tools to investigate microglia functions in human brain development, ageing and neurodegeneration. In this study, we have differentiated primitive macrophage precursors (PMPs) from human induced pluripotent stem cells (hiPSCs). PMPs can efficiently mature into functional microglia in 3-dimensional cerebral organoid in vitro, as well as in chimeric mouse brain in vivo. These new models provide unique opportunities for studying the pathophysiology of human microglia in health and disease.

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**Poster #54**

Impact of OPRM1 A118G on synaptic transmission in both human and mouse neuron

**Authors**


**PI Name:** Zhiping Pang

The A118G Single Nucleotide Polymorphism (SNP) in the OPRM1 gene causes a substitution of asparagine with aspartate at position 40 (N40D) in the mu opioid receptor (MOR) and is hypothesized to be associated with drug and alcohol use disorders. Our lab aims to determine how the A118G SNP contributes to altered sensitivity to opioids as well as EtOH. To address this, we used isogenic human stem cell lines harboring the A118G gene variant as well as a knock-in mouse model A112G, the homologous variant of A118G in humans. Data show enhanced suppression of synaptic release and neuronal excitability in inhibitory-induced neuronal (iN) cells following acute application of the MOR agonist DAMGO in D40 MOR variant carriers. In addition, ethanol induced facilitation of inhibitory synaptic release was more pronounced in iNs harboring the A118G gene variant as well as a knock-in mouse model A112G, the homologous variant of A118G in humans. Data show enhanced suppression of synaptic release and neuronal excitability in inhibitory-induced neuronal (iN) cells following acute application of the MOR agonist DAMGO in D40 MOR variant carriers. In addition, ethanol induced facilitation of inhibitory synaptic release was more pronounced in iNs harboring the A112G allelic variant. Interestingly, co-application of DAMGO and EtOH caused a reduction in neurotransmitter release in both genotypes, but the strength of inhibition was much greater in D40 containing iNs. In the A112G mouse model, we focused on the modulatory effects of DAMGO on ventral tegmental area (VTA) dopaminergic (DA) neurons. We discovered that DAMGO suppressed both inhibitory and excitatory input to the VTA, leading to a shift in firing of DA neurons, these effects were stronger in D40 mice. We hypothesize that the differential effects caused by the N40D SNP could be mediated by differential expression of MORs or altered downstream signaling. Currently we are in the process of determining the mechanism by which the N40D SNP impacts synaptic transmission, which we expect will give greater insight into the fundamentals of opioid receptor signaling.

*This study is supported by NIH NIAAA R01 AA023797.*
Poster #55
Rab11 is required for the proper development and organization of the mammalian cerebellum.

Authors
Edward Martinez, Nan Gao, Tracy S. Tran

PI Name: Tracy S. Tran

Members of the small GTPase family of Rabs are important for many aspects of intracellular trafficking that control sorting and distributing key proteins to distinct subcellular compartments. Rab11 resides within recycling endosomes, which are responsible for redistributing internalized proteins back to the surface of the plasma membrane. Previous studies showed that disruption of Rab11 function in vitro has led to defects in important developmental events and a mutation found in Rab11b showed a slightly smaller cerebellar phenotype in humans. However, little is known about the role of Rab11 during cerebellum development in vivo. Since both Rab11a and Rab11b isoforms are present within the nervous system, we generated a double knockout (dKO) of Rab11a/b specifically in developing cerebellar granule cells. Analysis of the Rab11 dKO adult brain revealed a significant decrease to the overall size of the cerebellum, with a severe impairment on the formation of the anterior lobe. We demonstrated that loss of Rab11a and Rab11b increase cell death at later embryonic stages and impair granule cell differentiation in early postnatal development, specifically in the anterior lobe. Taken together, our findings suggest a key in vivo role for Rab11a/b for distinct anterior and posterior lobe developmental mechanisms of the cerebellum.

This study is supported by the NSF (IOS-1556968) and the NJ Governor’s Council for Medical Research and Treatment of Autism (CAUT17BSP022 and CAUT17BSP011) to T.S.T.

Poster #56
Identification of Evolutionarily Conserved Regulators of Microtubule Stability and Function in Neurons

Authors

PI Name: Maureen M. Barr.

Microtubules (MTs) are a major component of the neuronal cytoskeleton. Spatiotemporal tuning of MT stability and dynamics is important for neuronal survival, transport, and function. Misregulation of MT properties leads to neurodegeneration and is characteristic of disorders, such as Alzheimer’s, Parkinson’s, and Huntington’s diseases. Our lab uses nematode and mammalian models to identify factors that regulate diverse neuronal MT populations. We harness the genetic tractability of the nematode C. elegans, and use fluorescence-based and behavioral assays to identify factors that affect MT stability in sensory neurons. Our work in C. elegans identified proteins that regulate MT numbers, MT stability, and movement of kinesin motors along MTs (Silva et al. 2017; O’Hagan et al. 2011; O’Hagan et al. 2017). A subset of these MT regulators work via tubulin post-translational modifications (PTMs), and these PTMs are important for establishing neuronal polarity that is crucial to directional transport (Witte et al. 2008; Konishi et al. 2009). Strikingly, dysregulation of PTMs that cause MT degeneration in C. elegans sensory neurons also lead to neurodegeneration in mouse models and retinitis pigmentosa in humans (O’Hagan et al. 2011; O’Hagan et al. 2017; Harris et al. 2000; Rogowski et al. 2010; Sun et al. 2017). Thus, we optimized an in vitro rodent model of excitotoxic injury to understand how changes in tubulin PTMs affect neuronal survival after injury. We confirmed that PTMs do indeed play a role in neuronal survival, and we are now identifying the mechanisms by which tubulin PTMs act.

This study is supported by NIH 5R01DK059418, NJCSCR (New Jersey Center for Spinal Cord Research).
Poster #57
CBN Society: Neuronal development

Authors

Entity: Rutgers CBN Society.

The Rutgers University Cell Biology and Neuroscience (CBN) Society is a prominent academic organization that aims to promote neuroscience research and education among undergraduate students. CBN Society members are investigating how neuronal development is regulated by proteins such as HuD, Acidic, Sushi, PSD-95 (post-synaptic density 95), and CRIPT (cysteine-rich interactor of PDZ3). Abnormalities in neocortical development, dendrite branching, spine morphology, and synapse formation are associated with neurological disorders such as Alzheimer’s disease, Autism Spectrum Disorder, and schizophrenia. This research will provide important insight into the protein interactions that affect healthy brain function.

Poster #58
CBN Society: Neuronal disease and injury

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Ansley J. Kunnath, Kirsten C. Svane, Ericka-Kate Asis, Anton Omelchenko, Linda M. Brzustowicz, Steven M. Silverstein, Bonnie L. Firestein; Clairisse Whang; Agamjot Sangotra, Anton Omelchenko, Annie Gonor, Isabel Biermann, Bonnie L. Firestein; Kusuma Ananth, Gina M. Giunta, Vanessa H. Routh, Luis de Lecea, Nicholas T. Bello.

Entity: Rutgers CBN Society.

The Rutgers University Cell Biology and Neuroscience (CBN) Society is a prominent academic organization that aims to promote neuroscience research and education among undergraduate students. CBN Society members are investigating the molecular mechanisms underlying neurological disorders. We are exploring the role of orexin in binge-eating disorders and oleic acid in Alzheimer’s disease. Additionally, we are investigating the therapeutic use of D-serine for schizophrenia and inosine for spinal cord injury. These debilitating disorders affect millions of Americans every year. This research will help elucidate their pathologies so that better treatments may be developed.
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