Sunday Joseph Fajobi Advisor(s): Peter Bergold

Human 3R tau expression correlates with increased synaptic density in mice

Beyond its established role in microtubule stabilization, tau protein has poorly defined functions at the synapse. Six tau isoforms exist, having either 3 (3R) or four (4R) microtubule-binding sites. Mice with the human tau gene knocked in (MAPTKI) express all six human 3R and 4R isoforms, similar to adult humans. This contrasts with wild-type (WT) mice that express only three murine 4R tau isoforms. Unlike WT mice, MAPTKI mice have fewer injury-induced memory and cognitive deficits on two hippocampus-dependent tasks, active place avoidance and the Barnes maze. To better understand the differing responses to head injury between the two strains, we examined neuronal, axonal, and synaptic densities in uninjured WT and MAPTKI mice. Neuronal density was assessed using NeuN+, and axon density was assessed by silver stain. Excitatory synaptic density was assessed by the colocalization of the presynaptic protein synaptophysin and the postsynaptic density protein PSD-95.

CA1 and CA3 neuronal density is similar in WT and MAPTKI mice. Axonal density in the corpus callosum is also similar in the two strains. Surprisingly, MAPTKI CA1 stratum radiatum or CA3 stratum lucidum has a significantly higher density of excitatory synapses. In contrast, WT mice have more synaptophysin puncta that did not co-localize with PSD-95. These data suggest WT mice have more inhibitory synapses, resulting in different synaptic excitation/inhibition ratios between the two strains. Studies using the postsynaptic inhibitory protein gephyrin will directly test whether WT mice have more inhibitory synapses than MAPTKI.

These findings suggest that human 3R tau expression correlates with an altered synaptic excitation/inhibition balance, independent of neuronal or axonal density. This newly identified synaptic role for 3R tau may underlie the improved recovery of MAPTKI mice after head injury and has broader implications for traumatic brain injury and other neurodegenerative disorders in humans.

DOWNSTATE HEALTH SCIENCES UNIVERSITY

2026 Annual Research Day Oral Presentation Abstracts

Molly Leitner Advisor(s): Salvador Dura-Bernal Ph.D.

Leveraging neural modeling of channelopathies to elucidate neural mechanisms underlying neurodevelopmental disorders and potential interventions

Neurodevelopmental disorders (NDDs), such as epilepsy, autism spectrum disorder, and developmental delays, present with considerable clinical variability and often impair social interactions, speech, and cognitive development. A key feature of these disorders is an imbalance in excitatory/inhibitory (E/I) input, which disrupts neuronal circuit function during development. Brain channelopathies, where neuronal ion channel activity is altered due to genetic mutations or acquired pathologies, provide an ideal model for studying E/I imbalance, as their effects can be directly linked to neuronal excitability. Ion channels are crucial in generating electrical activity in neurons, and disruptions to this activity are strongly associated with NDDs. Studying channelopathies at the single-cell level is well-established, however, investigating the impact of specific channel mutations on neuronal circuits is limited. By utilizing a previously developed murine primary motor cortex model built using the NetPyNE multiscale modeling tool and the NEURON simulator, I employ large-scale, highly detailed biophysical neuronal simulations to examine how channel mutations influence individual and circuit neuronal activity. Through the simulations, I can measure the effects of biophysical changes in ion channels on network excitability and neuronal firing patterns, providing insights into the pathophysiology of simulated NDD-associated channelopathies. I implement specific genetic mutations associated with NDDs to study channelopathies by modeling alterations in channel biophysical properties. By altering neuronal activity through channelopathies, I am then able to model pharmacological interventions, such as sodium channel blockers, to explore how these drugs may be able to restore neuronal activity back to baseline. This model not only serves as a tool for investigating specific channelopathy cases but also enables the exploration of pharmacological agents aimed at restoring E/I balance.

Lina Marcela Pedraza Ortiz Advisor(s): Robert Foronjy M.D.

SERINC3 regulates epithelial cell-cycle competence through membrane-dependent signaling mechanisms

Efficient airway epithelial repair requires coordinated growth-factor signaling and timely re-entry into the cell cycle. Impaired proliferative responses contribute to chronic lung diseases, including chronic obstructive pulmonary disease (COPD), and are exacerbated in people living with human immunodeficiency virus (HIV). Cell-cycle entry is critically dependent on growth factor receptor signaling at the plasma membrane, which induces transcriptional programs necessary for replication licensing and S-phase progression. SERINC3 (Serine Incorporator 3) is a membrane-associated protein known to regulate lipid organization and membrane microdomains, yet its role in epithelial cell biology remains poorly understood. We hypothesized that SERINC3 regulates epithelial cell-cycle competence by shaping membrane environments required for efficient growth-factor signaling. To test this, we performed RNA sequencing in human bronchial epithelial cells overexpressing SERINC3. Differential expression analysis revealed suppression of cell-cycle inhibitory genes including CDKN2D, CDKN3, and TGFB2, alongside increased expression of proliferation-associated markers such as MKI67 and TOP2A. These transcriptional changes are consistent with enhanced G1/S transition and S-phase entry. Notably, SERINC3 has previously been shown to be downregulated by the HIV accessory protein Nef in T cells and macrophages, and we hypothesize that HIV infection may act via Nef to downregulate SERINC3 and impair epithelial repair. Together, these findings identify SERINC3 as a novel membrane-based regulator of epithelial cell-cycle competence and suggest that disruption of SERINC3-dependent signaling may contribute to defective lung repair in HIV-associated lung disease.

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2026 Annual Research Day Oral Presentation Abstracts

Dativo Sanchez Gonzalez Advisor(s): Itsaso Garcia Arcos Ph.D.

LRP1 regulates substrate uptake by alveolar type 2 cells.

Pulmonary surfactant, a lipoprotein complex essential for correct lung function, is produced by alveolar type 2 cells (AT2C) and is altered in adult lung diseases such as pulmonary fibrosis or chronic obstructive pulmonary disease (COPD). Our lab showed that patients with COPD have decreased total lipid concentration in the surfactant, strongly correlating with worse pulmonary function. Nevertheless, the regulation of surfactant-related metabolism in adults is poorly understood and remains unapproached for therapeutic targeting.

The low-density lipoprotein receptor-related protein 1 (LRP1) is a multiligand receptor with prominent roles in lipid metabolism. SNPs in LRP1 are associated with worse pulmonary function in patients with COPD. Our mouse model of AT2C-specific LRP1 knockout (SPC-LRP1-/- mice) shows decreased surfactant lipids and worse pulmonary function after long-term smoke exposure, a common model of COPD in mice. Our goal was to determine whether LRP1 expression dictates surfactant production through its function as a lipid receptor.

We used SPC-LRP1-/- mice and A549, a human cell line of AT2C, stably transfected with LRP1 shRNA (LRP1 KD cells), endogenously radiolabeled chylomicrons, radiolabeled free fatty acid (FFA) and a fluorescent glucose analogue to trace the use of metabolic precursors for surfactant production by AT2C.

AT2C-like A549 did not lipolyze chylomicrons, suggesting that they may require other cell types to use chylomicrons as a source for surfactant lipids. Glucose uptake was lower in LRP1 KD and AT2Cs from SPC-LRP1-/- than controls. Consistently, fatty acid synthase activity and protein expression were decreased. Additionally, FFA uptake was decreased with LRP1 loss. Further profiling showed that intracellular fatty acid oxidation rate, media glucose consumption and lactate production were not altered in LRP1 KD cells.

We conclude that LRP1 determines lipid and glucose substrate uptake in AT2C and their subsequent metabolism.

Anika Sanjana Advisor(s): Douglas S. F. Ling Ph.D.

Co-authors: C. Hsieh, T. M. Rodriguez, T.H. Wroblewski, A. Mejia-Bautista, P. A. Serrano

Effects of acute, pre-injury stress on chronic spatial working memory deficits caused by severe traumatic brain injury in rats

A major pathological sequel of traumatic brain injury (TBI) is cognitive dysfunction. Our previous studies showed that timely pre-injury administration of the antiseizure medication (ASM), brivaracetam (BRV), prevents the development TBI-induced cognitive deficits in rats following severe controlled cortical impact (CCI) neurotrauma. In the present study, we aimed to examine the effects of pre-exposure to acute stress on CCI-induced changes in cognitive function. We also investigated whether the neuroprotective effects of BRV are preserved in the presence of acute stress exposure in stress-induced CCI rats. Rats (P25â€“36) were randomly assigned to receive a single 1-hour exposure to acute platform stress, followed by a 5-minute Open Field Test (OFT), immediately prior to CCI injury. Stress-control animals were placed in their home cage for one hour, followed by a 5-minute OFT immediately before injury. Animals then received a single intraperitoneal (IP) dose of BRV 15â€“30 minutes prior to CCI injury, while drug-control animals received saline vehicle. Sham controls did not undergo CCI injury. At â‰¥5 weeks post-injury, spatial memory was assessed using Active Place Avoidance (APA) test. APA performance was evaluated using: (1) time to first entry, (2) number of entries, (3) percentage of time spent in the shock zone, and (4) maximum avoidance time. CCI-saline rats without pre-injury platform stress exhibited significant working memory deficits across all metrics compared to sham-saline rats. In contrast, CCI-rats exposed to pre-injury platform stress with saline, as well as those receiving a single pre-injury BRV, showed significantly improved memory performance relative to CCI-saline rats, comparable to sham controls. These findings suggest that a single pre-injury exposure to acute stress may confer long-term neuroprotective effects against TBI-induced cognitive deficits.

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2026 Annual Research Day Oral Presentation Abstracts

Fathema Uddin Advisor(s): Charlie Rudin Ph.D.,M.D.

Co-authors: Esther Redin, PhD, Patrick Geraghty, PhD

DNA Damage Repair Pathways Enable a Drug-Tolerant Persister State in RET-Fusion NSCLC and Precedes TKI Resistance

RET-fusion lung adenocarcinomas are a rare and aggressive subtype of lung cancer, often affecting young, non-smoker populations. While targeted RET-TKI therapies are initially highly effective, they often fail to provide durable responses, with resistance mechanisms emerging over time. To uncover unknown mechanisms of resistance, we performed a comprehensive multi-omic analysis of clinical samples from patients with RET-fusion lung cancers before and after RET-TKI therapy. RNA sequencing analysis revealed inactivation of RB1 and upregulation of DNA damage repair (DDR) pathways in resistant tumors. We hypothesized that DDR pathway upregulation was a result of inhibition of Rb1 during TKI treatment. Isogenic knockdown of Rb1 or overexpression of E2F confirmed upregulation of key DDR genes such as BRCA1, MSH6, and Rad18 in RET cell lines. Furthermore, drug tolerant persister (DTP) assays revealed reduced generation of DTPs when knocking out these DDR genes while overexpression was advantageous to the DTP state. We next evaluated the inhibition of XPO1, an exportin protein linked to DDR pathway activation, as a strategy to target DTPs. Treatment with selinexor, an FDA-approved XPO1 inhibitor, in combination with selpercatinib strongly reduced the number of DTPs in vitro, and overexpression of the DDR genes BRCA1, MSH6, and Rad18 rescued this effect. In vivo experiments using RET-driven patient derived xenograft (PDX) models confirmed that treatment with combination of selpercatinib with selinexor significantly delayed tumor relapse. Our research highlights DDR pathways as a critical mechanism of resistance via Rb1 inactivation in TKI-treated RET-driven lung cancers and identifies XPO1 inhibition as a promising therapeutic strategy to overcome this resistance.

Tadeusz Wroblewski Advisor(s): Tim; Ernest Bigdeli; Barthelemy Ph.D.,M.D.

Co-authors: Shwetha Phatarpekar, Chris Chatzinakos, Erdal Cavusoglu, Tim B. Bigdeli*, and Ernest J. Barthelemy* on behalf of the Downstate Global Neurosurgery Laboratory

Methylation Profiling of Cerebrospinal Fluid Cell-Free DNA Reveals Cell-of-Origin Signatures After Acquired Brain Injury

Neurosurgeons have unique and medically necessary access to central nervous system (CNS) tissue during routine clinical care ï¼ e.g., the management of acquired brain injury (ABI) may require removal of skull tissue, dura, cerebrospinal fluid (CSF), and parenchyma. While a portion of this tissue may be required for clinical diagnostic purposes, much is routinely discarded. We developed a scalable, translational toolkit for cost-efficient storage and multi-omic analysis of otherwise discarded CNS tissue. In this pilot study, supported by a NIMHD CREST Fellowship and the Institute for Genomics in Health, cell-free DNA (cfDNA) was extracted from CSF collected after clinically indicated external ventricular drain or ventriculoperitoneal shunt placement. The quantity of cfDNA (144-2905 ng/mL) was observed to be higher in post-ABI CSF (median 1887 ng/mL; IQR 1019-2779) compared to arterial plasma samples from the Downstate Cardiac Catheterization GeneBank (median 394 ng/mL; IQR 348-497, p=0.033). We performed long-read sequencing on the Oxford Nanopore PromethION instrument to simultaneously classify nucleotide sequence and methylation state. Sequenced cfDNA had a median coverage of 61% and depth of 1X. Leveraging available methylation information (5-methylcytosine CpGs), we performed tissue- and cell-of-origin deconvolution using a custom reference panel. We observed distinct apoptotic profiles for ABI, including cfDNA of neuronal (8-10%), glial (12-21%), and bone origin (12-25%). Arterial plasma demonstrated a distinct cardiomyocyte signature (up to 7%) and CNS cell types were largely absent (<1.5%). These observations support cfDNA as a surrogate for cellular turnover and injury, representing a promising avenue for ABI biomarker development. This novel molecular epidemiology pilot lays the groundwork for broader translational neurosurgery research efforts at Downstate and its affiliated hospitals, which serve a unique and historically under-represented population.

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2026 Annual Research Day Oral Presentation Abstracts

Maria Mia Carmencita Yabut Wiese Advisor(s): Joseph Scandura Ph.D.,M.D.

Defining the Role of Malignant Megakaryocytes on Clonal Hematopoiesis

Myeloproliferative neoplasms (MPNs) occur when a hematopoietic stem cell (HSC) acquires a driver mutation, often decades before disease presents. Over time, the mutant HSC exhibits a fitness advantage, allowing a single clone to outcompete wild-type (WT) counterparts, termed clonal hematopoiesis (CH). Elucidating how CH occurs may allow us to prevent mutant HSCs from acquiring a fitness advantage, representing a potential therapeutic target. HSCs reside in the bone marrow (BM) stem cell niche and their function is directly altered by nearby cells. Megakaryocyte (Mk) cells live proximally to HSCs and drive HSC behavior in both homeostasis and stress. However, MPNs are defined by aberrant Mk signaling and morphology. We seek to determine if mutant Mk directly alter MPN niche function to favor mutant HSCs over WT HSCs.

To distinguish the differences between mutant and WT HSC fitness in MPNs, we conducted competitive transplantations of lethally irradiated CD45.1 mice with congenic CD45.2 donor whole BM cells harboring the most common MPN driver mutation, JAK2V617F, or WT JAK2 (JAK2WT). Measuring CD45.2 chimerism in HSCs and red blood cells from engrafted mice revealed that CD45.2 cells harboring JAK2V617F disproportionally contributed to the myeloid lineage. JAK2V617F HSCs display increased fitness relative to their JAK2WT counterparts during myeloproliferation. To determine if mutant Mk are responsible for this increased JAK2V617F HSC fitness, we cloned a lentiviral construct which will specifically ablate JAK2V617F Mk from the MPN niche.

To identify the key transcriptomic differences between JAK2V617F and JAK2WT Mk, we developed strains of mice which fluorescently report JAK2V617F expression. These tools will allow us to specifically sort JAK2V617F and JAK2WT Mk and elucidate how they alter the HSC niche. Because the specific contributions of Mk to MPN pathogenesis remain unclear, this work is essential to determining the specific role of Mk in CH.