Quiana Jones Advisor(s): Xian C Jiang Ph.D.

Apolipoprotein M specifically promotes chylomicron secretion through influencing vesicle trafficking in enterocytes

Chylomicron, enriched with triglyceride, are formed by enterocytes of the small intestine from dietary lipids and play an important role in promoting cardiovascular diseases. Recent studies indicated the effect of apolipoprotein M (apoM) on plasma triglyceride, however, the mechanism is not well understood. We confirmed that apoM deficiency attenuate postprandial triglyceride levels, an effect that is directly related with small intestine but not liver. We also found that both mouse and human chylomicron contain apoM which is increased in the time-dependent fashion after fat loading. Further, we found that apoM deficiency causes lipid retention in the small intestine and, under electronic microscope, we observed that chylomicrons are retained in endoplasmic reticulum and lipid droplets are accumulated in the cytosol of enterocytes. Furthermore, we found that the deficiency dramatically reduces (90%) Sar1B, whose mutation leading to chylomicron retention disease, and its associated protein partners, including Sec 24 and Sec23. Additionally, we found a dramatical reduction of microsomal triglyceride transfer protein (MTP) and its activity. To eliminate the possible mechanism that circulating apoM may contribute to the observed intestinal phenotype, we increased plasma apoM by injection of adenovirus associated virus (AAV8)-apoM into apoM deficient mice. We found that plasma apoM does not influence postprandial triglyceride levels. We also measured sphigosine-1-phosphate (S1P) levels which are closely associated with apoM in the blood and we could not detect S1P in the small intestine of the deficient and control mice. We conclude that apoM participates in chylomicron, but not very low-density lipoprotein (VLDL) intracellular trafficking, thus, influencing postprandial triglyceride metabolism. This effect is independent of plasma apoM-S1P. Manipulating apoM could provide a novel and unique approach to regulate postprandial lipid metabolism.

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Ji Youn Jung Advisor(s): Samuel Neymotin Ph.D.

Cortical Oscillatory Dynamics in Parkinsonian Networks: Biomarkers and the Potential of Theta Frequency Stimulation

Parkinson's disease (PD) causes motor impairments such as tremors, rigidity, bradykinesia, and balance issues, along with cognitive deficits. While the degeneration of dopaminergic neurons in the substantia nigra pars compacta is a well-known driver of motor symptoms, recent studies highlight the role of disrupted oscillatory activity in the primary motor cortex (M1). PD models, including 6-OHDA mice, mitoPark mice, and MPTP-treated primates, consistently show corticospinal pyramidal tract (PT) neuron hypoexcitability and increased beta-frequency oscillations in M1. This study developed a computational Parkinsonian M1 model (PD M1) to simulate disease-related oscillatory changes. Adapted from an established mouse M1 framework, the model incorporates experimentally observed PD features, including ion channel dysfunction, altered gating, and progressive thalamocortical input reductions to PT neurons. In mitoPark mice, thalamocortical input declines 25% at 16–18 weeks and 50% at 25–28 weeks, paralleling disease progression. Using this model, we examined how reduced PT excitability and weakened thalamocortical input contribute to pathological beta oscillations. Additionally, we assessed beta-gamma coupling and phase-amplitude modulation index (MI) as potential biomarkers of disease severity and explored the effects of theta-frequency (4–8 Hz) stimulation targeting inhibitory interneurons as a therapeutic intervention. Our results show that beta-gamma coupling and MI are significantly reduced in Parkinsonian conditions, with MI decline tracking disease progression, aligning with mitoPark findings. Theta stimulation effectively suppressed beta bursts, improved beta-gamma coupling, and restored cortical network function disrupted by PT hypoexcitability. These findings suggest that MI could serve as a biomarker for PD severity, while theta stimulation may offer a potential alternative or complementary approach to subthalamic deep brain stimulation (DBS) in PD treatment.

Ana Mejia-Bautista Advisor(s): Douglas Ling Ph.D.

Effect of brivaracetam on changes in synaptic transmission after TBI

Posttraumatic epilepsy (PTE) can occur in up to 40% of patients who sustain a severe traumatic brain injury (TBI). Despite decades of research, there are no therapeutic interventions to prevent PTE. Moreover, in many cases of PTE, seizures cannot be controlled adequately with standard antiseizure medications (ASMs). Results from our prior studies suggest that early, post-injury administration of brivaracetam (BRV), an FDA-approved SV2A-ligand ASM, may prevent the development of PTE. The aims of this study are to investigate the changes in cortical synaptic transmission that may give rise to PTE and test the hypothesis that BRV exerts its protective, antiepileptogenic effects by limiting these changes. Specifically, we are investigating the mechanisms by which TBI alters the balance of cortical excitation and inhibition, and how BRV may prevent this pathogenic process. Experiments use the controlled cortical impact (CCI) model of severe TBI in rats and employ whole-cell electrophysiological recordings from layer V pyramidal cells in ex vivo brain slices of neocortex to assess injury-induced changes in excitatory and inhibitory postsynaptic currents (EPSCs and IPSCs). Drug-treated rats are given a single dose of BRV immediately after CCI, and electrophysiological assessments are made 2 – 4 weeks after TBI to determine the chronic changes in cortical circuit physiology and the preventative effects of early BRV treatment. At 2 weeks post-injury, we observed a significant loss of inhibitory synaptic function in slices from TBI rats, with a 39% decrease in the peak amplitude of the maximal IPSC that can be recruited in pyramidal cells with externally applied electrical stimulation. These findings provide critical insight into the pathophysiological changes that occur following TBI, and ongoing studies will determine whether early BRV administration through its SV2A-binding mechanism can preserve synaptic function and prevent epileptogenesis following severe brain injury.

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Joao Moreira Advisor(s): Salvador Dura-Bernal Ph.D.

Deciphering Thalamocortical Circuitry through a Computational Model of Sensory Processing and Sleep Rhythms

The mouse whisker pathway is an excellent model for studying thalamocortical interactions, with well-defined brainstem, thalamic, and cortical structures representing each whisker. The thalamus serves as a relay station, preprocessing and forwarding sensory information to the cortex during wakefulness. During sleep, it shifts to generating rhythmic oscillations, such as sleep spindles, which play key roles in sensory gating and memory consolidation.

Recent advances in mapping thalamocortical and corticothalamic pathways have improved our understanding of these circuits, but intrathalamic connectivity remains poorly resolved. Specifically, it is unclear whether these connections form closed- or open-loop structures, a distinction difficult to determine experimentally. Addressing this question requires systematic approaches to test different connectivity patterns and their functional implications.

To tackle this challenge, we developed a biophysically detailed computational model of the mouse whisker thalamocortical circuit, systematically varying intrathalamic connectivity from fully closed-loop to uniform to fully open-loop. Our model incorporates realistic neuronal morphologies, short-term synaptic plasticity, and biologically constrained connectivity. It successfully replicates key experimental features, including angular tuning responses and sleep-like oscillations marked by alternating synchronized and desynchronized activity.

Our results show that topological feedforward projections from the ventral posteromedial to the reticular nucleus are critical for preserving angular tuning, while a combination of closed-loop and uniform connectivity supports the waxing-waning dynamics of sleep spindles. These findings refine our understanding of intrathalamic organization and provide testable predictions for future experiments. More broadly, our work highlights the power of computational models in uncovering fundamental principles of sensory processing and sleep dynamics

Leibish Nash Advisor(s): Jeremy Coplan M.D.

Hippocampal Pkm ζ , Neurotrophic Activity in the NHP Hippocampus, and Affective Dysfunction

Our laboratory has demonstrated that early life stress (ELS), results in decreased adult PKMζ expression in the anterior hippocampus, and behavioral deficits in affective behavior as adults. Since decreased neurogenesis has been implicated in depression and affective dysfunction, we undertook exploration of variations of neurogenesis in the hippocampus of NHP macaque monkeys. Extensive behavioral data was collected on a range of affective activity. The neuromodulators of doublecortin, NeuN, and BRDU, a nucleotide, as well as expression of PKMζ were monitored during histological examination of brain tissue after animal sacrifice. Findings included evidence of an inverse relationship between affective competence and neurogenesis activity, as well as PKMζ expression. Behavioral data is being further analyzed for clinical implications of treatment for depressive and anxiety-related disorders.

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Shreya Shai Advisor(s): Chongmin Huan Ph.D.,M.D.

The Potential Role of Insufficient X Chromosome Inactivation in Impairing SMS2-Regulated Germinal Center B Cell Tolerance in Systemic Lupus Erythematosus

Background: Systemic Lupus Erythematosus (SLE) is a female-biased autoimmune disease that is normally prevented by the self-protective mechanism of B cell tolerance. Current evidence points to the overexpression of X-linked genes, caused by dysregulated X chromosome inactivation (XCI), as a key mechanism underlying the female-bias of SLE. However, how this may contribute to the loss of B cell tolerance remains unknown. We have reported a germinal center (GC) B cell tolerance mechanism regulated by sphingomyelin synthetase 2 (SMS2), whose expression is drastically reduced in SLE patients' B cells. Here, we study whether loss of SMS2 expression in GC B cells is female biased, and if this defect is caused by overexpressed lysine demethylase 6A (KDM6A), an XCI escapee and transcriptional regulator that promotes lupus pathogenesis.
Methods: Analysis of published genetic studies identified KDM6A as a candidate X-linked inhibitor of SMS2 expression. RNAseq data was used to analyze KDM6A expression in SLE patient B cells. Sgms2 and KDM6A mRNA levels in the NZBWF1 SLE mouse model were measured by RT-PCR. SMS2 expression in GC B cell specific KDM6A deficient mice was analyzed by flow cytometry. GC B cell specific KDM6A overexpression mice were generated by CRISPR-Cas9 gene editing.
Results: 1) Loss of SMS2 expression in the GC of NZBWF1 mice is female specific. We found that impaired SMS2-regulated GC B cell tolerance in female NZBWF1 mice was associated with reduced GC B cell Sgms2 mRNA but increased KDM6A mRNA compared to males. 2) SLE patient B cells have higher KDM6A mRNA but lower SGMS2 mRNA compared to healthy controls. 3) KDM6A deficient GC B cells have increased SMS2 protein expression.
Conclusions: Loss of SMS2 expression in the GC is female-specific, likely due to overexpression of KDM6A. GC B cell specific KDM6A knock-in mice will be studied to establish whether KDM6A overexpression inhibits SMS2-regulated GC B cell tolerance and results in SLE autoimmunity.

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

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

RET-fusion-driven lung adenocarcinomas (LUADs) are a rare and particularly aggressive subtype of lung cancer, often affecting young, non-smoker populations. While selective RET-TKI therapies are initially highly effective, they often fail to provide durable responses, with resistance mechanisms emerging over time. Notably, approximately 40% of patients exhibit resistance mechanisms that remain unidentified. To uncover these unknown mechanisms, we performed RNA sequencing on clinical samples from patients before and after RET-TKI treatment, which 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. Rb1 knockdown and E2F overexpression experiments confirmed upregulation of key DDR genes such as BRCA1, MSH6, and Rad18 in RET cell lines. To validate the role of DDR pathways in resistance, we established isogenic cell lines by overexpressing or knocking out BRCA1, MSH6, and Rad18, and conducted drug-tolerant persister (DTP) assays. DDR gene KO reduced the generation of DTPs while overexpression increased it. We next explored 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 significantly 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 in TKI-sensitive PDX models and resensitized resistant PDX tumors to selpercatinib. Our research highlights DDR pathways as a critical mechanism of resistance in TKI-treated RET-driven lung cancers and identifies XPO1 inhibition as a promising therapeutic strategy to overcome resistance.

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Andrew Wang Advisor(s): Jin Montclare Ph.D.

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Protein Micelles for Enhanced Drug Delivery to Glioblastoma

Protein-based nanocarriers bear highly desirable properties such as biodegradability and ability to facilitate passage through biological barriers such as the blood-brain-barrier. We have developed fusion proteins combining a helical domain with an intrinsically disordered domain. These fusion proteins form temperature-responsive micelles that can be used for drug delivery. Using modular protein engineering, we develop a strategy for improving the drug delivery efficacy of these protein micelles for the treatment of glioblastoma multiforme (GBM). Near-infrared (NIR) dye-labelled protein was injected into mice orthotopically implanted with GBM cells, and serum fluorescence measurements over time were fit to a 2-compartment pharmacokinetic model. The dye-labelled protein demonstrates prolonged short-phase half-life in tumor-bearing mice compared to control with similar slow-phase half-life, leading to an increased area-under-the-curve clearance and pointing to its sequestration in the tumor site. Endpoint fluorescence analysis of mouse organs ex vivo also supports this conclusion. Therefore, protein micelles bear potential for targeted treatment of GBM.