## C1

**Subhashini Sivagnanam** Advisor(s): Salvador Dura-Bernal Ph.D.

Co-author(s): William Lytton

### Enhancing the Integrity and Reproducibility of Computational Neuroscience Models through Provenance Tracking and Similarity Analysis

The reproducibility and validation of computational neuroscience simulations remain challenging due to the complexity of maintaining comprehensive records of datasets, parameters, and execution processes. This poster describes a pipeline for tracking and verifying the provenance of computational neuroscience experiments through three specific aims.First, we develop an automated pipeline that captures and stores cryptographic hashes of datasets alongside their associated metadata in an immutable distributed ledger, enabling independent validation of research artifacts.The system automatically extracts execution parameters, generates integrity checksums, and creates verifiable records of computational experiments. Second, we demonstrate this provenance tracking system using a neuroscience connectivity analysis workflow. Our implementation captures standardized metadata at each stage of the analysis pipeline, including data pre-processing, signal coupling computation, and topological analysis. The system records critical experimental parameters such as epoch duration, coupling measures, and execution environment details while maintaining cryptographic verification of input and output files. This comprehensive tracking ensures that researchers can reproduce experiments with identical parameters and verify the integrity of their results. Third, we enhance the system with similarity detection capabilities using Locality Sensitive Hashing techniques, enabling researchers to identify related computational models based on their parameters and structures. This feature facilitates the discovery of similar experiments and promotes knowledge sharing within the research community. Our implementation leverages existing computational infrastructure while establishing a pipeline for verifiable research practices.This approach promotes transparent, verifiable computational neuroscience that enhances reproducibility, enables independent validation, and accelerates scientific progress.

## C2

**Michelle Lam M.S.** Advisor(s): Thomas Postler Ph.D.

Co-author(s): -

### Investigating Mucosal Immunity with Dual-Immunogen VSV-based Vaccines

The mucosal immune system serves as the body's first line of defense, utilizing secretory IgA, mucins, antimicrobial peptides, and cytokines to combat infection. Intranasal vaccines leverage this system to induce localized immune responses thereby reducing viral replication, preventing infection, and limiting transmission. This strategy is particularly relevant for mucosally transmitted pathogens like human immunodeficiency virus (HIV). A key question is whether immune responses generated in lung mucosa can disseminate protection to other mucosal sites with VSV-based vaccinations, which we explore in this study.

The VSV platform is highly immunogenic and adaptable, allowing for the expression of diverse antigens by replacing its glycoprotein (G) with those from other pathogens. Our research focuses on developing dual-immunogen VSV vectors that express a stabilized HIV envelope glycoprotein (Env) alongside a functional glycoprotein to enable viral infection. We are evaluating several VSV vector candidates incorporating glycoproteins from Lassa virus (LASV GPC), SARS-CoV-2 (SCV2 Spike), and Marburg virus (MARV GP), selected for their ability to facilitate mucosal infection and their proximity to human trials. Our studies include dual constructs combining LASV GPC and SCV2 Spike, alongside constructs expressing Env with or without a transmembrane domain addition (EnvG), which enhances stability and infectivity.

Using a hamster model, we aim to identify the most effective vector candidates capable of eliciting strong mucosal immune responses and protective immunity. This research advances our understanding of mucosal vaccine strategies and informs the development of novel vaccines against mucosally transmitted pathogens.

## C3

**Xiang Li M.S.** Advisor(s): Xian-Cheng Jiang Ph.D.

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### Sphingomyelin Synthase Related Protein (SMSr) is a Regulator of Serine Palmitoyltransferase (SPT)

Sphingomyelin synthase-related protein (SMSr) is a member of the SMS family but lacks sphingomyelin (SM) synthase activity. We recently identified SMSr as a phosphatidylethanolamine-specific phospholipase C (PE-PLC) linked to metabolic dysfunction-associated fatty liver disease (MAFLD). However, its precise biological function remains unclear. Hierarchical clustering of human Genotype-Tissue Expression (GTEx) data revealed that SMSr co-expresses with SPT, the rate-limiting enzyme in sphingolipid biosynthesis, along with other sphingolipid metabolism-related genes in liver and adipose tissues. SMSr expression highly correlates with SPT expression in both tissues across genders and is associated with age and obesity. In mice, SMSr overexpression increased SPT activity, while knockout (KO) under a high-fat diet reduced it, altering levels of ceramide, SM, and glucosylceramide. Furthermore, PE treatment significantly suppressed SPT activity in vivo and in vitro in a dose-dependent manner. These findings suggest that SMSr regulates SPT and sphingolipid biosynthesis. Given the challenge of developing specific SPT inhibitors for MAFLD and cardiovascular disease treatment, targeting SMSr/PE-PLC activity may offer a novel therapeutic approach. Notably, unlike SPT KO mice, global Smsr KO mice are viable, fertile, and healthy, supporting the feasibility of this strategy.

## C4

**Pargol Mashati M.S.** Advisor(s): Prem Premsrirut Ph.D.,M.D.

Co-author(s): -

### Evaluating the therapeutic potential of a novel ADAM10 modulator in colorectal cancer

The ADAM10 metalloproteinase contributes to colorectal cancer tumorigenesis, predominantly through the activation of critical oncogenic pathways, including Notch and EGFR. This enzyme uniquely exhibits two conformations: an open, active state and a closed, inhibited state. Significantly, the active conformation, associated with elevated proteolytic activity, is prevalently observed in colorectal cancer cells. Our research investigates a novel human monoclonal antibody designed to selectively bind the active conformation of ADAM10, targeting its substrate-binding cysteine-rich domain.

Methodology: We assessed the anti-tumoral effects of this antibody in vitro through cell viability assays and signaling pathway analyses. We examined the antibody's efficacy across various colorectal cancer cell lines, including COLO205, SW620, and DLD-1, as well as CRC KrasG12D; Apc+/-; Trp53-/- (KAP) organoids. Additionally, we conducted in vivo studies using COLO205 and DLD-1 xenograft models, along with in vitro assays to evaluate anti-invasive properties in the SW620 metastatic cell line.

Results: Our data shows that the antibody can inhibit the activation of the Notch signaling pathway in COLO205 and SW620 cell lines, as well as in KAP organoids. In the DLD-1 cell line, which is characterized by active EGFR signaling but lacks active Notch signaling, the antibody effectively blocks EGFR phosphorylation. These molecular interactions correlate with reduction in cell viability across the tested cell lines. In vivo assessments reveal that the antibody substantially attenuates tumor growth in xenograft models. Additionally, it significantly decreases cell invasion in SW620 cells, indicating potential anti-metastatic properties.

Conclusion: This study highlights the therapeutic potential of targeting the active conformation of ADAM10 in colorectal cancer. The demonstrated efficacy of this novel antibody in diminishing tumor viability and interfering with major oncogenic pathways, comb

## C5

**Jenessa Holder M.S.** Advisor(s): André Fenton Ph.D.

Co-author(s): -

### Learning to Learn: How Cognitive Control Training Improves Learning

We use prior experiences to understand novel situations. However, most learning and memory animal research studies use naïve subjects with no prior experience to minimize confounds of prior experience. Accordingly, "Learning to Learn" (LtL) is understudied and arises from specific experiences that enable improved learning across unrelated tasks or settings, but the mechanism underlying LtL remains poorly understood. Our lab developed an active place avoidance (APA) task where mice needed to avoid a mild foot shock by using cognitive control, the ability to suppress distractions while focusing on task-relevant information. Using APA, we recently established that cognitive control training (CCT) caused neural circuit changes lasting months and resulted in LtL that was measured in multiple aversively conditioned tasks. Whether this LtL is general or specific to APA-related tasks is unclear. The present study investigates whether the CCT improves performance on all types of tasks, consistent with the general hypothesis, by testing whether the CCT improves subsequent learning of a set of unconditioned recognition tasks that have no cognitive or sensory features of APA.

Mice received CCT as before. A control group received the identical experience but were never shocked. Three days after training, recognition memory was assessed using an object recognition paradigm, during which the mice received object-context, object-place, and object-location recognition memory tests. Preliminarily, we observe that mice can detect a change in the environment during each memory test. However, we don't see a difference in learning between the CCT and control groups. This suggests that the CCT effect previously observed is not generalized to all tasks and may be instead specific to tasks that have features related to the CCT itself.

## C6

**Sailee Chavan M.S.,B.S.** Advisor(s): Chongmin Huan Ph.D.,M.D.

Co-author(s): -

### Improving Hydroxychloroquine's Efficacy for Systemic Lupus Erythematosus (Lupus) Treatment in a Preclinical Mouse Model

Rationale: Systemic lupus erythematosus is an autoimmune disease driven by antinuclear antibodies. Hydroxychloroquine (HCQ), a first-line lupus treatment for nearly 60 years, prevents flares by suppressing lupus autoimmunity while sparing normal immune function. However, its mechanism remains unclear. We hypothesize that HCQ enhances protective B cell tolerance via sphingomyelin synthase 2 (SMS2) in the germinal center (GC). SMS2 prevents lupus in mice by activating PKCÎ´-mediated apoptosis in autoreactive GC B cells. The antitumor drug 2OHOA alleviates lupus in NZBWF1 mice by activating the SMS2/PKCÎ´ pathway. Since HCQ has been linked to increased SM synthesis, we propose that HCQ may function by activating the SMS2/PKCÎ´ tolerance pathway in GC B cells.
Methods: NZBWF1 mice received HCQ (10, 13, or 16 mg/kg/day) and 2OHOA (200 or 400 mg/kg/day) via oral gavage for four weeks to determine the most effective dosage in reducing lupus markers, including serum anti-dsDNA IgGs, proteinuria, GC B cell proportion, and kidney morphology. Control mice received PBS and corn oil. The most effective HCQ and 2OHOA doses were then halved and combined in a four-week treatment to assess whether reduced dosages maintained or enhanced therapeutic effects.
Results: HCQ at 16mg/kg/day and 2OHOA at 400mg/kg/day significantly reduced lupus markers, with an even greater reduction observed in the combination treatment (HCQ 8 mg/kg/day and 2OHOA 200 mg/kg/day). In cultured B cells, HCQ increased SMS2 expression, and its effect on apoptosis was SMS2-dependent. These findings suggest that both HCQ and 2OHOA may activate SMS2/PKCÎ´ regulated tolerance in GC B cells, potentially enhancing their therapeutic effect.
Significance: Long-term HCQ accumulation can lead to adverse effects, often forcing patients to discontinue treatment and increasing the risk of lupus flares. Understanding HCQ’s mechanism of action may help develop strategies to inhibit lupus autoimmunity with reduced HCQ dosage.

**C7**

**Joseph Fajobi** Advisor(s): Peter Bergold Ph.D.

Co-author(s):-

**Boldine improves behavioral and histological outcomes following traumatic brain injury in mice**

Traumatic brain injury (TBI) represents a major public health burden due to the lack of available treatments and its contribution to the development of neurological conditions. Boldine is a naturally occurring alkaloid found in various plant species, including the Chilean boldo tree. Its safety and therapeutic properties have been demonstrated in rodent models of human disease, and it is widely used as a nutraceutical. We evaluated the effects of boldine treatment on behavioral and histological outcomes using a clinically relevant murine closed-head injury (CHI) model of TBI. Eight hours post-injury, mice were treated with either saline/DMSO or boldine/DMSO, followed by two daily injections for 3 days. At 7 days post-injury (DPI), mice underwent four days of Barnes maze training to assess spatial learning, followed by a probe trial at 12 DPI for memory recall. Boldine/DMSO-treated injured mice performed similarly to saline/DMSO-treated shams in latency, errors, and time spent in the correct quadrant, indicating that boldine treatment improved Barnes maze acquisition and retention to sham levels. NeuN+ and glial acidic fibrillary protein staining were used to assess neuronal density and astrocyte activation, respectively. At 14 DPI, injury lowered CA3 neuronal density in injured saline/DMSO-treated mice, while injured boldine/DMSO-treated mice maintained densities comparable to shams. These data showed that boldine prevents neuronal loss. Surprisingly, boldine treatment increased astrocyte activation in the contralesional hippocampus compared with injured saline/DMSO-treated mice. These findings suggest that boldine reversed CHI-induced spatial learning and memory deficits on Barnes maze due to its neuroprotective action. The increased astrocyte activation by boldine may also be beneficial for the large improvement in brain function following CHI.

## C8

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

Co-author(s): -

### Use of plasma free fatty acids by alveolar epithelial type 2 cell for surfactant lipid synthesis.

Surfactant is a lipoprotein complex that reduces surface tension during inspiration and prevents alveolar collapse during expiration. It is produced by alveolar epithelial type 2 cells (AT2) and is composed of phospholipids, proteins, and cholesterol. AT2 must tightly regulate lipid metabolism to ensure surfactant homeostasis. Disruptions in surfactant lipid levels are linked to adult lung diseases, but the pathways and extracellular substrates used for AT2 to maintain precise lipid metabolism are not understood. Prior research in the lab showed that expression of the low-density-lipoprotein receptor-related protein 1 (LRP1) is needed in AT2 for surfactant availability, and its loss compromises pulmonary function in vivo. In humans, SNPs in LRP1 are associated with multiple diseases, including chronic obstructive pulmonary disease. Understanding AT2 lipid metabolism will provide a foundation for future therapeutic strategies to improve lung function.

We studied the use of plasma free fatty acids (FFA) as a substrate for AT2 surfactant lipid production. Primary AT2 isolated from wild type (WT) and AT2-specific LRP1 inducible knockout mice (LRP1-/-) were incubated with [3H]-FFA and intracellular radioactivity was detected after 5 minutes. No differences were attributable to LRP1. In vivo, mice were intravenously injected with radiolabeled FFA. Blood was collected at 0.5, 5, 15 minutes and 4 h, and liver, heart, lung and surfactant were harvested at 4h. Most FFA was taken by tissues within 5 minutes equally for both genotypes. However, LRP1-/- showed lower radiolabel in lungs than WT mice 4h post-injection. No tracer was detected in surfactant for either genotype. In WT mice, there was a decrease of label detected from 15 minutes to 4h in hearts and lungs, without increased detection in blood.

These data show that lungs can take plasma FFA and suggest that they are consumed and not used as a source for surfactant lipid synthesis. LRP1 in AT2 is needed for this process.

**C9**

**Siddhartha Mitra M.S.** Advisor(s): William Lytton Ph.D.

Co-author(s): -

**NMDA driven spikes modulate plateau potentials in D1 and D2 Spiny Neurons**

The striatum receives and integrates excitatory inputs from the cortex and thalamus and outputs inhibitory signals to the thalamus and other subcortical structures via the globus pallidus. It also receives strong dopaminergic innervation from the substantia nigra pars compacta; degeneration of the input dopaminergic input contributes to the hypokinesia observed in Parkinson's Disease (PD). Around 95% of the striatum is composed of GABAergic cells known as Spiny Projection Neurons (SPNs) or MEdium Spiny Neurons (MSNs). Around half of these SPN's exclusively present D1 type metabotropic dopaminergic receptors (D1Rs) while the other half exclusively presents D2 type receptors (D2Rs). The D1R cells are involved in the 'go' or direct pathway, promoting motor movement, the D2R cells are considered to be part of the 'no go' pathway or indirect pathway, inhibiting motor movement. In anesthetized model animals, SPN's have been observed to display a cyclic state of depolarization from a somatic resting membrane potential of a 'DOWN state' of about -85 mV to a relatively depolarized -55mV 'UP state'. Evidence indicates similar regenerative dendritic plateaus exist in dendrites.It is hypothesized that the 'UP states' and plateaus create a spatio-temporal window allowing for integration of input information. Understanding of the generative mechanisms of these states is severely limited. Determining the factors could help determine targets for the treatment of PD. We performed computer simulations of neurons using physiologically plausible multi-compartment cell models to explore the generation of plateaus in SPN dendrites using the NEURON simulation software. Our simulations showed that NMDA-generated dendritic plateau potentials could occur in dendrites. Width of the plateaus differed between D1 and D2 neurons, which are morphologically different. Further modeling and simulation of the SPN will help identify specific channels and potential drug targets for PD.

## C10

**Tyler Lu M.S.** Advisor(s): Franke Barone Ph.D.

Co-author(s): -

### Generation of Function Pluripotent Cell-Derived Brain Endothelial Cells for in vitro Modelling of the Neurovascular Unit and Blood Brain Barrier

Highly specialized endothelial cells (ECs) in the brain endothelial cells (BECs) interact with various other cell types such as astrocytes and pericytes to form the basis of the blood brain barrier (BBB). BECs exhibit unique properties, including tight junctions, selective permeability, and specific transport systems, which distinguish them from endothelial cells in other tissues. These cells play a vital role in maintaining homeostatic brain function as well as regulating interactions between the immune and nervous systems. The development of an in vitro model of the human neurovascular unit (NVU) hinges on the use of ECs which can faithfully recapitulate multiple key organotypic functions. Human pluripotent stem cell (hPSC)-derived BMECs (iBMEC) have been widely used for this purpose; however, transcriptomic and functional characterization of their cellular identity has revealed that these cells are epithelial barrier-forming cells (Epi-iBFC) rather than BMECs. Here, we describe the development of a transcription factor-mediated strategy to generate ECs from hPSCs and their use for generation of 3D NVU models. We report that constitutive overexpression of two EC transcription factors, SOX7 and ERG, converts Epi-iBFC into adult vascular ECs (SE-rEC) that express an EC gene repertoire and respond to inflammatory cues. Moreover, co-culture of SE-rECs with astrocytes and pericytes in 2D and 3D induces a BBB-specific transcriptional profile in SE-rECs. Functionally, co-culture of SE-rECs with primary brain pericytes and astrocytes in a 3D microfluidics system reduces significantly EC permeability to biocytin and 70 KDa dextran compared to ECs cultured alone, primarily due to induction of the tight junction protein Claudin-5 and acquisition of BBB-inducing gene expression. We aim to use these reprogrammed SE-rECs to develop more faithful human BBB system in vitro to understand disease mechanisms and develop methods for drug delivery to the brain.

## C11

**Mohamed ElSayed M.D.** Advisor(s): William Lytton M.D.

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### Using Machine Learning to Predict Smoking Cessation in Serious Mental Illness: Study Timeline

Tobacco use disorder (TUD) is a disabling illness with 2-4 times higher prevalence in people with serious mental illness (SMI) compared to the general population. Many interventions have been devised to achieve smoking cessation, including pharmacotherapy (e.g., nicotine replacement therapy (NRT), Bupropion, Varenicline), contingency management, and behavioral support. All of these approaches work for some, but not the majority of individuals in controlled clinical trials. Predicting responses to specific interventions from individual characteristics would significantly improve abstinence and tobacco harm reduction outcomes. Machine learning approaches could achieve this, potentially preventing the development of chronic disease and preventing premature mortality for millions of individuals. One category of machine learning problems, classification, could be used to predict outcomes from specific inputs. During model development, a classification model is trained on labeled data before getting tested on data with concealed labels to determine the model's prediction accuracy. "Ideal" model performance requires high accuracy and low complexity.

Twelve previous studies have examined the prediction of smoking cessation in the general population using Random Forests or Deep Neural Networks. These studies have only focused on smoking in the general population and did not include participants with SMI. Moreover, only one of these studies directly compared the performance of RF to DNN and found them to be essentially similar. Machine-learning algorithms created from data on people in the general population who smoke may not be generalizable to people with SMI who smoke due to differences in smoking behavior, quit rates, relapse rates, and neurobiological vulnerability to nicotine. We here present the timeline of a project aiming to compare the accuracy of DNNs and RFs in predicting smoking cessation in people with SMI and comorbid TUD.

## C12

**Evan Davis B.S.** Advisor(s): John Danias Ph.D.,M.D.

Co-author(s): -

### The link between oral health and glaucoma in the Finnish population

Glaucoma is the leading cause of irreversible blindness worldwide. The disease is characterized by damage to the optic nerve, resulting in distinct visual field deficits corresponding to the damaged areas. Local inflammatory responses are implicated in the pathology of glaucoma. One such area of current research is the role of the oral microbiome and the effect of dental conditions on the development and progression of glaucoma. FinnGen is a research project that collects genomic and health record data to better understand the genetic basis of disease using multiple Finnish biobanks. The information is publicly available on the web. Using Risteys R10 to view FinnGen electronic health record data, we examined the relationship between having certain dental billing codes and then developing glaucoma at a later time. We obtained hazard ratios (HRs) for developing primary open-angle glaucoma (POAG) measured at two different time intervals, (1) between 1-5 years and (2) any/all years, after meeting criteria for inclusion in the following Risteys R10 endpoints: chronic periapical parodontitis; chronic periodontitis; dental caries 1 and operation codes, only avohilmo; dental caries 2 and operation codes, only avohilmo; dental caries 3 and operation codes, only avohilmo; dental pulpitis 1, only avohilmo; dentinal caries, gingivitis and periodontal disease, parodontitis or operation codes. For both time horizons and all dental conditions endpoints, we observed HRs > 2 with low p-values, the largest HRs being dental pulpitis (HR = 5.05, p = 5.15e-179) for any/all years and dental caries 2 (HR = 4.70, p = 1.03e-26) for incidence between 1-5 years, respectively. Overall, this data suggests that dental conditions, specifically diseases of tooth, gingiva, and periodontium, are associated with an increased risk of developing primary open-angle glaucoma.

## C13

**Daniel Mishan B.S.** Advisor(s): Harris Huberman M.D.

Co-author(s): -

### Investigation of L-leucovorin treatment on language impaired ASD children through behavior, folate receptor autoantibody status and biomarkers of blood brain barrier efficacy.

Autism Spectrum Disorder (ASD) is a neurodevelopmental disability, affecting approximately 1 in 36 individuals in the USA (Maenner 2023). Core symptoms of ASD include impairments in social communication and restrictive repetitive behaviors (RRBs) (APA 2013), leading to difficulties in daily functioning. Early diagnosis and intervention are critical for achieving optimal outcomes, yet the average age of diagnosis in the US remains around 54 months. Currently, behavioral and speech therapies are the mainstays of treatment, with no FDA-approved pharmacological interventions targeting core symptoms.
Research has shown a strong association between Folate Receptor Autoantibodies (FRAA) and ASD, with FRAAs blocking folate transport across the blood-brain barrier (BBB) and contributing to CNS folate deficiency (a.k.a. vitamin B deficiency) in a majority of ASD-diagnosed children. Leucovorin, a derivative of vitamin B9, has shown promise in alleviating some core symptoms, particularly in language and RRBs, in older children (3 to 15 years, median age 7.2yrs) with ASD (Frye 2018).
The project encompasses three aims: assessment of treatment efficacy, exploring FRAA status and treatment response, and lastly investigating whether FRAA status is associated with biomarkers of blood brain barrier (BBB) damage and/or neuroinflammation.
The expected outcomes of this project are 1) to determine the efficacy of l-leucovorin in treating core ASD symptoms; 2) to establish links between FRAA positivity, symptom severity, and treatment response; and 3) to explore changes in biomarkers of BBB efficacy and neuroinflammation. This research holds the potential to significantly impact early interventions for ASD, paving the way for targeted pharmacological approaches to improve outcomes for affected children.

## C14

**Scott McElroy** Advisor(s): Salvador Dura-Bernal Ph.D.

Co-author(s): -

**Title: Identifying cell-type-specific alterations underlying schizophrenia-related deficits in auditory steady-state response and aperiodic spectral activity: insights from a multiscale model of audit**

Individuals with schizophrenia exhibit a variety of symptoms categorized as positive, negative, and cognitive. A cognitive symptom extensively studied using electroencephalography (EEG), is sensory processing deficits, particularly in the auditory system. These deficits manifest as abnormalities in event-related potentials and cortical oscillations. In particular, this work focuses on the reduced 40 Hz Auditory Steady State Response (ASSR) and alterations in spontaneous 1/f slope, which are thought to reflect impaired inhibitory interneuron activity and gamma oscillations. We have extended our previously developed model of auditory thalamocortical circuits to investigate the source of these schizophrenia-related EEG biomarkers. This model simulates a cortical column containing over 12k neurons and 30M synapses. Neuron densities, laminar locations, biophysics, and connectivity at the long-range, local, and dendritic scale were derived from published experimental data. Auditory stimulus-related inputs to the thalamus were simulated using a phenomenological model of the cochlea. The model reproduced in vivo cell type and layer-specific firing rates, local field potentials, and EEG signals consistent with controls. Changes made to the model to reproduce schizophrenia patient EEG biomarkers were informed using data from positron emission tomography imaging, genetics, and transcriptomics specific to schizophrenia patients. Specifically, we have employed experimental findings such as layer-specific reductions in somatostatin and parvalbumin expression in interneurons, reduced NMDA efficacy, and feedforward circuit-specific connectivity changes to explore mechanistic explanations for EEG biomarkers of schizophrenia. This work aims to bridge the gap between experimentally determined molecular and genetic changes associated with schizophrenia and the resulting circuit and network behavior that give rise to robust EEG biomarkers.

## C15

**Riley Morrone B.S.** Advisor(s): Peter Bergold Ph.D.

Co-author(s): -

### Human 3R and 4R tau expression improves function and decreases axonal injury following traumatic brain injury in mice

Clinical traumatic brain injury and closed head injury (CHI) in mice damage the brain in many ways, yet the axonal cytoskeleton is particularly vulnerable. Tau protein expression may alter the extent of brain injury since tau crosslinks and stabilizes axonal microtubules. Adult humans express six tau protein isoforms with either three (3R) or four (4R) microtubule binding sites yet adult mice express only 4R isoforms. 3R tau containing microtubules are more flexible since 3R binds tubulin with lower affinity than 4R. Recent studies show tau in synapses with pre- and post- synaptic functions. I tested whether 3R tau expression alters outcomes following CHI. Cognition and brain damage following CHI is examined in C57/BL6 wildtype mice (WT) that express murine 4R tau or in human tau locus knock-in (MAPTKI) mice that express human 3R and 4R tau. CHI produces similar initial injury in WT and MAPTKI mice as measured by righting reflex. At 14 days post injury, Active Place Avoidance (APA) evaluates spatial memory in WT and MAPTKI mice. Injured MAPTKI mice acquire APA, whereas injured WT mice are impaired. APA acquisition is hippocampal-dependent so hippocampal injury was compared in WT and MAPTKI mice. Injured WT and MAPTKI mice have similar hippocampal neuronal loss. Injured WT mice have a selective 4R tau loss compared to injured MAPTKI mice. 3R tau expression is unaffected in injured MAPTKI mice. Injured WT mice lose 4R tau in major hippocampal axons including the perforant path and mossy fiber. Injured WT mice lower 4R tau expression in CA1 stratum radiatum and CA3 stratum lucidum suggesting loss of synaptic tau. These data suggest that despite similar initial injury, CHI causes axonal and synaptic 4R tau loss in WT mice compared to MAPTKI mice. APA deficits in injured WT mice likely arise due to impaired axonal transport and synaptic dysfunction. These data also suggest that 3R tau expression improves brain function by limiting hippocampal injury following CHI.

## C16

**Tarek Khashan** Advisor(s): Salvador Dura-Bernal Ph.D.

Co-author(s): -

### Towards a detailed mechanistic model of human cortical microcircuits that accurately predicts the cellular- and circuit-level effects of TMS

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique that alters activity in a small brain region and can treat neurological conditions. TMS parameters, including location, intensity, and frequency, are typically chosen using a "one-size-fits-all" approach. Personalizing TMS can enhance target engagement and treatment efficacy but requires accurately predicting its effects on brain circuits, which remains unsolved. Mechanistic biophysical simulations offer a powerful approach to integrate experimental data and predict TMS effects at molecular, cellular, and circuit scales. They can simulate local field potentials (LFP), EEG, and TMS effects, informing optimal parameter selection.

We present preliminary results from simulating TMS in a detailed human cortical circuit model. Adapted from a rat somatosensory cortex model, our model includes 6,796 neurons of 55 cell types across 6 layers, with human-like morphology, physiology, and axons necessary for accurate TMS simulation. It incorporates distance-dependent connectivity, synaptic background activity, and short-term plasticity to reproduce in vivo-like firing. We implemented the model using NEURON and NetPyNE.

Simulating biphasic TMS pulses at 30 Hz (1 sec, 60 V/m) induced layer 5 pyramidal neuron spiking synchronized to stimulation pulses. At 80 V/m, neurons across all layers fired synchronously. Disconnected neurons did not spike, indicating that circuit connectivity and activity lower the TMS response threshold.

These results highlight the need to simulate circuit activity to characterize TMS effects. Next, we will validate against human TMS-EEG data, simulate disease-related electrophysiological biomarkers, and evaluate TMS parameters for restoring healthy dynamics.

## C17

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

Co-author(s): -

### Linking Neuronal Channelopathies to Circuit E/I imbalances and Neurodevelopmental Disorders in a Multiscale Model of Motor Cortex

Neurodevelopmental disorders (NDDs) such as epilepsy, autism spectrum disorder, and developmental delays vary greatly clinically and often impair social interaction, speech, and cognitive development. The hallmark of these disorders is an imbalance in excitatory/inhibitory input (E/I), which leads to dysfunction in neuronal circuits during development. Disorders in which the activity of neuronal ion channels become altered, known as brain channelopathies, are particularly attractive for studying E/I imbalance because their function can be directly linked to neuronal excitability. Ion channels play a vital role in generating the electrical activity in neurons and disruptions to their normal activity are highly associated with NDDs. Studying channelopathies in single cells is a robustly established procedure, however, studying how specific channel mutations affect the neuronal circuit requires a much more complicated protocol. Using a previously published primary motor cortex (M1) model, we utilize a large-scale, highly detailed biophysical neuronal simulation to investigate how channel mutations affect individual and network neuronal activity. These simulations can provide a mechanistic understanding of the role of channelopathies in E/I imbalance and how they contribute to NDD pathology. Using the M1 cortical column simulation, we measured how channel biophysical changes affect the overall excitability of the network and changes in neuronal population firing patterns to better understand the pathophysiology of the simulated channelopathy. This model provides a tool for modeling specific channelopathy cases and also exploring the effects of known pharmacological agents to return E/I balance in a time and cost efficient manner. This will allow us to better understand therapeutic targets that specifically target disease symptoms and possibly unveil novel therapeutics that can be translated clinically.

## C18

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

Co-author(s): -

### Pre-injury intervention with SV2A-ligand antiseizure drug prevents injury-induced changes in memory performance after traumatic brain injury in rats

Traumatic brain injury (TBI) is a leading cause of disability worldwide, with an estimated global incidence of 27–69 million cases annually. Two major pathological sequelae of TBI are cognitive dysfunction and posttraumatic epileptogenesis (PTE). Our past electrophysiological, behavioral, and biochemical studies suggested that timely post-injury administration of the SV2A ligand antiseizure drugs (ASDs), levetiracetam (LEV) or brivaracetam (BRV), prevents PTE following controlled cortical impact (CCI) injury. This effect was marked by reduced stimulus-evoked and spontaneous epileptiform activity, and prevention of increased seizure susceptibility and hippocampal GluR1/GluR2 ratio elevation. In this pilot study, we tested whether prophylactic administration of BRV (0.21 – 21.0 mg/kg) provides neuroprotection against injury-induced deficits in cognitive function. Rats (postnatal days 25–36) underwent severe CCI trauma (2.0 mm depth) and were randomly assigned to receive a single dose of either BRV (IP) or the saline vehicle at 15–20 minutes before injury. Uninjured controls (sham) did not undergo CCI. Five to eight weeks post-injury, rats completed a four-day active place avoidance test (APA), consisting of one priming day, two training days, and retention test on the last day. Cognitive performance was assessed using four metrics: time to first shock-zone entry, number of shock-zone entries, percentage of time spent in the shock zone, and maximum shock-zone avoidance time. Sham-injured rats outperformed CCI-saline rats across all metrics, confirming cognitive impairment. However, CCI-BRV rats showed significantly better performance than CCI-saline rats, reaching levels equivalent to sham controls. These findings suggest that pre-injury BRV administration provides neuroprotection against TBI-induced cognitive deficits. This study provides insights into potential neuroprotective effects of SV2A ligand ASDs, contributing to future therapeutic strategies.

## C19

**Radhika Singh-Agarwal M.S.** Advisor(s): David Christini Ph.D.

Co-author(s): -

### Characterizing Differences in hERG Expression between Suspended vs Attached iPSC-CMs

The need to engineer an assay for assessment of proarrhythmic potential of new drugs, which does not only depend on hERG assays has sparked an interest in using iPSC-derived cardiomyocytes as an alternative to hERG-only cell lines. hERG, also known as delayed rectifier K+ current (IKr) is important for cardiac repolarization and its inhibition causes acquired long QT syndrome, which can lead to cardiac arrhythmia. In vitro-derived iPSC-CMs can be used for electrophysiology studies using patch-clamping to evaluate the effect of drugs on different ion channels. Nonetheless, variations in measured electrical properties between the labor-intensive manual patch-clamp and high-throughput automated patch clamp (APC) pose challenges. Particularly concerning is the absence of hERG current in iPSC-CMs, rendering the use of APC impractical for hERG assays. The focus of this study is to determine what causes the absence of hERG in iPSC-CMs and explore potential resolutions. A notable difference between the two techniques is the nature of the sample: iPSC-CMs for manual patch-clamp are attached to a matrigelcoated culture dish whereas APC requires suspended cells. Hence, the detachment of cells from the extracellular matrix (ECM) proteins may deactivate or alter the localization of hERG channels. Additionally, cell dissociation enzymes employed during detachment may compromise the integrity of this ion channel. To address these issues, two iPSC cell lines have been differentiated into cardiomyocytes to investigate the molecular and cellular differences between cells in suspended and ECM-adherent states. The findings are poised to provide insights into the challenges identified above and enhance patch-clamping procedures with the APC.

## C20

**Benjamin Tessler B.S.** Advisor(s): Steven Fox Ph.D.

Co-author(s): Jeffrey Goodman

### Temporal Interference Stimulation for Precise Non-Invasive Motor Mapping: Simulation and In Vivo Validation

Electrical brain stimulation is vital for investigating neural function and developing therapeutic interventions. Traditional non-invasive transcranial electrical stimulation (TES) methods, while safe and accessible, are limited by diffuse activation and a lack of precision. To address these limitations, we employed Temporal Interference (TI) stimulation—a novel technique that enhances specificity with minimal current spread. We simulated electric field profiles using a virtual rat head model to predict motor maps during motor cortex stimulation and subsequently validated these predictions with in vivo experiments. Simulation results revealed that, compared to conventional TES, TI produced motor maps with higher resolution, characterized by clearly defined regions, sharper borders, and reduced overlap. The replicated in vivo experiments confirmed these findings. These results demonstrate that TI can more accurately target specific brain regions, potentially improving the efficacy of non-invasive brain stimulation therapies while minimizing off-target effects. Overall, these findings demonstrate the transformative potential of precise non-invasive targeting, paving the way for safe, low-cost treatments and experimental tools to modulate previously inaccessible brain regions.

## C21

**Tadeusz Wroblewski B.S.** Advisor(s): Ernest Barthélemy M.D.,MPH, MA

Co-author(s): Peter B. Barr, Tim B. Bigdeli

### Allostatic load and neuropsychiatric outcomes following TBI in the AoU Database

Chronic stress causes autonomic and hypothalamic-pituitary-adrenal axis dysregulation which has profound impacts on the brain. There is an inherent bidirectional relationship between chronic stress and traumatic brain injury (TBI), with TBI causing increased physiological stress and chronic stress impacting TBI recovery. Allostatic load (AL) is a conceptual framework developed to capture the burden of chronic stress using an aggregate of blood-based and anthropomorphic biomarkers. Utilizing the All of Us (AoU) Database, we have developed a comprehensive AL index (ALI) to investigate the relationship between AL and incident neuropsychiatric outcomes following TBI. ALI was estimated with a single-factor confirmatory factor analysis model using seven previously established markers: systolic BP, diastolic BP, HDL, triglycerides, BMI, HbA1c, and c-reactive protein. Neuropsychiatric outcomes were assessed in individuals with an established diagnosis of TBI and estimated ALI. The final ALI model achieved appropriate fit (CFI=.988; RMSEA=.035) with partial scalar invariance observed across race/ethnicity groups, gender, and medication status ($\Delta$CFI<-.01; $\Delta$RMSEA<.015); subsequent comparisons used the model that was invariant across race/ethnicity. We observed disparities in ALI, with the non-Hispanic (NH) White group having the lowest ALI while the NH-Black group had the highest ($p<.001$). Consistent with prior research, ALI was positively correlated with area-level social deprivation ($R=.17$; $p<.001$). Amongst the TBI cohort, higher ALI was observed in those diagnosed with schizophrenia or psychosis; mood disorders; PTSD; sleep disorders; substance use disorders; suicidal ideation or attempt, and headache disorders ($p<.01$). ALI may serve as an important measure to investigate the role of pre-existing chronic stress on outcomes following TBI, and further work aims to understand the underlying genetic architecture of stress resilience in the context of TBI.

**C22**

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

Co-author(s): -

**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 are conducting 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 are cloning 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 are developing 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.

## C23

**Dan Kamen B.A.** Advisor(s): Sergei Grivennikov Ph.D.

Co-author(s): -

### Reassessing the Role of Epithelial IL-23 Signaling in Intestinal Inflammation

Background: Interleukin-23 (IL-23) is a key pro-inflammatory cytokine primarily released by dendritic cells and macrophages, crucial for both the differentiation and maintenance of Th17 cells. Research into the specific role of epithelial IL-23 signaling has linked the protective role of epithelial IL-23 signaling in intestinal inflammation. However, our findings have raised questions regarding these results.
Methods: A murine model lacking the IL-23 receptor in villus and crypt epithelial cells (IL-23VilCre) of the intestines was established using Cre recombinase. Subsequently, IL-23VilCre and mice without the Cre recombinase were exposed to Dextran Sodium Sulfate (DSS) water to induce colitis, with weight loss and colon length serving as metrics for evaluating inflammation severity.
Results: Contrary to previous findings suggesting a protective effect of epithelial IL-23 signaling in intestinal inflammation, our results demonstrated no significant differences in weight loss or colon length between IL-23VilCre mice and mice with IL-23 receptor in the intestinal epithelial intact. These findings indicate a discrepancy between our results and previous literature regarding the role of epithelial IL-23 signaling in intestinal inflammation.
Discussion: Our findings present notable discrepancies compared to previous literature, prompting questions regarding the involvement of epithelial IL-23 signaling in intestinal inflammation.

## C24

**Masataka Mizuno B.S.** Advisor(s): Kyung-Hyun Park-Min Ph.D.

Co-author(s): -

### Single-cell genome analyses determine the trajectory of osteoclast differentiation in healthy subjects and osteoporosis patients

Background and Significance
Osteoporosis is a systemic bone disorder causing low bone mass and compromised bone strength, leading to an increased risk of fracture. Osteoporosis is more prevalent in the aging population and provides significant health challenges to the elderly. Even a single fracture in the elderly results in impaired quality of life, significant morbidity, and mortality. Osteoporosis can be preventable if it is treated. However, osteoporosis is a silent disease, and there are no symptoms until fractures occur. Thus, the early diagnosis of osteoporosis is important. One important cause of osteoporosis is the dysregulation of osteoclast activities. Our previous study identified human circulating osteoclast precursor cells (cOCPs) that have higher osteoclastogenic potential. We hypothesize that cOCPs travel to bone marrow and then fuse with mature osteoclasts, which can be used as a biomarker for in vivo osteoclast activity. Our goal is to identify relevant marrow OCPs (mOCPs) within the bone marrow and blood of patients with osteoporosis.
Methods
Single-cell RNA sequencing (scRNA-seq) data and bulk RNA sequencing data were obtained from both our lab and publicly available datasets. scRNA-seq analysis was performed using Seurat, an R package for single-cell analysis. Seurat calculated highly variable genes across the single cells and found ~2,000 variable genes. Gene expressions of the target populations were characterized and analyzed for osteoclastogenic potential. Cells were also analyzed by flow cytometry analysis and were cultured with M-CSF and RANKL to test osteoclastogenesis.
Results
Through the combined use of flow cytometric and functional analyses, we have identified a population of circulating osteoclast precursor cells (cOCPs). The frequency of cOCPs is affected by bone diseases and their response to anti-resorptive medications. We have also discovered that cOCPs have a unique transcriptomic signature. To further investigate their res

## C25

**Matthew Heider B.S.** Advisor(s): John Danias Ph.D.,M.D.

Co-author(s): -

### An Ex-Vivo Human Corneal Rim Perfusion Model

Purpose: Trabecular meshwork (TM) dysfunction is a primary factor in glaucoma pathophysiology, necessitating reliable models to investigate aqueous humor dynamics. We developed an ex vivo perfusion model utilizing bisected human corneal rims to assess feasibility as an alternative to anterior segment perfusion systems. The paired design minimizes inter-sample variability while maximizing tissue use. Methods: A custom perfusion chamber was designed using CAD modeling and 3D printing. Human corneal rims, obtained under an IRB exempt protocol from tissue discarded after penetrating keratoplasty, were bisected and affixed to the perfusion device using cyanoacrylate glue. Samples were subjected to constant pressure of 8 mmHg controlled by an air compressor and water column. Flow rate and pressure data were collected via CorSolutions Flow Meter Plus and pressure transducer. After 48h perfusion, pressure was changed in increments of 7.5mmHg to 30mmHg, while flow rate was recorded. Outflow facility was calculated at the slope of the pressure–flow relationship.Results: Pressure and flow readings demonstrated stability throughout the constant pressure period. Flow increased with increasing pressure but variability in flow was noted. The experimental outflow facility averaged 22.05-27.57 nL/min/mmHg, significantly lower than the expected 445 nL/min/mmHg, potentially due to tissue degradation or adhesive interference with the TM. Conclusion: Our findings show the feasibility of using a bisected corneal rim as a perfusion model for studying aqueous humor outflow. The paired experimental design offers a platform for evaluating pharmacological intervention while improving tissue utilization efficiency. Observed flow rate variability highlights the need for further methodological refinements. Future work will focus on optimizing tissue preparation, improving sealing techniques, and enhancing data reproducibility to strengthen the model's utility in translational glaucoma research.

## C26

**Dhruva Chhabra B.S.** Advisor(s): Qais Naziri M.D.,MBA

Co-author(s): -

### Essential Tremor is Associated with Longer Hospital Length of Stay and Greater Risk of Institutional Discharge in Patients Undergoing Total Joint Arthroplasty

Introduction
Essential Tremor is a prevalent condition in the elderly population and is associated with a higher fall risk that can subsequently lead to physical injury. This is especially relevant when older patients have other comorbidities such as muscular atrophy and osteoporosis. Given the elevated risk of falls and injury, it's postulated that these patients would have greater rates of orthopedic surgery. In this study, we analyzed surgical outcomes for patients with Essential Tremor undergoing a total joint arthroplasty.
Methods
A retrospective cohort study was performed using the National Readmissions Database between 2009-2019. All patients undergoing a total hip arthroplasty or a total knee arthroplasty during this period were included and classified based on the presence of underlying Essential Tremor. Important demographic information (Age, Gender, BMI, Charlson Comorbidity Index, Osteoporosis/Arthritis diagnosis, Smoking History, Insurance status, Hospital Characteristics) was accessed for the two groups. Multivariable logistic regression was done for various outcome measurements (length of stay, in-hospital mortality, institutional discharge, medical/post-op complications, readmission, and reoperation).

Results
Patients with Essential Tremor tended to have an advanced age ($p<0.001$), higher Charlson comorbidity indices ($p<0.001$), as well as history of osteoporosis ($p<0.001$). A multivariable regression analysis found that essential tremor was independently associated with a prolonged hospital length of stay (OR 1.326, 95%CI 1.261 to 1.395, $p < 0.001$) and risk for institutional disposition (OR 1.211, 95% CI 1.156 to 1.268, $p < 0.001$).

Conclusion
Essential Tremor was independently associated with increased hospital length of stay and institutional discharge without significantly elevated medical/post-op complications. This investigation lays the groundwork for medical optimization for patients with Essential Tremor receiving a orthopedic procedure.

**C27**

**Jason Lam B.S.** Advisor(s): Jordan Kreidberg Ph.D.,M.D.

Co-author(s): Valerie Schumacher

## Alpha V Integrins on Podocytes Have a Protective Role During Adriamycin-Induced Glomerular Injury in Murine Models

Integrins are an important class of cell-surface proteins that mediate extracellular-matrix adhesion. Our interest is in the role of integrins during glomerular disease. In this study, we investigate the role of αV integrins on podocytes in the repair response after Adriamycin-induced glomerular injury in adult mice. We hypothesize that αV integrins have a protective function during injury, and can be used as a therapeutic target to treat kidney diseases such as focal segmental glomerulosclerosis. To test our hypothesis, we conditionally deleted the ItgaV gene in podocytes of adult mice, using a podocyte-specific, tamoxifen-inducible Cre-loxP system. We successfully generated viable mice with the inactivated ItgaV gene. Prior to Adriamycin-induced injury, knockout mice were non-proteinuric and had intact glomerular filtration barriers, although glomerular capillaries were segmentally dilated. After Adriamycin-induced injury, we observed massive proteinuria in knockout compared to control mice, indicating the role of αV integrins in response to injury. In conclusion, our studies reveal that in normal non-injury contexts αV integrins on podocytes are not essential; however, after injury their role becomes crucial for the ability of podocytes to respond to injury. We suggest that αV integrins have a protective function during glomerular injury and are a potential therapeutic target.

## C28

**Samuel Sabzanov M.S.** Advisor(s): Todd Sacktor M.D.

Co-author(s): -

### PKCι/λ compensates for PKMζ during long-term spatial memory storage in PKMζ-null mice

Rationale: How are long-term memories (LTMs) stored in the brain? Maintenance of LTMs requires protein synthesis soon after strong synaptic stimulation or learning, and these proteins are believed to sustain synaptic potentiation or behavioral modification. One hypothesis for a mechanism of LTM maintenance involves the persistent increase of an atypical protein kinase C (aPKC) isoform, PKMζ. Previous findings have shown that PKMζ persistently increases in the hippocampus region CA1, including stratum radiatum (1), and that this increase positively correlates to the strength of spatial LTM (2). While PKMζ is essential for LTM in wild-type (WT) mice, redundant compensatory mechanisms have been shown in PKMζ-null mice, such as with another aPKC isoform, PKCι/λ (3). Here, we eliminated both aPKCs, by conditional knockout (cKO) of PKCι/λ in the hippocampus (PKCι/λ-null mice are lethal) in PRKCIfl/fl-PRKCZ-/- mice, and examined the maintenance of spatial LTM and PKCι/λ compensation for PKMζ in the hippocampus by immunohistochemistry (IHC).
Methods:The PRKCIfl/fl-PRKCZ-/- mice received either Cre- or eGFP-adeno-associated virus (AAV) injections bilaterally into the hippocampus 3 weeks prior to an active place avoidance (APA) task, which requires three 30-min training trials in one day with a 2 hour inter-trial interval and rapidly forms spatial LTM. The LTM retention was examined 24 hours later, and brains were harvested, fixed, and analyzed by IHC. WT mice received Cre-AAV as a control.
Results/Discussion: Compared to WT mice, PRKCIfl/fl-PRKCZ-/- mice that received Cre-AAV (PKCι/λ cKO and-PKMζ KO) showed significant impairment in the memory retention test, while PRKCIfl/fl-PRKCZ-/- mice that received eGFP-AAV (PKMζ-KO) did not. The IHC results confirm that PKMζ-KO mice show increased expression of PKCι/λ in the stratum radiatum of hippocampal region CA1 during spatial memory storage due to compensation for PKMζ. These data support a key role for aPKC in LTM maintenance.

**C29**

**Jesus Lopez B.S.** Advisor(s): Ivan Hernandez Ph.D.

Co-author(s): -

**Vascular cognitive impairment (VCI) decreases cognitive flexibility in a murine model of Alzheimer's disease**

Vascular cognitive impairment (VCI) and Alzheimer's disease (AD) are neurological disorders characterized by progressive neuronal death and cognitive decline. Previously it has been hypothesized that VCI and AD may have a relationship where VCI can lead to AD; thus, the co-occurrence of vascular disease and AD is the rule (not the exception) in the context of cognitive impairment and dementia, conceptualizing VCI as an important component of AD. Therefore, we prepare a murine model using the partial occlusion of the left common carotid artery (LCCA) as a VCI model on transgenic-AD (APP/PS1) mice compared with WT animals. These mice were subjected to cognition tasks: novel object recognition (NOR) on days 33-36 and active place avoidance (APA) on days 37 and 38, and its conflict (APAc) on day 39 after the surgery. We found a trend but no statistical difference in the NOR task associated with phenotype or surgery. Whereas APA shows significant inter-trial and intra-trial differences associated with phenotype, the APAc task shows a statistically significant synergistic effect of phenotype and surgery, suggesting that hypoperfusion exacerbates cognitive problems in APP/PS1 mice. Since a decrease in performance in the APAc task has been associated with decreased cognitive flexibility and neurogenesis impairment in the dentate gyrus, we will now be comparing biogenesis of ribosomes and neurogenesis across the groups. For that, we will perform immunohistochemistry and confocal microscopy to determine whether we find differences amongst groups.

## C30

**Alexia Collins B.S.** Advisor(s): Simon Rabinowitz Ph.D.,M.D.

Co-author(s): Sharon A. Glick

### Concordance of Inflammatory Bowel Disease and Hidradenitis Suppurativa

Introduction: Inflammatory bowel disease (IBD) and Hidradenitis Suppurativa (HS) (1) are both genetically and phenotypically distinct autoimmune conditions that are associated with pyoderma gangrenosum (2). As the US prevalences of IBD and HS are 0.7% (3) and 0.7-1.2% (4) identifying four patients with coincident IBD and HS in our practice, suggests the possibility of overlapping pathogeneses.
Methods: To provide insight into potentially shared mechanisms between IBD and HS, a retrospective chart review of the four patients is summarized in the table.
Results: All four had Crohn disease. Maximum BMI, age and PCDAI at diagnosis were recorded. Both females required several steroid injections for HS and ultimately surgical sinus tract removal. Both diseases were most aggressive in the younger female. She required loop ileostomy and Seton placement for rectal stenosis/fistula, and widespread HS sinus tract removal.
Discussion: Two cases had a delay in diagnosis, despite typical clinical characteristics (F#:IBD; M#:HS). HS should be considered in an IBD patient with extremely high BMI and/or skin findings including recurrent abscesses, sinus tracts and comedones in intertriginous areas.
Our cohort suggests that TNF alpha participates in both diseases and that surgical removal of all sinus tracts in an anatomic area for HS may decrease the inflammatory burden and may increase the efficacy of anti-TNF agents.
Anecdotally, the ability of risankizumab to attenuate symptoms in the patient with the most aggressive form of both diseases suggests that IL-23 sensitive trafficking of TH17 cells could participate in the shared pathogenesis.

## C31

**Jenelle Cocorpus B.S.** Advisor(s): Tamar Smith-Norowitz Ph.D.

Co-author(s): Stephan Kohlhoff, Susan Holman, Jessica E. Yager, Elizabeth Helzner, Mohsin Sardar

### Racial and Ethnic Disparities and HIV Viral Load Among People Living with HIV During the Coronavirus-19 Pandemic in Brooklyn, New York

Rationale: Racial/ethnic disparities exist in the diagnosis of human immunodeficiency virus (HIV) and viral load suppression among people living with HIV (PWH). Previous studies in our laboratory demonstrated the association between Coronavirus-19 (COVID-19) and viral load suppression in PWH in NYC. Lower viral load suppression in certain racial groups could lead to the risk of higher HIV transmission and disease progression. This study examines the association between racial/ethnic disparities and viral load, including CD4+ T-cell counts in PWH.

Methods: A retrospective chart review was conducted for 1,130 adult patients receiving care (Brooklyn, NY). Patients were stratified by race and ethnicity. HIV viral load and CD4+ T cell counts were compared across three timeframes (pre-pandemic, January 1, 2019, to December 31, 2019; first pandemic phase, March 19, 2020, to December 31, 2020; and second pandemic phase, January 1, 2021, to May 11, 2023) with analysis of variance (ANOVA) and Kruskal-Wallis tests.

Results: The distribution of mean HIV viral load was different across races during the first phase of the pandemic (P = 0.006), but not CD4+ T cell counts. Specifically, the mean (standard deviation [SD]) HIV viral load was higher in Black compared with White patients (5,015.1 (43,772.3) vs 3,735.0 (16,945.9), P = 0.015) during the first pandemic phase. Non-Hispanic versus Hispanic had higher mean (SD) HIV viral load (3,878.4 (30,138.9) vs 2,809.1 (13,145.9), P = 0.028) during the pre-pandemic phase. No differences in race were observed pre-pandemic or during the second phase (ANOVA, Kruskal-Wallis tests).

Conclusions: HIV viral load differed among racial groups during the first pandemic phase, highlighting exacerbated racial disparities.

## C32

**Olivia Rau B.A.** Advisor(s): Ellen Casey M.D.

Co-author(s): -

### Differential effects of oral contraceptives on the structure and function of the anterior cruciate ligament

Background: Fluctuations in estrogen and progesterone concentrations affect athletic performance and connective tissue mechanisms during various stages of the menstrual cycle and may contribute to sex differences in sports-related injuries. Prior database studies suggest that oral contraceptives (OCPs) may reduce the risk of anterior cruciate ligament (ACL) injury by 20%. However, the underlying mechanisms for this protective effect are unknown. The estrous cycle seen in rodents is commonly studied to inform understanding of the menstrual cycle. Mouse models assessing OCPs impact on the estrous cycle can inform this clinical phenomenon.

Hypothesis: Mice exposed to OCPs with low ethinyl estradiol and highly androgenic progesterone will demonstrate increased ACL size, stiffness, and load to failure. Hormones were administered in diet, estrous cycle staging was conducted 4x/week. After 8 weeks the mice were sacrificed. Serum hormone levels were measured at time of death and various organs were harvested. Knees were dissected down to the ACL and mechanical testing was performed to calculate force to failure.

Methods: 18 female 12-week old C57BL/6 mice were placed into 3 groups of 6: one group received levonorgestrel (highly androgenic progesterone) and a low dose of ethinyl estradiol (EE), another group received desogestrel (minimally androgenic progesterone) and a high dose of EE, and controls.

Results: The minimally estrogenic and highly androgenic progesterone had a statistically significantly greater load to failure (N) than the highly estrogenic and lowly androgenic and controls.

Significance of Study: Given the high prevalence of OCP use in active females, delineating the musculoskeletal effects of the hormones contained in OCPs is warranted. Findings from this study will add to knowledge of the potential protective mechanisms of OCPs for ACL injury. This data will be used to support further research needed to prevent ACL injuries and personalize care.

## C33

**Nicole Gladstein B.S.** Advisor(s): Kevin Tehrani M.D.

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### Systemic Tranexamic Acid in Breast Reduction Mammoplasty

Purpose Statement: Tranexamic acid (TXA) is administered to reduce perioperative blood loss and prevent hematoma formation. Its use has been studied in several contexts including trauma surgery, obstetrics, orthopedic surgery, orthognathic and maxillofacial surgery, and plastic surgery. However, there is limited research examining TXA in breast surgery with conflicting findings in the existing literature. While the literature on topical TXA for breast surgery remains mixed, there is limited evidence on systemically administered TXA. Previous literature supports the use of systemic TXA to reduce hematoma and seroma formation following mastectomy. The purpose of this study is to analyze the effects of systemic TXA on BBR complications.

Methods: A single practice retrospective review of patients who underwent BBR by a single surgeon from 1/1/2015 to 1/1/2024 was performed. Demographics and complication rates including hematoma, seroma, wound dehiscence, skin necrosis, fat necrosis, nipple loss, rehospitalization, and reoperation were collected. Univariate analysis using chi-square was performed with a significance level of $p<0.05$.

Results: 47 BBR patients were identified, of which 28 (60%) received 1 g IV TXA intraoperatively, and 19 (40%) did not. There were no significant demographic differences between the groups, except the non-TXA group had a longer mean length of follow-up (854.9 vs 341.6, $p=0.004$). Overall, 15% of patients experienced complications. There were no statistically significant differences between the groups for incidence of fat necrosis (11% vs. 11%, $p=0.41$), delayed wound healing (4% vs. 11%, $p=0.98$), hematoma (4% vs. 0%, $p=0.90$) and seroma (4% vs. 0%, $p=0.41$). No other complications were found.

Conclusions: The use of systemic TXA in BBR does not reduce intraoperative or postoperative complication rates overall. However, this study is limited by sample size and larger studies may be necessary to further investigate the use of TXA in BBR.

## C34

**Maissa Trabilsy MA, BA** Advisor(s): Antonio Forte Ph.D.,M.D.

Co-author(s): -

### Utilizing Generative Text to Image AI Models to Explore Race, Sex, and Age in Aesthetic Plastic Surgery

It is unclear how representative and inclusive of various patient populations text to image AI models are. Therefore, this project explores the diversity of race, gender, and age in the images generated by AI models: DALL-E3, Midjourney, and Adobe Firefly, in response to prompts focused on popular aesthetic procedures: liposuction, blepharoplasty, and rhinoplasty.

Prompts were designed to ask each AI model to generate images of surgical outcomes for liposuction, blepharoplasty, and rhinoplasty for each gender, race and age combination: male vs. female, Caucasian or white, Black or African American, Latino or Hispanic, and age groups: 20-30 years, 31-45 years, and 46+ years. Each generated image was evaluated for representation of skin color by Fitzpatrick and Monk scales, and sex parity using a 4-item questionnaire. The Kruskal-Walis test was used for the overall comparison of continuous variables between the 3 models ($p<0.05$) and the Wilcoxon rank sum test for pairwise comparisons ($p<0.017$, after adjustment based on the Bonferroni method for multiple comparisons). The Fischer's east test was used for the overall comparison of categorical variables between the 3 models ($p<0.05$) as well as pairwise comparisons ($p<0.017$).

There was no significant difference between representation of light skin color (Fitzpatrick I-III & Monk 1-5) vs. dark skin color (Fitzpatrick IV-VI & Monk 6-10) between the 3 AI text to image generative models ($p=0.26$ & $p=0.31$). A significant difference was found generally between all 3 AI models ($p<0.0001$) as well as when comparing female vs male ($p=0.0009$) regarding the depiction of aging.

There appears to be inclusivity and fair representation of light skin colors and dark skin colors, but there is still room for improvement regarding the depiction of gender bias.

## C35

**Lucy Wei B.S.** Advisor(s): David Otterburn M.D.

Co-author(s): -

### Topical Tacrolimus: A Game-Changer in Full Thickness Necrosis Prevention In Alloplastic Breast Reconstruction

Purpose: Skin necrosis is a common complication following mastectomy, with reported incidence rates as high as 30%. Previous studies in rodent models demonstrated that topical tacrolimus significantly reduces skin flap necrosis and outperforms other studied topicals, but its use in human ischemic skin has yet to be described. This study aims to introduce topical tacrolimus as an effective adjunctive treatment for skin necrosis after immediate breast reconstruction.
Methods: A retrospective review was conducted on patients after mastectomy with immediate tissue expander breast reconstruction between October 2023 and December 2024. Patients deemed at risk for skin ischemia by either gross observation or abnormal indocyanine green angiography findings, were prescribed topical tacrolimus and instructed to apply twice a day. Patient demographics, medication timelines, surgical details, complications, and clinical outcomes were analyzed using descriptive statistics.
Results: 15 patients (n= 20 breasts) were analyzed. The mean age and BMI were 55.20± 3.31 and 22.53±0.71 respectively. The average length of tacrolimus usage was 18.85±2.63 days. Of all at-risk breasts, only one breast developed full-thickness necrosis, resulting in a 95% salvage rate. Necrosis was completely prevented in ten breasts (50.0%). All patients were able to continue their scheduled breast cancer treatment and reconstruction without any significant delays. No adverse effects related to topical tacrolimus use were reported by all patients.
Conclusion: This study demonstrates that topical tacrolimus is a safe and effective strategy for preventing full-thickness necrosis in threatened mastectomy flaps. These promising results should be followed up with a randomized control trial to determine the efficacy of topical tacrolimus in treatment for mastectomy flap necrosis.

## C36

**Bayle Smith-Salzberg B.A.** Advisor(s): Jonathan Klein M.D.

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### Financial Toxicity and Quality of Life in Breast Cancer Patients at a Safety Net Hospital

INTRODUCTION
Financial toxicity (FT) is the burden faced from out-of-pocket expenses related to cancer care, including treatments, lost income, and travel costs. Increased FT has been associated with decreased quality of life (QOL) and, possibly, worse survival. Patients from potentially marginalized groups may be particularly vulnerable to FT. Maimonides Medical Center (MMC) treats many such patients. We present preliminary data from a prospective, longitudinal study of FT in breast cancer (BC) patients at MMC.
METHODS
All patients undergoing curative-intent treatment for BC at MMC were eligible. We collected patient data from medical records. We assessed FT via the Comprehensive Score for Financial Toxicity (COST) version 2 questionnaire and QOL via the EORTC Quality of Life Core-30 questionnaire before treatment initiation. We analyzed data using R (version 4.4.1, R Core Team).
RESULTS
37 patients were included. Mean age was 57 (SD: 10). 13 patients did not speak English. 6 patients identified as Asian, 18 as Black, 8 white, and 5 declined to answer. 8 patients reported household yearly incomes greater than $60k. 14 patients had private insurance, 9 Medicare, and 13 Medicaid. 27 patients had early-stage (DCIS or T1) BC.
Mean COST score was 22 (SD: 10) and mean EORTC summary score was 83 (SD: 17). Better FWB (COST score) positively correlated with better overall QOL (EORTC summary score) ($p = 0.004$). There was a significant association between higher COST score and patients with household incomes >$60k ($p = 0.002$). Early-stage was associated with higher COST score ($p = 0.047$). There was no difference between the COST scores of patients of differing age, insurance type, language, or ethnicity (p > 0.05).
CONCLUSION
Worse FT is associated with lower QOL in BC patients, underscoring the importance of financial burdens for cancer patients. Patients with lower household incomes and those with more advanced disease experience worse FT even before treatment begins.

## C37

**Daana Bajnauth** Advisor(s): Yolanda Bryce M.D.

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### Impact of Genetic Mutations on Response and Time to Progression After Radioembolization of Breast Cancer Liver Metastasis

Purpose
To evaluate the association between genetic mutations and clinical outcomes, including response rate and time to progression, in patients with breast cancer liver metastasis treated with Y-90 radioembolization.
Methods
This is a retrospective, single-institution study. 110 patients with biopsy-proven breast cancer liver metastasis who underwent Y-90 radioembolization were included. Genomic profiling was conducted using MSK-IMPACT. Data was collected from electronic medical records (EMR) and Picture Archiving and Communication System (PACS) for patient demographics and treatment response. Treatment responses were categorized as complete, partial, none, or progression. For patients with an initial treatment response, complete and partial, statistical analysis was used to assess the correlation between genetic mutations and time to progression. Median survival using Kaplan Meier estimation was performed and correlated to genetic mutations. 17 patients died before progression was assessed, and 6 patients were not yet evaluated post-procedure.
Results
The overall median survival was 32.8 months. Patients with the ERBB2 mutation had the longest median survival (70.2 months) while those with the RAD21 mutation had the shortest median survival (25.5 months). KDM5C and CBFB mutations had the highest response rates (100%, $p=0.00346$ and $p=0.01462$, respectively) while the H3C13 mutation had the lowest response rate (0%, $p=0.00222$). Of patients with an initial response to therapy, median time to progression was 32.8 months. The H3F3B mutation had the longest time to progression (105 months) while the RUNX1 mutation had the shortest time to progression (1.4 months).
Conclusion
Specific genetic mutations are associated with response and time to progression in patients with breast cancer liver metastasis treated with Y-90 radioembolization. This study underscores the impact genetic profiling can have in individualizing treatment plans and improving patient outcomes.

## C38

**Christopher Magloire B.S.** Advisor(s): Mathue Duhaney M.D.

Co-author(s): Justin Heholt

### Infectious Patellar Tenosynovitis: A Rare Case of Patellar Tendon Abscess and Traumatic Rupture

Introduction: Infectious tenosynovitis of the patellar tendon is a rare condition, with only two cases previously reported in literature. We present a case of a 63-year-old diabetic male who developed infectious patellar tenosynovitis complicated by an intratendinous abscess and subsequent traumatic rupture after a fall. The patient presented with progressive left knee pain, swelling, and an inability to extend the knee. His history was significant for a draining wound inferior to the patella treated with a short course of antibiotics two months prior.

Imaging: MRI from an outside facility revealed bony erosion of the tibial tuberosity and inflammatory changes of the patellar tendon but did not demonstrate a rupture. However, radiographs indicated patellar alta and signs suggestive of tendon rupture, with possible avulsion fracture or erosive changes at the tibial tuberosity for which infectious or neoplastic processes were not excluded. A non-contrast CT scan identified a central low-attenuation focus within the tendon and erosive changes at the tibial tuberosity. Definitive evaluation with contrast-enhanced MRI delineated a large intratendinous abscess extending into the subcutaneous fat, tibial tuberosity osteomyelitis, and clear discontinuity of the tendon, consistent with a tendon rupture.

Treatment: The patient underwent incision and drainage with intraoperative cultures yielding Staphylococcus aureus. Following a course of vancomycin, antibiotic therapy was narrowed to IV cefazolin for 6 weeks due to osteomyelitis and patellar tendon repair was successfully performed 3 weeks after debridement.

Conclusion: This case highlights the importance of considering infectious etiologies in tendon injuries, particularly in patients with risk factors such as diabetes and prior soft tissue infections. It also highlights the role of MRI with contrast in differentiating infectious, traumatic, and neoplastic processes, ensuring timely diagnosis and appropriate management.

## C39

**Irina Stavrovskaya Ph.D.** Advisor(s):

Co-author(s): -

### Loss of LRP1 expression in alveolar epithelial type 2 cells affects hepatic tissue metabolism.

The low-density lipoprotein (LDL) receptor-related protein 1 (LRP1) is a lipoprotein receptor involved in multiple cellular functions. To investigate its role in alveolar epithelial type 2 cells (T2C), which are specialized in pulmonary surfactant synthesis, our lab generated an inducible, T2C-specific LRP1 knockout model (SPC-LRP1$^{-/-}$). Loss of LRP1 in T2C impacted surfactant homeostasis in 6-month-old mice. Notably, LRP1 loss in T2C also had extrapulmonary effects. In 11–13-week-old mice, SPC-LRP1$^{-/-}$ mice showed increased hepatic ceramide, triglyceride and cholesterol accumulation, activation of fatty acid synthesis pathways, and reduced β-oxidation, collectively resembling non-alcoholic fatty liver disease (NAFLD). To explore this further, we assessed hepatic mitochondrial function. Respiratory complex I, II, and IV activity remained unchanged between WT and SPC-LRP1$^{-/-}$ mice. However, we observed a sexual dimorphism in complex II and IV activity, with females exhibiting higher activity than males in both (WT and SPC-LRP1$^{-/-}$) groups. Interestingly, ATP synthase activity was elevated in SPC-LRP1$^{-/-}$ mice. This, along with reduced FA β-oxidation, could indicate a shift in mitochondrial efficiency to maintain energy homeostasis in response to metabolic stress. Mitochondrial malondialdehyde levels and glutathione peroxidase activity remained unchanged, suggesting lipid peroxidation was at physiological levels. These findings support the existing notion of a lung-liver connection, where T2C dysfunction may contribute to systemic metabolic disturbances, highlighting the need for further investigation into the roles of T2C in extrapulmonary metabolic regulation.

## C40

**Sunil Kumar Surapaneni Ph.D**. Advisor(s): William Chirico Ph.D.

Co-author(s): Howard Yu, Hamza Hamza, Dinesh Nirmal, Patrick Geraghty

### Loss of Extended Synaptotagmin 2 expression enhances cigarette smoke-induced plasma membrane damage in lung epithelial cells

Maintaining plasma membrane (PM) integrity is essential for cellular homeostasis. Cigarette smoke and its constituents compromise the PM integrity of lung cells, necessitating rapid damage evasion and repair processes. $Ca^{2+}$ influx serves as a key trigger for PM repair through lysosomal exocytosis, microparticle shedding, patch formation, or endocytosis. We have utilized a yeast deletion screen to identify $Ca^{2+}$-binding tricalbins, which are mammalian homologs of extended synaptotagmins (ESyts), as key PM repair genes. Subsequently, the role of ESyt1–3 proteins in lung epithelial cell PM repair were investigated. To achieve this, lentiviral short hairpin RNA (shRNA) approaches were utilized to knock down the expression of ESYT1–3 genes in A549 cells. Scrambled and ESYT1–3 shRNA-transfected A549 cells were exposed to either cigarette smoke extract (CSE) or saponin, a nonionic detergent, under both $Ca^{2+}$-containing and $Ca^{2+}$-depleted conditions. PM damage was assessed using a SYTOX Orange permeability assay. Exposure to 2.5% CSE induced PM damage approximately 2.2-, 2.3-, and 1.9-fold higher in A549 cells transfected with ESYT1, ESYT2, and ESYT3 shRNA, respectively, compared to scrambled shRNA-transfected A549 cells. Similarly, silencing each ESYT gene enhanced saponin-induced PM damage. Cells transfected with ESYT2 shRNA showed the highest PM damage with both CSE and saponin. CSE (5%) exposure increased the expression of the ESYT genes in a $Ca^{2+}$-dependent manner in A549 cells. Collectively, these findings underscore the critical role of ESYT genes, particularly ESYT2, in maintaining PM integrity and highlight the need for further investigation into PM repair mechanisms in pulmonary diseases.

## C41

**Emma Xiao** Advisor(s): Sabina Hrabetova Ph.D.,M.D.

Co-author(s): Jan Hrabe

### Monte Carlo simulation of dead-space microdomains with a 1D diffusion model

Brain extracellular space (ECS), dominating over 20% of the total brain tissue volume, serves as a major transport system for molecules involved in drug delivery and signal communication between cells. Diffusion governs molecule movement in the ECS. It is quantified by diffusion permeability $\theta = D^* / D$, where $D^*$ is the effective diffusion coefficient in brain tissue and D is the free diffusion coefficient. Although experimental studies of small molecules in healthy brain tissue identified $\theta$ at ~ 0.40, simulations and theoretical studies of geometrical models with convex elements can only yield values above 0.66. Concave invaginations within the ECS, termed dead-space microdomains (DMs), were proposed as a possible explanation for lower experimental $\theta$, by temporarily trapping molecules. However, most DM models were built on the assumption of narrow DM entrance sizes, which is likely violated given the non-uniform nature of the brain ECS. Here we systematically investigated how a wider range of DM entrance sizes impacts $\theta$ in a 1D model. We started with a 40% DM ratio (DMR = DM volume / total ECS volume) to reflect the proportion of dead space previously estimated in healthy brain tissue. Molecules were released at the center of the geometry and let to diffuse in Monte Carlo simulations using the MCell program. We found that the delay effect diminished with larger DM entrance sizes. Given the wide range of DM entrance sizes in the brain, this implies that 40% DMR is not enough to reduce overall $\theta$ to 0.40. Thus, we tested a series of DMRs to understand the combined effect of DM entrance size and DMR on $\theta$. We found that, for the same entrance size, a larger DMR produced a lower $\theta$. In conclusion, our findings suggest the DMR is likely greater than 40% in healthy brain tissue which contains a range of DM entrance sizes. We explored patterns of the influence of DM entrance size and DMR on $\theta$ that may advance our quantitative understanding of the ECS structure.

**C42**

**Soumya Krishnan Ph.D.** Advisor(s): Itsaso Garcia Arcos Ph.D.

Co-author(s): -

**Pulmonary fibrosis and alveolar lipid levels in Bleomycin challenged Type 2 cell LRP1 KO mice.**

Pulmonary fibrosis (PF) is an interstitial lung disease with poor prognosis and limited treatment options. Recurrent damage to the alveolar type 2 cells (T2C) is a proposed cause of PF. Our prior research showed that mice with T2C-loss of LDL-related protein 1 (LRP1 (SPC-LRP1-/-) have decline in pulmonary compliance, a hallmark of PF, and decreased surfactant lipids. We hypothesized that LRP1 loss in T2C primes the alveoli for fibrosis and used bleomycin (BLM) as a profibrotic agent in 6-months old WT and SPC-LRP1-/- mice.

Inducible SPC-LRP1-/- mice were bred by crossing LRP1-floxed mice with mice expressing Cre recombinase under the control of the promoter of T2C-specific surfactant protein C (SP-C). The knockout was induced at 7 weeks of age, and at 6 months of age mice were challenged with repeated low dose of BLM (0.035 U/g) twice weekly for 4 weeks. At 33 days after initiation of the challenge, mice were euthanized. Inflammation was assessed by body weight tracking, and after euthanasia by bronchoalveolar lavage (BAL) protein concentration. Pulmonary function was measured, fibrosis was assessed by Ashcroft grading of histological sections, and BAL lipids were analyzed by mass spectrometry.

SPC-LRP1-/- mice showed exacerbated body weight loss and higher protein concentration in BAL than WT mice, suggesting increased inflammation. BAL lipid profiling showed lower concentration of surfactant total phosphatidylcholine (PC) and of other lipid species in SPC-LRP1-/- than in WT mice after BLM challenge. Higher fibrotic scores were observed in the lung sections of SPC-LRP1 -/- mice. However, pulmonary function showed a similar decline in static compliance, inspiratory capacity and forced vital capacity for WT and SPC-LRP1-/- mice.

We conclude that LRP1 loss in T2C exacerbates BLM-triggered inflammation, lung function defects, and fibrosis development.

**C43**

**Adam Newton Ph.D.** Advisor(s): William Lytton Ph.D.

Co-author(s): -

**Human capillary identification used to simulate spreading depression in control and ischemic neocortical microcircuits**

Spreading depolarization (SD) is a wave of neuronal depolarization that propagates through gray matter at 2-7mm/min: a brief period of hyperexcitability at the wavefront is followed by spreading depression, neuronal silence from depolarization block; as well as by disruption of ion homeostasis. Blood vessels play a key role in SD as the source of the energy needed for ion pumps. Multiple mechanisms underlie SD initiation and propagation which we explored using simulation.

NEURON/RxD/NetPyNE were used: point neurons with Hodgkin-Huxley style ion channels augmented with homeostatic mechanisms, including Na+/K+-ATPase, NKCC1, KCC2, and dynamic volume changes. We simulated the intracellular and extracellular concentrations of Na+, K+, Cl-, and O2. The contribution of astrocytes was modeled as the O2-dependent clearance of K+. The evolutional-optimization Python framework Optuna was used to find parameters in simulating 13,000 neurons representing ~1 mm3 of mouse cortex.

Oxygen sources in the model were determined using histologic images showing capillary locations from human tissue: a 2.0 x 2.3 cm cross-section of the V1 cortex was immunostained for CD34. This identified 918 capillaries with mean density of 199.6/cm2 and capillary cross-sectional area of 16.7±11.9μm2. For simulation, we used a biased random walk to expand the 2D cross-section of capillaries to a 3-dimensional distribution of oxygen sources. SD was reliably triggered in this model by a bolus of extracellular K+ applied to cortical layer 4. Our model showed neurons closer to capillaries were more able to maintain homeostasis and physiological firing. We also found that neuronal depolarization occurred in all cortical layers, with pathological activity spreading both through extracellular K+ diffusion and through network connectivity.

**C44**

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

Co-author(s):

**Neurotrophic Activity in the NHP Hippocampus, Fluoxetine, and Affective Dysfunction**

To be added

## C45

**Shwetha Phatarpekar Ph.D.** Advisor(s): Tim Bigdeli Ph.D.

Co-author(s): Harris Huberman, Christos Chatzinakos, Daniel Mishan

### Convergent Transcriptomic Signatures: Identifying ASD Genetic Pathways Through Integrated Blood and Neural Developmental Analysis

Autism Spectrum Disorder (ASD) affects 1 in 54 children in the United States, with substantial evidence supporting a genetic basis; however, connecting developmental genetic alterations with persistent peripheral biomarkers remains a significant challenge. Our research employs a dual-platform approach combining RNA sequencing of peripheral blood samples from ASD individuals and neurotypical controls and meta-analysis of published iPSC-derived and peripheral blood transcriptomics. For biomarker discovery, we implement high-throughput RNA sequencing followed by qPCR validation in independent cohorts, while our developmental transcriptomic analysis utilizes a bioinformatics pipeline with stringent quality control measures including FASTQC/MultiQC assessment, STAR alignment, and feature Counts quantification. Published data indicate significant dysregulation in several gene categories: synaptic function genes (SYN1, PSD95, SYP, NR2B) affecting neurotransmission; cell adhesion molecules (PCDHA1, PCDHHA6, CNTN3) disrupting neural connectivity; ion channels and receptors (CACNA2D3, SCN9A, GRIK2) altering neuronal excitability; and neural development genes (ERBB4, NTNG1, TSHZ3) influencing critical neurodevelopmental processes. By pairing "big data" analytic approaches with ongoing clinical programs, our research program has potential to advance our understanding of molecular pathways associated with developmental alterations, which may facilitate earlier ASD diagnosis and reveal novel therapeutic targets.

## C46

**Gloria P. Baena Caldas Ph.D.** Advisor(s): Alejandro Ivan Hernandez Ph.D.

Co-author(s): Frank C. Barone

### RNS60 Substantially Reduces Early Vasogenic Edema, Mitigates Infarct Area, and Decreases Expression of HIF1α Four Days Post-Ischemic Stroke

Introduction: RNS60 is a proprietary 0.9% saline solution with an elevated oxygen concentration. Previously, we showed that 13 days of daily RNS60 treatment after transient middle cerebral artery occlusion (tMCAo) stroke reduced brain pathology (e.g., infarction, amyloid pathology, neuronal death, microglial activation, and white matter damage) while increasing microvascular perfusion and memory (Baena Caldas et al. 2024). Here, we examine earlier brain-protective effects of daily RNS60 treatment 4 days after stroke.

Methods: Male C57BL/6J mice, 3-4 months old, were randomly divided into sham surgery or unilateral 60-minute tMCAo. Each group was subdivided into three treatment arms: an experimental arm receiving daily intraperitoneal injections of 0.2 mL of stabilized RNS60, and control arms of pressurized normal saline with the same oxygen content as RNS60 (PNS60) or normal saline (NS). Injections began 2 hours after stroke, once daily for 3 days. An additional group without treatment was used as a control. Treatment group assignments were blinded throughout the study. On day 4, mice from each group were euthanized to assess infarct volume using TTC staining or were perfused with 4% PFA to perform immunohistochemistry.

Results: Four days after ischemic stroke, daily injections of RNS60 treatment significantly reduced early post-stroke vasogenic edema by 41% and infarct size by 39% compared to controls. These RNS60 brain-protective effects were related to decreased expression of hypoxia-inducible factor 1α (HIF1α), suggesting that RNS60 treatment may reduce hypoxia.

Discussion: RNS60-treated mice exhibit early and long-term significant brain protection after ischemic stroke associated with decreased expression of HIF1α, suggesting reduced hypoxia in the ischemic brain. Ongoing studies aim to identify the effect of RNS60 on blood brain barrier integrity to further elucidate the underlying molecular mechanism.

**C47**

**Vidhi Parikh MBBS** Advisor(s): Sarita Dhuper M.D.

Co-author(s): Sunaina Saharan, Asma Niazi, Sarita Dhuper

**To validate the utility of a modified step test and appropriate criteria for HHR that correlates best with fitness levels for children of all age groups and body mass index.**

The step test has been widely used to assess cardiorespiratory fitness (CRF) in children, a key indicator of cardiovascular health. It correlates well with the gold standard of Vo2 max assessment. Post-exercise heart rate recovery (HRR) is related to CRF and autonomic function. However, no accepted standards exist for assessing HRR in a step test across all ages and BMI.
Aim: To validate a modified step test to identify appropriate HRR criteria that correlate with fitness levels across age groups and BMI.
Methods: Patients referred to cardiology and obesity outpatient clinics underwent a modified step test with HRR calculated using:
Formula 1 (mean HR during 1 min 5 sec post-exercise) and Formula 2 (peak HR at test end - HR at 1 min post-exercise). Fitness categories (poor to excellent) were created using validated protocols. Data analysis and ANOVA modeling assessed fitness level correlations with BMI percentiles (0 ≤ 95th, 95th–120th, 120th–140th, >140th), age, and gender using SAS 9.4. Group comparisons used Tukey test. Vo2 max was derived using:
V02max = 22.246 + 0.343*(HRR-1min) + 11.722*(SEX) ml/kg/min
Results:
123 patients (46% female), mean BMI 31.8 (SD 8.9),mean age:14.5 (SD 3.73)
Fitness levels by formula:
Formula 1: Excellent (18%), Good (23.8%), Sufficient (18.85%), Poor (39.34%) (n=122).
Formula 2: Excellent (9.9%), Good (37.2%), Moderate (33.1%), Poor (19.83%) (n=121).
Formula 1 (mean post-HRR for 1 min 5 sec) correlated significantly with BMI percentiles ($p<0.005$), showing lower fitness with increasing BMI percentiles.Age and gender did not alter model significance ($p<0.002$), which was driven by BMI, with significant differences between groups 0 and 1 vs. 2 and 3.
Conclusion: Mean HRR for 1 min 5 sec post-step test is a better surrogate marker than HRR at 1 min for assessing fitness in children across all ages, genders, and BMI categories. This supports recording HRR in clinical practice for cardiovascular risk assessment and prognosis.

## C48

**Shahana Shankar Kuniyil MBBS** Advisor(s): Sarita Dhuper M.D.

Co-author(s): -

### Bringing Cardiogenetics to the Clinic: Challenges and Opportunities

Background: Advances in genetics have improved understanding of health conditions, yet integration into routine practice remains limited. This study examines the benefits of office-based genetic testing and its impact on patient care and decision-making.
Methods: We conducted a cross-sectional study with 54 pediatric cardiology outpatients who underwent genetic testing through GeneDx, a genetic testing company that provides in-office testing kits for streamlined diagnostics. Samples were collected using oral cheek swabs, and clinical data were extracted from medical records for analysis.
Results: The most common indications for genetic testing were familial dyslipidemia, Left ventricular hypertrophy with a family history of cardiomyopathy, and early cardiac arrest in relatives. Other reasons included syndromic features (marfanoid habitus), recurrent syncope, and abnormal EKG/ECHO. Among 54 patients (28 males, 26 females), 16 (30%) had pathogenic or likely pathogenic mutations, 30 (55.5%) had variants of unknown significance (VUS), and 14 (26%) were mutation-negative. Familial hyperlipidemia was most common (10 patients), followed by Brugada syndrome (2), cardiomyopathies (2), BRAF-related RASopathy (1), and arrhythmogenic right ventricular dysplasia (1). Recommendations included ICD placement, sports clearance decisions, electrophysiological studies, lipid center referral, genetic counseling and testing for family members at an earlier time than would have happened with routine referral to Geneticist. High-risk VUS cases, based on clinical phenotype and family clustering, were referred for further evaluation.
Conclusion: Our study emphasizes that office-based genetic testing enables early diagnosis, timely treatment, and preventive care. As genomic databases grow, the rise of VUS is inevitable, making their interpretation a key challenge. Sharing emerging gene data and advancing molecular biology knowledge are essential for reclassifying VUS as benign or pathogenic.

**C49**

**Vidhi Parikh MBBS** Advisor(s): Sarita Dhuper M.D.

Co-author(s): Sunaina Saharan, Asma Niazi

## Feasibility and effectiveness of early use of anti-obesity medications (AOM) to treat severe adolescent obesity in addition to a lifestyle modification program (LMP) - Live Light Live Right.

Anti-obesity medications (AOM) usage in adolescent weight management was recently implemented due to the latency of its FDA acceptance and limited insurance coverage. The AAP recommends immediate intensive health behavior and lifestyle treatment for children with obesity. Pharmacologic interventions and metabolic surgery are indicated for severe obesity.
Aim: Our study assessed the feasibility/effectiveness of early AOM use alongside the Live Light Live Right lifestyle modification program (LMP). Medical records of patients prescribed AOM [metformin, phentermine, topiramate (alone or in combination), semaglutide (Ozempic), and Zepbound] were reviewed. Pre-AOM weights were compared to the most recent visit weight. Short- and medium-term weight loss was assessed by pre/post weight loss percentages. Most medications lacked insurance approval, requiring patients to self-pay via discount coupons or nonprofit pharmacies.
Results: The study included 135 patients (45.2% male, 54.8% female), mean age 16.72 years (range 5-31), and mean BMI 40.06 kg/m², with a follow-up of 16.01 months (range 1-53). Medications used: Metformin 88 (65.1%), Ozempic 12 (8.9%), Topiramate 75 (55.55%), Phentermine 72 (53.33%), Wegovy 6 (4.44%), in isolation or combinations. Of the cohort, 99 (73.33%) lost weight, while 36 (26.7%) did not lose or gained weight. Weight loss distribution: 31% lost 0-5%, 24% lost 5-10%, 17% lost 11-15%, 8% lost 16-20%, and 19% lost >20%, with 44% losing >10% from baseline. The average weight change was -8.86% (range 1%-77%).
Conclusion: Our study demonstrates AOM as an effective adjunctive intervention for severe obesity in underserved inner-city youth even without insurance. Reported side effects were minimal, but adherence, compliance, and cost were significant barriers. Response to similar medications varied. Long-term treatment and monitoring are needed to determine the biological and social factors influencing successful weight loss.

## C50

**Michael Copeland B.S.** Advisor(s): Alexandro Ramirez Ph.D.

Co-author(s): -

### Neural Signals May Take a Distinct Route to the Hindbrain when Generating Spontaneous Eye Movements

The visuomotor system enables animals to move their eyes in response to visual stimulation. In vertebrates it includes the superior colliculus, homologous to the optic tectum in non-mammals, which relays signals downstream to hindbrain regions that direct eye movements. If this system or a different one accounts for eye movements that occur absent visual stimulation is unknown. We address this question by studying horizontal eye movements in larval Danio rerio (zebrafish). Zebrafish are an ideal model because the visuomotor system is well conserved in vertebrates and the entire brain can be imaged at once in small and transparent larvae. We hypothesize that the tectum does not contribute to eye movements absent visual stimulation and by extension, that zebrafish bypass it to do so. We employed two-photon calcium imaging to observe activity in the tectum positively correlated with rapid eye movements from side to side, called horizontal saccades. Larvae were immobilized in agarose dorsal side up, given space to move their eyes, and most of the brain was imaged with a custom-built two-photon laser scanning microscope. Eye movements were simultaneously recorded with a camera from below the animal. The animal was kept in darkness during the experiment to prevent visual stimulation. Analysis of these data corroborated our hypothesis and produced unexpected results. First, we did not find neurons positively correlated with horizontal saccades in the optic tectum. This finding corroborates the idea that the tectum does not contribute to saccades made in the absence of visual stimulation. Second, we observed neurons positively correlated with eye position in unexpected regions of the forebrain. This finding provides preliminary evidence of another circuit for nonvisual eye movements, one that may bypass the tectum and involve the forebrain.

## C51

**Ela Bicki M.D.** Advisor(s): Sarita Dhuper M.D.

Co-author(s): Andrew Kahnauth, Emily Needles

### A Case of Asymptomatic Siblings with Brugada Syndrome

Background: Brugada Syndrome is a rare, inherited cardiac channelopathy that predisposes individuals to life-threatening arrhythmias and sudden cardiac death (SCD), and often presents diagnostic challenges due to its subtle clinical manifestations. Case:We present a case of two asymptomatic African American siblings, both found to have identical rare pathogenic variants associated with Brugada syndrome through genetic testing in the outpatient setting. The siblings were referred for evaluation following the sudden cardiac death of their father. Initial electrocardiogram (ECG) showed sinus rhythm with a right bundle branch block and a saddle-shaped QRS pattern. A subsequent 15-lead ECG revealed sinus rhythm with right axis deviation, right ventricular conduction delay, and ST elevation in lead V2. A repeated ECG with Brugada leads showed an incomplete right bundle branch block but no ST elevation. Genetic testing using the GeneDx Brugada Syndrome Sequencing and Deletion/Duplication Panel for both siblings identified a heterozygous pathogenic variant p.(Arg367Cys)(CGC>TGC): c.1099 C>T in exon 9 of the SCN5A gene. Both siblings were diagnosed with type 3 Brugada syndrome and were referred to cardiogenetics and electrophysiology for further evaluation and management. Discussion:Genetic testing plays a crucial role in diagnosing and managing hereditary cardiac diseases, especially in asymptomatic patients with clinical suspicion. Recent studies emphasize its importance in risk stratification and determining the appropriate management strategies. The availability of genetic testing in the outpatient setting provides a valuable tool for early identification and intervention in patients at risk for arrhythmic events.Conclusion:This case highlights the importance of genetic testing in diagnosing Brugada syndrome, even in asymptomatic patients, and underscores the need for further evaluation and management in at-risk individuals, especially those with a family history of SCD.

## C52

**Ela Bicki M.D.** Advisor(s): Sarita Dhuper M.D.

Co-author(s): Midhat Khan

### Management of Giant Coronary Artery Aneurysm With Long-Term Infliximab Therapy in IVIG-Resistant Kawasaki Disease with Three-Vessel Coronary Artery Aneurysms

Background: Kawasaki Disease (KD) is a medium-vessel vasculitis that can lead to coronary artery aneurysms (CAA). Infliximab is used for IVIG-resistant KD, and recent studies suggest it may help treat CAA due to elevated anti-tumor necrosis factor levels in KD patients, making it the medication of choice in this case. Case: A 2-year-old male with fever >5 days, oropharyngeal erythema, cracked lips, desquamating rash, hand swelling, and cervical lymphadenopathy was diagnosed with KD. Due to persistent fever and elevated C-reactive protein (CRP), he received high-dose aspirin, 2 doses of intravenous immunoglobulin (IVIG) (2 g/kg), and IV methylprednisolone, resulting in fever resolution and CRP reduction. The initial echocardiogram showed prominent coronary arteries without dilation. Discharged on low-dose aspirin, he was readmitted 7 days later with fever and rising CRP. Cardiac CT and echocardiogram revealed a giant aneurysm in the left anterior descending artery (LAD, Z score +11.7), as well as aneurysms in the right coronary artery (RCA, Z score +3.85) and left circumflex artery. He received infliximab (5 mg/kg), prednisolone, aspirin, and warfarin. Monthly infliximab infusions (5-10 mg/kg) were started due to elevated CRP. Over 5 years, serial imaging showed improvement, and infliximab infusions were spaced and stopped. Warfarin was continued for 4 years. At 5 years, the LAD aneurysm had regressed to 3.6mm (Z score +4), with a small distal fusiform aneurysm. The patient remains stable on aspirin. Discussion: IVIG resistance occurs in 10-20% of KD patients and may lead to severe coronary artery disease, with giant aneurysms being often persistent. Infliximab is used for IVIG-resistant cases, but more studies are needed to guide treatment for giant aneurysms. Conclusion: Early and prolonged infliximab therapy led to regression of a giant aneurysm in this case. Close follow-up is essential, as overlap with other vasculitis conditions is possible.

## C53

**Charlotte Banayan M.D.** Advisor(s): Simon Rabinowitz Ph.D.,M.D.

Co-author(s): -

### The Relationship Between Gastroesophageal Reflux and Constipation

Intro
Gastroesophageal reflux (R) and constipation (C) are two of the most common indications for children to seek care. Establishing their coexistence may result in recommendations to modify clinical practice.
Methods
TriNetX, a worldwide database of >100 million patients from >80 healthcare organizations, contains >20 million patients with C and >10 million with R. Patients with C (C+) were defined by ICD diagnoses or documented laxative use. Patients with R (R+) were defined by ICD diagnoses. Patients who were R+ or had documentation of acid suppression therapy were also analyzed (RA+).
The total population was divided into C+ or C-. It was also divided into R+ or R- and also into RA+ or RA-.
Prevalence rates were determined for each pair of clinical subgroups. The ratio of prevalence rates was defined as associated risk. Specifically:
-Among those w/ reflux, the proportion who also had constipation [(C+R+)/R+]
-Among those w/o reflux, the proportion who had constipation [(C+R-)/R-]
-Among those w/ constipation, the proportion who also had reflux [(R+C+)/C+]
-Among those w/o constipation, the proportion who had reflux [(R+C-)/C-]
-Among those w/ constipation, how many had either a diagnosis of reflux OR received acid suppression [(RA+C+)/C+]
-Among those w/o constipation, how many had either a diagnosis of reflux OR received acid suppression [(RA+C-)/C-]
The associations were examined over the entire patient population to determine if any associations were unique to children.
Results
C (22.4%) and R (10.8%) were common diagnoses. Each was noted about 4 to 7 times more frequently in patients diagnosed with the other. For constipated children, likelihood of receiving acid suppression was more pronounced compared to those with normal bowel habits.
Conclusion
C and R often coexist from early childhood through adolescence. For children with one, recognizing and treating the other can reduce pain and improve quality of life.

## C54

**Charlotte Banayan M.D.** Advisor(s): Thomas Wallach M.D.

Co-author(s): -

### Racial Distribution of Endoscopic Volume in Children Before and After the COVID Pandemic

Background
Endoscopy is essential for diagnosis and management of gastrointestinal (GI) disorders. In children, the most frequently utilized endoscopies include esophagogastroduodenoscopy (EGD) and colonoscopy.
Objective
We seek to assess if variation exists in the distribution of endoscopic evaluation by race prior to the COVID pandemic (2018-2019) and after the pandemic (2022-2023).
Design/Methods
We used TriNetX, a database with electronic medical records from >100 million patients across >80 healthcare organizations worldwide, to identify endoscopic evaluation volume among patients age ≤18 years from 2018 to 2019 and from 2022 to 2023. The EGD and colonoscopy groups identified patients who were age ≤18 years within these timeframes and at the time of the respective procedure. We utilized z statistics to determine statistical significance of population proportions.
Results
Among pre-pandemic data, while 50% of the general pediatric population (GPP) was White, this group made up 74% of the EGDs and 74% of the colonoscopies performed. Among other racial groups with significant differences, there was a decrease in the number of procedures performed.
Among post-pandemic data, White and American Indian or Alaska Native (AIAN) populations illustrated significant increases in EGDs; all other races demonstrated significant decreases. The White population demonstrated a significant increase in colonoscopies. All other groups with significant differences demonstrated decreases.
Conclusions
The overall increase in post-pandemic procedures may reflect “catch-up” procedures not performed during the pandemic or an increase in post-viral GI symptoms that led to increased procedures.
Also, the White population represented most procedures performed despite representing half of the GPP. We demonstrate a need for further investigation to identify underlying factors that contribute to such disparities and for the development of interventions to ensure equitable access to care.

## C55

**Hyung-Gyo Cho M.D.** Advisor(s): Thomas Wallach M.D.

Co-author(s): -

### Access to Care and Health Care Utilization Among Patients with Inflammatory Bowel Disease

Introduction
Inflammatory Bowel Disease (IBD) is a chronic, relapsing inflammatory condition associated with a high burden of illness, with its prevalence rising globally. This poses a significant impact on individuals, families, and society, with associated healthcare costs escalating. Notably, disparities in healthcare outcomes have been observed, with Black, Asian, and Hispanic individuals often experiencing poorer outcomes. Literature exploring the role of race and socioeconomic status (SES) in IBD outcomes is fragmented. This study aims to clarify the association between race, SES, and healthcare access among IBD patients.
Method
We conducted a retrospective study utilizing the All of Us database from the NIH. Patients with a diagnosis of IBD were included. Health care access was assessed using self-reported questionnaires, along with demographic data (age, sex, race, ethnicity) and SES indicators (income, education, insurance status). The primary outcomes were self-reported measures of healthcare access and affordability, specifically the inability to afford care, delayed care, and having more than one year since the last provider visit. Logistic regression analysis was used to adjust for confounding factors, with reference demographics set as male, White, non-Hispanic, >$200k income, college graduate or higher, and insured.
Results
A total of 5,094 patients diagnosed with IBD were included. The reference group was less likely to report difficulty affording care or having more than one year since a provider visit. In contrast, females, Black patients, individuals with lower income, and those without insurance were more likely to face challenges in affording care. Delayed care was more frequently reported by females, individuals with lower income, and those with lower education levels. Black patients, those with lower education levels, and uninsured individuals were more likely to report more than one year since their last provider visit.

## C56

**Shagun Sharma M.D.** Advisor(s): Annie Levine M.D.

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### Genetic Risk Variants are Common in Native-Born and Immigrant Pediatric Inflammatory Bowel Disease Patients from Minoritized Backgrounds

Introduction:IBD comprised of Crohn's disease (CD) and ulcerative colitis (UC),are traditionally thought of as affecting individuals of European and Ashkenazi Jewish heritage.There is a significant genetic component to disease risk, and genome-wide association studies (GWAS) have identified over 200 risk genes.Majority of IBD patients at our center are of Afro-Caribbean descent,and many are first- or second-generation immigrants.Frequency and significance of many risk alleles is unknown in our population; thus, we aimed to describe the frequency of a limited number of risk alleles.
Methods:Retrospective chart review of individuals aged 0-21 diagnosed with IBD between 2009-2024 was done. Data collected from the electronic medical record (EMR) included demographics, including ethnic background and immigration status,clinical characteristics, disease phenotype, and laboratory results, including the Prometheus Laboratories SGI panel,which reports genotypes for known IBD risk variants in ATG16L1, ECM1, NKX2-3, and STAT3.
Results:19 patients met inclusion criteria and had sufficient data available for analysis.4 were native-born Americans(21.1%),3 first-generation immigrants (15.8%) and 12 second-generation immigrants (63.2%).Majority were African American(10,52.6%),2 Hispanics (10.5%), and 7 from other ethnic backgrounds (36.8%).We noted a high frequency of disease associated variants in ATG16L1 and STAT3, with less frequency in ECM1 and NKX2-3. Second-generation immigrant exhibited the highest genotypic diversity across all genes, particularly with variants in ATG16L1 and STAT3.African Americans showed the highest genetic diversity, predominantly within the second generation immigrant group, with significant representation of both ATG16L1 and STAT3
Discussion:Our data reveals that IBD risk alleles, well-documented in Caucasians, are also common in Afro-Caribbean patients, though their effect remains unclear,highlighting the need for further study in diverse populations.

## C57

**Janani Dinakaran M.D.** Advisor(s): Ratna Basak M.D.

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### Acute Ischemic Stroke in a Pediatric Patient with Cerebral Arteriovenous Malformation

Background:
Pediatric stroke is a rare entity with high mortality and morbidity. This case report details a complex ischemic stroke with a mimicking diagnosis and multiple risk factors, leading to the possibility of different stroke etiologies.
Case description:
A 7-year-old male with a history of patent foramen ovale (PFO), an episode pneumococcal meningitis, and a left-sided grade 3 arteriovenous malformation presented with fever, headache, and tiredness. He was initially treated with ceftriaxone for suspected bacteremia. However, he worsened with altered mental status and nuchal rigidity. Blood cultures grew S.pneumoniae, and cerebrospinal fluid (CSF) confirmed bacterial meningitis. Vancomycin was added with ceftriaxone. The patient also developed a new-onset cardiac murmur. Transthoracic echocardiogram (TTE) revealed new mitral regurgitation meeting criteria for possible infectious endocarditis (IE), that was managed with the same antibiotics. After an initial improvement, he developed right-sided weakness. The MRI angiogram revealed an acute left middle cerebral artery (MCA) infarct with worsening mass effect. However, he suffered from significant right-sided hemiplegia requiring long-term physical and occupational therapy.
Discussion:
Pediatric stroke and meningitis can be difficult to differentiate, often leading to delays in diagnosis. In this case, several possible mechanisms for the stroke were considered, including bacterial meningitis, septic emboli, vascular steal, and cryptogenic stroke. Pneumococcal meningitis-induced stroke is unlikely, as it typically involves bilateral deep brain structures. Embolism from IE is also less likely since no vegetation was seen on TTE. However, a vascular steal from an AVM is supported by the patient's history of transient right-sided weakness, and a cryptogenic stroke due to paradoxical embolism because of the presence of patent foramen ovale (PFO). Further investigations are needed to determine the exact cause.

## C58

**Dinesh Nirmal M.D.** Advisor(s): Patrick Geraghty Ph.D.

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### CIP2A-Mediated Activation of Akt and SMAD3 Pathways Drives Pulmonary Fibrosis: Restoring PP2A Activity as a Therapeutic Strategy

Objectives:
This study examined whether a PP2A activator (PA) reduces fibrosis progression and preserves lung function in a bleomycin (BLM) mouse model. We also investigated how CIP2A regulates fibrotic responses in lung fibroblasts.
Materials and Methods:
A diarylmethyl-pyran-sulfonamide PA was tested in primary human lung fibroblasts exposed to TGFβ or BLM. C57BL/6J mice received daily PA for 2 weeks, starting 8 days after intratracheal BLM instillation. CIP2A was overexpressed in fibroblasts using lentiviral technology. Pathway inhibitors targeting Akt (MK-2206), ERK (SCH772984), and SMAD3 (SIS3) were used to assess CIP2A-driven fibrotic signaling.
Results and Discussion:
PA-treated fibroblasts and mice showed enhanced PP2A activity and reduced α-smooth muscle actin (α-SMC actin) and fibronectin expression. PA administration also mitigated BLM-induced lung physiological and histological changes associated with fibrosis. CIP2A overexpression (CIP2A OE) significantly upregulated COL1A1 and CTHRC1 at both mRNA and protein levels. Akt and ERK inhibition markedly reduced CIP2A-driven COL1A1 and CTHRC1 expression, whereas SMAD3 inhibition had a lesser effect. PCR, Western blot, and densitometry confirmed CIP2A OE increased COL1A1 and CTHRC1 protein levels, which were significantly reduced by Akt and SMAD3 inhibition, respectively. CIP2A suppression correlated with p21 upregulation in lung fibroblasts, but PA treatment did not suppress BLM-induced p21 indicating the regulation of p21 by CIP2A is independent of PP2A.
Conclusions:
PA administration appears to restore PP2A activity and preserve lung function in experimental models of IPF. CIP2A negatively regulates PP2A activity while promoting COL1A1 and CTHRC1 expression via Akt and SMAD3 signaling. Targeting CIP2A-mediated pathways may offer novel therapeutic strategies for IPF.

**C59**

**David Inzerillo M.S.** Advisor(s): Thomas Wallach M.D.

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## Inpatient Feeding Program for a Vulnerable, Underserved, Pediatric Population: A Pilot Study

Background: Pediatric feeding disorders (PFD) encompass a variety of conditions that interfere with a child's ability to consume a developmentally appropriate diet essential for growth. These disorders, clustered in complex care patients, lead to nutritional deficiencies, social/behavioral delays and poor physical growth. Unfortunately, services such as intensive, multidisciplinary feeding programs have traditionally been limited for underserved populations. Our study describes a multidisciplinary pilot program highlighted by one week of comprehensive inpatient stay in an inner-city medical center. Methods: We describe 11 children between ages 8 months to 9 years with a diagnosis of failure to thrive or avoidant restrictive food intake disorder (ARFID) who underwent 1-week intensive in-patient feeding therapy. Each patient was assessed by a pediatric gastroenterologist and had baseline laboratory testing as part of the initial intake. Intensive feeding therapy sessions were conducted twice a day with a trained pediatric speech language pathologist who assessed barriers to oral feeding. Sensory and behavioral techniques were employed such as desensitization, texture fading, portion fading, demand fading, allowing choices and providing preferred foods to improve acceptance of age-appropriate foods. Outcomes were assessed as increased acceptance to variety of foods, increased intake during mealtimes and caregiver carry-over of feeding strategies. Patients were also monitored for changes in weight, caloric intake and subjective reporting by caregiver of improved oral intake. Behavioral and Development team was utilized to assess current developmental needs and optimize service provision. Results: Out of the eleven patients, five patients demonstrated weight gain during the in-patient admission week with only one patient having a documented weight loss. Ten out of eleven patients had acceptance to an increased variety of foods and successful carry-over of strategies